



**SAARC Regional Training Manual**  
**on**  
**Anti-Retroviral Therapy**

**2017**

**SAARC TB and HIV/AIDS Centre**



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**on**

## **Anti-Retroviral Therapy**

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## Preface

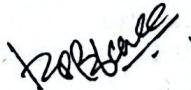
The first HIV infected persons were diagnosed in 1986 in India and Pakistan. By 1993, all SAARC Member States had reported the existence of HIV infection in their countries. The HIV situation epidemic in SAARC region is a collection of diverse epidemics in countries, provinces & districts. HIV and AIDS continue to be a major public health problem in the SAARC Region. Overall 2.24 million estimated HIV infected people are living within the region and 1.56 lakh AIDS deaths in 2012. Overall HIV prevalence is still less than 1%. Three states in India have generalized HIV epidemics; Nepal and Pakistan are at the stage of concentrated epidemic and others at low prevalence epidemic. Three countries, namely India, Nepal and Pakistan account for majority of the regional burden. HIV epidemic in the region is driven by sexual and IDU routes of transmission. Remarkable progress has been made in the region on scaling up HIV Anti Retro Viral Treatment. TB/HIV collaborative interventions are being developed as part of both programmes in all the member countries.

SAARC TB and HIV/AIDS Centre (STAC) have been supporting the National HIV/AIDS programmes in SAARC member countries i.e. Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka in different ways to contain HIV/AIDS epidemic in the region. Major activities carried out by the STAC to control HIV/AIDS in SAARC member countries were human resource development, advocacy programmes, strengthening epidemiological net working, research activities, and developed regional strategies for HIV/AIDS and TB/HIV co-infection (HIV & AIDS situation in the SAARC region 2013).

We feel elated to pen our feelings about the publication of first edition of SAARC Regional Training Manual on Anti-retroviral Therapy (ART) developed by SAARC Tuberculosis and HIV/AIDS Centre. This manual is an important document and provides the comprehensive picture regarding the management and delivery of high standard of HIV and AIDS care and support services. This manual has been adapted from the most recent national, regional and international guidelines and publications. This manual is a remarkable feat as it aims to facilitate trainings for medical personnel (Medical doctors, Health Assistants, Staff nurses and other HIV/AIDS care providers)

On behalf of STAC, I offer my sincere gratitude to STAC professionals and regional experts for their invaluable technical supports to make this endeavor a success.

We hope that this training manual will help the health care providers to deliver the high quality standard of care, treatment and support services in the SAARC region.

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Dr. R. P Bichha  
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## ABBREVIATIONS

3TC:	Lamivudine
ABC:	Abacavir
AIDS:	Acquired Immunodeficiency Syndrome
ALT:	Alanine Aminotransferase
ANC:	Antenatal Clinic
ART:	Antiretroviral Therapy
ARV:	Antiretroviral
AST:	Aspartate Aminotransferase
ATV:	Atazanavir
AZT:	Zidovudine (Also known as ZDV)
CBT:	Community-based Testing
CD4:	Cluster of Differentiation 4
CHW:	Community Health Workers
CITC:	Client-initiated Testing and Counselling
CLIA:	hemiluminescence Immunoassay
CMV:	Cytomegalovirus
CNS:	Central Nervous System
CPT:	Cotrimoxazole Preventive Therapy
CXR:	Chest X-Ray
DAA:	Direct Acting Antiviral Drug
DBS:	Dried Blood Spot
DNA:	Deoxyribonucleic Acid
DOT:	Directly Observed Therapy
DRV:	Darunavir
DTG:	Dolutegravir
ECL:	Electrochemiluminescence Immunoassay
ECP:	Emergency Contraceptive Pills
EFV:	Efavirenz
EIA:	Enzyme Immunoassay
EID:	Early Infant Diagnosis
EPTB:	Extra-pulmonary Tuberculosis
EQA:	External Quality Assessment
eVT:	elimination of Vertical Transmission
FBC:	Full Blood Count
FBT:	Facility-based Testing
FDC:	Fixed-Dose Combination
FSW:	Female Sex Worker(s)
FTC:	Emtricitabine
GI:	Gastrointestinal
Hb:	Haemoglobin
HBV:	Hepatitis B Virus
HCV:	Hepatitis C Virus
HIV:	Human Immunodeficiency Virus
HIVDR:	HIV Drug Resistance
HIVRNA:	Human Immunodeficiency Virus Ribonucleic Acid
HIVST:	HIV self-testing
HSV:	Herpes Simplex Virus
HTS:	HIV testing services
IDV:	Indinavir
INH:	Isoniazid
IPT:	Isoniazid Preventive Therapy

IRIS	Immune Reconstitution Inflammatory Syndrome
IVD	In Vitro Diagnostic
KP	Key Populations
LPV	Lopinavir
LPV/r	Lopinavir/Ritonavir
LTC	linkage to care
M&E	Monitoring and Evaluation
MCH	Maternal and Child Health
MSM	Men Who Have Sex with Men
MSW	Male Sex Worker
MTCT	Mother-To-Child Transmission (Of HIV)
NAT	Nucleic Acid Testing
NCASC	National Centre for AIDS and STI Control
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NPHL	National Public Health Laboratory
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NSAIDS	Non-Steroid Anti-Inflammatory Drugs
NSEP	Needle and Syringe Exchange Programme
NVP	Nevirapine
OCP	Oral Contraceptive Pills
OI	Opportunistic Infections
OST	Opioid Substitution Therapy
PCP	Pneumocystis Jiroveci Pneumonia
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PGL	Persistent Generalized Lymphadenopathy
PHC	Primary Health Care
PI	Protease Inhibitor
PITC	Provider-Initiated Testing and Counselling
PLHIV	People Living With HIV
PMTCT	Prevention of Mother-To-Child Transmission
PoC	Point-of-Care
PQ	Pre-qualification
PrEP	Pre-Exposure Prophylaxis
PWID	People Who Inject Drugs
QA	Quality Assurance
QC	Quality Control
QI	Quality Improvement
RAL	Raltegravir
RBV	Ribavirin
RDT	Rapid Diagnostic Test
RNA	Ribonucleic Acid
RT	Reverse Transcriptase
RTI	Reverse Transcriptase Inhibitor
RTV	Ritonavir
SAARC:	South Asian Association for Regional Cooperation
STAC:	SAARC TB and HIV/AIDS Centre
SJS	Stevens-Johnson Syndrome
SoP	Standard Operating Procedure
SQV	Saquinavir

## **Course Introduction: Module Introduction, Objectives, Duration, Methodology and Evaluation:**

**Introduction:** ART training manual has been prepared for medical personnel (Medical doctors, Health Assistants, Staff nurses and other HIV/AIDS care providers) who had taken basic HIV training. The training manual is developed to train and built capacity of doctors, nurses, health assistants and other HIV/AIDS care providers working in public as well as private health institutions in the region to diagnose and manage HIV and HIV-related diseases, including opportunistic infections (OI). Improving care for OIs and HIV-related conditions is a critical component of HIV programs.

The course presents the biomedical facts of care for people with HIV in the context of a comprehensive public health approach, taking into account the physical and psychosocial needs of clients, patients, and their households. It approaches the specific recommendations for diagnostic measures and patient treatment from a global perspective and incorporates regional guidelines for SAARC region. It helps to provide prompt qualitative and comprehensive service (information and clinical management & care /support) in a friendly environment to the clients suffering from and affected by the diseases.

**Training Duration:** The time duration allocated for this training course is five days.

**Methodology:** This course is designed to be taught over five days time including theory, group interaction sessions. The course uses participatory approaches and methodologies, such as clinical management algorithms and case studies as well. This has been designed the module based training course; so that participants will learn in a participatory manner. Participants will be divided in small groups (4-5) and read the module and discuss on issues not clear to them, with the support of the facilitators. Every day; main points and other reference material will be presented through PowerPoint presentations during review of previous day's session to develop common understanding and to give focus on the important topics.

**Evaluation:** A preliminary pre-test and self-assessment of knowledge and skills in the major areas of the workshop opens the course; a post-training assessment uses similar tools.

There are five modules, main topics and sub-topics with following objectives and methodology.

**Module I:** HIV Background and Epidemiology, Basic Clinical information of HIV/ AIDS, sign/symptoms, diagnosis and manifestation and Anti retroviral (ARV) Treatment delivering Preparedness

**Module II:** Antiretroviral Treatment

**Module III:** HIV Testing and Counseling (HTC) and Provider Initiated Testing and Counseling (PITC) and Post Exposure Prophylaxis (PEP)

**Module IV:** Public Private Partnership for ART

**Module V:** Research and Monitoring and Evaluation

## Schedule

### Day 1

#### Subject

Registration

Introduction

Pre-test

HIV Background and Epidemiology

Break

Basic Immunology and Natural History of HIV and AIDS

Diagnosis of HIV and HIV-specific Laboratory Investigations

Lunch

Clinical Presentation and WHO Staging

Overview of HIV Related Disease and

Cotrimoxazole prophylaxis

Comprehensive Care for PLHIV

Wrap up

#### Time Duration

30 minutes

15 minutes

30 minutes

45 minutes

15 minutes

45 minutes

60 minutes

60 minutes

60 minutes

60 minutes

60 minutes

15 minutes

### Day 2

#### Subject

Recap of previous days sessions

Respiratory Manifestations of HIV

Tea break

Neurological Manifestations and Gastrointestinal Manifestations

Dermatological Manifestations of HIV and Lymphadenopathy and Fever in HIV

Lunch

STIs and Gynecological Manifestations of HIV and

Ophthalmologic Manifestations

Country Preparedness and Community Preparedness

Break

Site Preparedness

Linkages and Referral Systems

Wrap up

#### Time Duration

30 minutes

45 minutes

15 minutes

60 minutes

60 minutes

60 minutes

60 minutes

60 minutes

15 minutes

30 minutes

30 minutes

15 minutes

### Day 3

#### Subject

Recap of previous days sessions

Goals, principles of ART

ART drug Mechanisms

When to start ART

Break

Pediatric HIV Infection and when to start ART

Lunch

#### Time Duration

30 minutes

30 minutes

45 minutes

45 minutes

15 minutes

45 minutes

60 minutes

First line ART and Patient Follow-up and Monitoring	45 minutes
ART drug interactions	30 minutes
HIV and Pregnancy: Prevention of Mother-to-Child Transmission, ART during Pregnancy and ART in Pregnant Women with Previous Exposure to NVP	45 minutes
Break	15 minutes
TB/HIV Co-infection (TB Infection Prevention, Active Case Finding, and Isoniazid Preventive Therapy)	60 minutes
Wrap up	15 minutes

#### Day 4

Subject	Time Duration
Recap of previous days sessions	30 minutes
HIV and Hepatitis, Co-infections	45 minutes
Break	15 minutes
ART for IDUs and PLHA on Substitution therapy including opioid Substitution therapy (OST)	30 minutes
Antiretroviral Drug Toxicity and management	30 minutes
What ART regimen to switch to (second-line ART) and Third-line ART	30minutes
Nutrition and HIV	30 minutes
Lunch	60 minutes
Community and Home-Based Care and Palliative Care	30 minutes
Adherence Counseling	30 minutes
HIV Testing and Counseling (HTC) and Provider Initiated Testing and Counseling (PITC)	45 minutes
Break	15 minutes
Post exposure Prophylaxis	45 minutes
Wrap up	15 minutes

#### Day 5

Subject	Time Duration
Recap of previous days sessions	30 minute
Public Private Partnership for ART	60 minute
Break	15 minute
Entry into HIV care	45 minute
Flow of patient at the ART center	30 minute
Stigma and Discrimination	30 minute
Lunch	60 minute
Introduction to Strategic information of HIV Services (monitoring, evaluation, surveillance and research)	60 minute
Overview of ART Recording and Reporting	30 minute
Training Evaluation and Feedback	30 minute
Post test	30 minute
Closing and certificate distribution	30 minute

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# **PART - I**

## DEFINITION OF KEY TERMS

### GENERAL

**HIV** refers to human immunodeficiency virus. There are two types of HIV: HIV-1 and HIV-2.

**HIV-1** is responsible for the vast majority of HIV infections globally. Within these guidelines,

**HIV** refers to both HIV-1 and HIV-2 unless otherwise specified.

### AGE GROUPS AND POPULATIONS

The following definitions for adults, adolescents, children and infants are used to ensure consistency within these consolidated guidelines, as well as with other WHO guidelines. It is recognized that other agencies may use different definitions.

**An adult** is a person older than 19 years of age unless national law defines a person as being an adult at an earlier age.

**An adolescent** is a person aged 10 to 19 years inclusive.

**A child** is a person 19 years or younger unless national law defines a person to be an adult at an earlier age. However, in these guidelines when a person falls into the 10 to 19 age category they are referred to as an adolescent (see adolescent definition).

**An infant** is a child younger than one year of age.

These guidelines define **key populations** to include both vulnerable and most-at-risk populations. They are important to the dynamics of HIV transmission in a given setting and are essential partners in an effective response to the epidemic. People living with HIV are considered a key population in all epidemic contexts.

These guidelines define **most-at-risk populations** as men who have sex with men, transgender people, people who inject drugs and sex workers. Most-at-risk populations are disproportionately affected by HIV in most, if not all, epidemic contexts.

**Vulnerable populations** are groups of people who are particularly vulnerable to HIV infection in certain situations or contexts, such as adolescents (particularly adolescent girls), orphans, street children, people in closed settings (such as prisons or detention centres), people with disabilities and migrant and mobile workers. Each country should define the specific populations that are particularly vulnerable and key to their epidemic and response based on the epidemiological and social context.

**Serodiscordant couples** are couples in which one partner is living with HIV and the other is HIV-negative. A couple refers to two people in an ongoing sexual relationship; each of these is referred to as a partner in the relationship. How individuals define their relationships varies considerably according to cultural and social context.

## HEALTH CARE SERVICES

**Continuum of HIV care** refers to a comprehensive package of HIV prevention, diagnostic, treatment and support services provided for people living with HIV and their families ranging across: initial HIV diagnosis and linkage to care; management of opportunistic infections and other comorbid conditions; initiating, maintaining and monitoring ART; switching to second line and third-line ART; and palliative care.

**A public health approach** addresses the health needs of a population or the collective health status of the people rather than just individuals. A public health approach involves a collaborative effort by all parts of the health sector, working to ensure the well-being of society through comprehensive prevention, treatment, care and support. For HIV, this involves: simplified limited formularies; large-scale use of fixed-dose combinations for first-line treatment for adults and children; care and drugs given free at the point of service delivery, decentralization; and integration of services, including task shifting and simplified clinical and toxicity monitoring.

## HIV TESTING AND PREVENTION

**Voluntary counseling and testing** (also referred to as client-initiated testing and counseling) describes a process initiated by an individual who wants to learn his or her HIV status. Since there are now many different community approaches to providing HIV testing and counseling and people often have mixed motivations for seeking testing (both recommended by a provider and sought by a client), WHO prefers to use the term **HIV testing and counseling**. All forms of HIV testing and counseling should be voluntary and adhere to the five C's: consent, confidentiality, counseling, correct test results and connections to care, treatment and prevention services. Quality assurance of both testing and counseling is essential in all approaches to HIV testing and counseling.

**Provider-initiated testing and counseling** is HIV testing and counseling recommended by a health-care provider in a clinical setting. Provider-initiated testing and counseling, as with all forms of HIV testing and counseling, should be voluntary and adhere to the five C's.

**Combination prevention** refers to a combination of behavioural, biomedical and structural approaches to HIV prevention to achieve maximum impact on reducing HIV transmission and acquisition.

## ART (ANTIRETROVIRAL THERAPY)

**ARV (antiretroviral) drugs** refer to the medicines themselves and not to their use.

**ART** refers to the use of a combination of three or more ARV drugs to achieve viral suppression. This generally refers to lifelong treatment. Synonyms are combination ART and highly active ART.

**ART for prevention** is used to describe the HIV prevention benefits of ART.

**Eligible for ART** refers to people living with HIV for whom ART is indicated according to the definitions of clinical and immunological eligibility in WHO treatment guidelines. The term is often used interchangeably with “needing treatment”, although this implies an immediate risk or an obligation to initiate treatment.

**Viral suppression** refers to the aim of ART to maintain viral load below the level of detection of available assays, generally less than 50 copies per ml. The current WHO virological criterion for treatment failure is 1000 copies per ml or more.

**Universal access to ART** is defined broadly as a move to a high level of access ( $\geq 80\%$  of the eligible population) for the most effective interventions that are equitable, accessible, affordable, comprehensive and sustainable over the long term; this does not necessarily mean 100% coverage.

## **HEALTH WORKFORCE**

**Community health workers** are health workers who have received standardized and nationally endorsed training outside the nursing, midwifery or medical curricula.

**Midwives** are people trained to assist in childbirth, including registered and enrolled midwives.

**Non-physician clinicians** are professional health workers capable of many of the diagnostic and clinical functions of a physician but who are not trained as physicians. These types of health workers are often known as health officers, clinical officers, physician assistants, nurse practitioners or nurse clinicians.

**Nurses** include professional nurses, enrolled nurses, auxiliary nurses and other nurses such as dental or primary care nurses.

## **EPIDEMIOLOGY**

**Concentrated HIV epidemic:** HIV has spread rapidly in one or more defined subpopulation but is not well established in the general population. Numerical proxy: HIV prevalence is consistently over 5% in at least one defined subpopulation but is less than 1% among pregnant women in urban areas.

**Generalized HIV epidemic:** HIV is firmly established in the general population. Numerical proxy: HIV prevalence consistently exceeding 1% among pregnant women. Most generalized HIV epidemics are mixed in nature, in which certain (key) subpopulations are disproportionately affected.

**Mixed epidemics:** people are acquiring HIV infection in one or more subpopulations and in the general population. Mixed epidemics are therefore one or more concentrated epidemics within a generalized epidemic.

**Low-level epidemic:** epidemics in which the prevalence of HIV infection has not consistently exceeded 1% in the general population nationally or 5% in any subpopulation.

**Low-, moderate- and high-uptake ART settings** refer to settings in which the uptake of ART among those eligible for ART is less than 50%, 50–80% and greater than 80%, respectively.

**A setting with a high burden of TB and HIV** refers to settings with adult HIV prevalence  $\geq 1\%$  or HIV prevalence among people with TB  $\geq 5\%$ .

**HIV incidence** is the number of new people acquiring HIV infection in a given period in a specified population.

**HIV prevalence** refers to the number of people living with HIV at a specific point in time and is expressed as a percentage of the population.

#### **PMTCT (PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV)**

In these guidelines, WHO is moving away from the previous terms "Options A, B and B+". Instead, these guidelines recommend two options: (i) providing lifelong ART to all pregnant and breastfeeding women living with HIV regardless of CD4 count or clinical stage or (ii) providing ART (ARV drugs) for pregnant and breastfeeding women with HIV during the mother-to-child transmission risk period and then continuing lifelong ART for those women eligible for treatment for their own health. In settings that are not implementing lifelong ART for all pregnant and breastfeeding women living with HIV, the distinction between prophylaxis (ARV drugs given for a limited time during the risk period for transmitting HIV from mother to child to prevent this) and treatment (ART given both for the mother's health, based on current adult eligibility, and to prevent vertical transmission) is still important.

**ARV drugs for women living with HIV during pregnancy and breastfeeding** refers to a triple-drug ARV drug regimen provided to mothers living with HIV primarily as prophylaxis during pregnancy and throughout breastfeeding (when there is breastfeeding) to prevent mother-to-child transmission of HIV. In this option, the mother's regimen is continued lifelong after delivery or after the breastfeeding ends only if she meets the ART eligibility criteria for her own health based on CD4 count or clinical stage. Previous WHO guidance referred to this as **option B**.

**Lifelong ART for all pregnant and breastfeeding women living with HIV** refers to the approach in which all pregnant women living with HIV receive a triple-drug ART regimen regardless of CD4 count or clinical stage, both for their own health and to prevent vertical HIV transmission and for additional HIV prevention benefits. Previous WHO guidance referred to this as **option B+**.

**Module-I: HIV Background and Epidemiology, Basic Clinical information of HIV/ AIDS, sign/symptoms, diagnosis and manifestation and Anti retroviral (ARV) Treatment delivering Preparedness**

**Section – A: HIV Background and Epidemiology, Basic Clinical information of HIV/ AIDS, Sign/symptoms, Diagnosis and manifestation**

## 1. HIV Background and Epidemiology

### PURPOSE:

In this session, participants will learn about the HIV epidemic and its impact worldwide. The session will address the epidemiology of HIV, mechanisms of transmission and disease progression. SAARC regional-specific information will be given.

### OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the impact of the HIV epidemic globally and SAARC region.
2. List the various types and subtypes of HIV.
3. Describe how HIV is transmitted and the biological and socioeconomic factors that facilitate transmission.

### Global HIV Epidemic:

#### People living with HIV

- In 2012, there were 35.3 million [32.2 million–38.8 million] people living with HIV.
- Since the start of the epidemic around 75 million [63 million–89 million] have become infected with HIV.

#### New HIV infections

- New HIV infections have fallen by 33% since 2001.
- Worldwide, 2.3 million [1.9 million–2.7 million] people became newly infected with HIV in 2012, down from 3.4 million [3.1 million–3.7 million] in 2001.
- New HIV infections among adults and adolescents decreased by 50% or more in 26 countries between 2001 and 2012.
- New HIV infections among children have declined by 52% since 2001.
- Worldwide, 260 000 [230 000–320 000] children became newly infected with HIV in 2012, down from 550 000 [500 000–620 000] in 2001.

#### AIDS-related deaths

- a. AIDS-related deaths have fallen by 30% since the peak in 2005.
- In 2012, 1.6 million [1.4 million–1.9 million] people died from AIDS-related causes worldwide compared to 2.3 million [2.1 million–2.6 million] in 2005.
- Since the start of the epidemic an estimated 36 million [30 million – 42 million] people have died of AIDS-related illnesses.

#### About 6,300 new HIV infections a day in 2012

- About 95% are in low- and middle-income countries
- About 700 are in children under 15 years of age

- About 5,500 are in adults aged 15 years and older, of whom:

- Almost 47% are among women

- About 39% are among young people (15-24)

#### 2012 Global of HIV and AID estimates Children (>15 Years):

Children living with HIV ----- 3.3 million [3.0 million – 3.7 million]

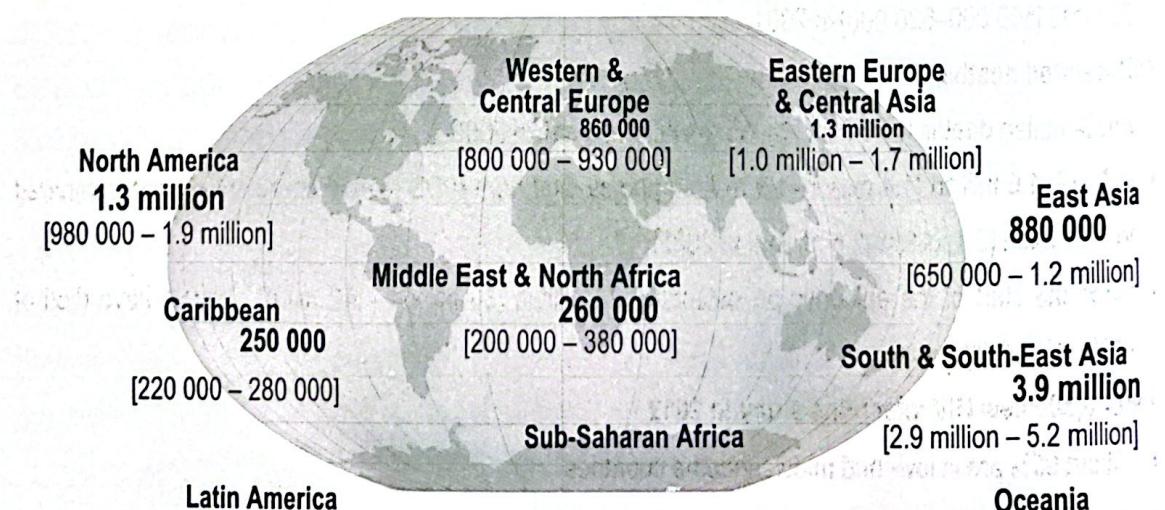
New HIV infections in 2012 ----- 260 000 [230 000 – 320 000]

Deaths due to AIDS in 2012 ----- 210 000 [190 000 – 250 000]

**Table 1: Regional HIV and AIDS statistics and features 2012**

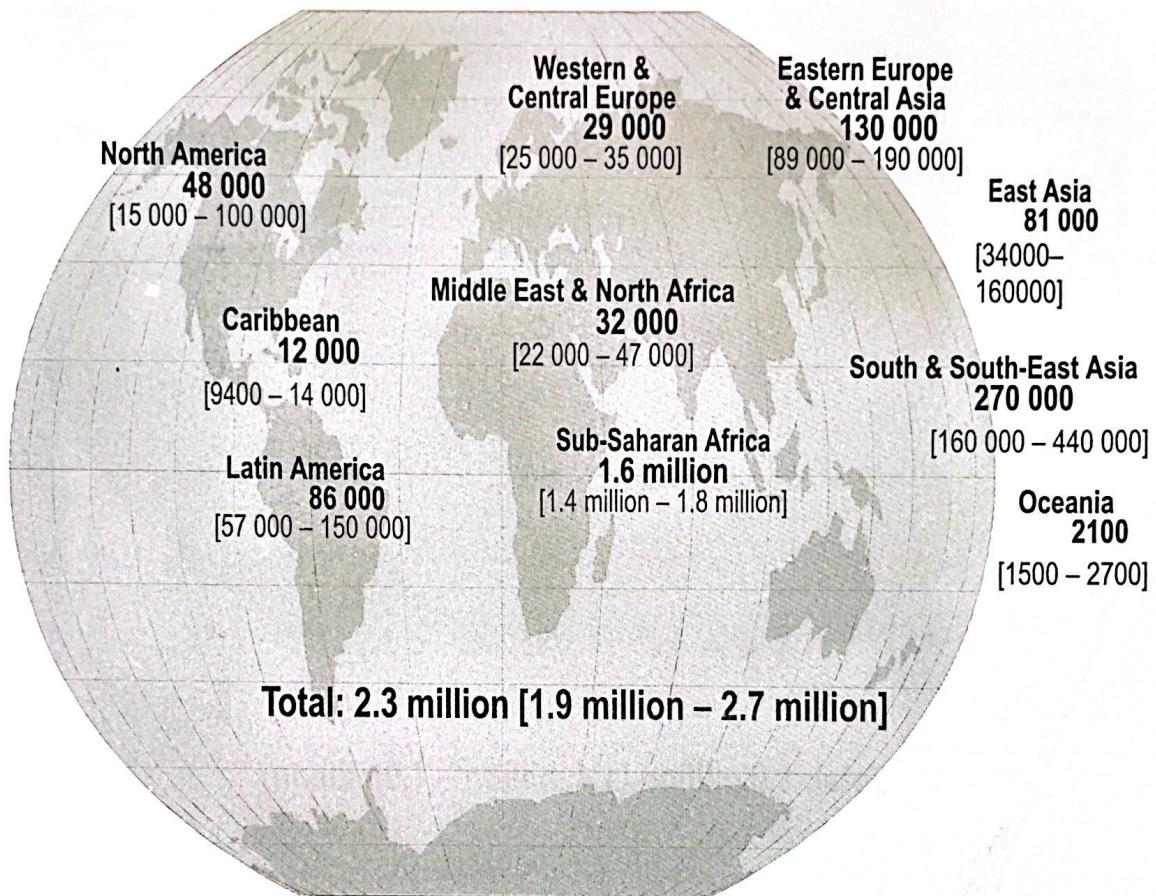
WHO Regions	Adults and children living with HIV	Adults and children newly infected with HIV	Adults prevalence (15-49) %	Adult and child deaths due to AIDS
Sub-Saharan Africa	25.0 million	1.6 million	4.7%	1.2 million
Middle East and North Africa	260 000	32 000	0.1%	17000
South and South-East Asia	3.9 million	270 000	0.3%	220000
East Asia	880 000	81 000	<0.1%	41000
Latin America	1.5 million	86 000	0.4%	52000
Caribbean	250 000	12 000	1.0%	11000
Eastern Europe and Central Asia	1.3 million	130 000	0.7%	91000
Western and Central Europe	860 000	29 000	0.2%	7600
North America	1.3 million	48 000	0.5%	20000
Oceania	51 000	2100	0.2%	1200
<b>TOTAL</b>	<b>35.3 million</b> [32.2 – 38.8 million]	<b>2.3 million</b> [1.9 – 2.7 million]	<b>0.8%</b> [0.7 - 0.9%]	<b>1.6 million</b> 1.4 – 1.9 million
<b>Total Ranges</b>				

**Figure 1: Adults and children estimated to be living with HIV 2012:**

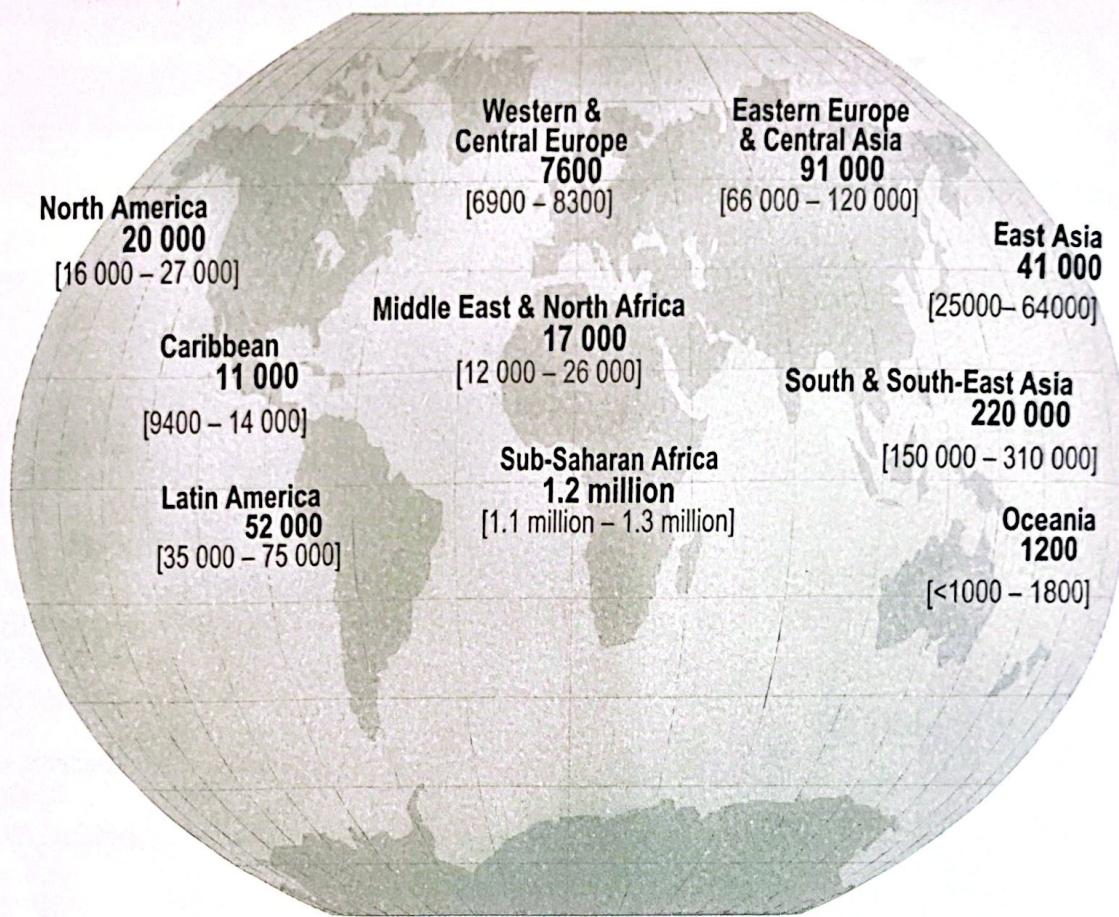




**Figure 2: Estimated number of adults and children newly infected with HIV 2012:**

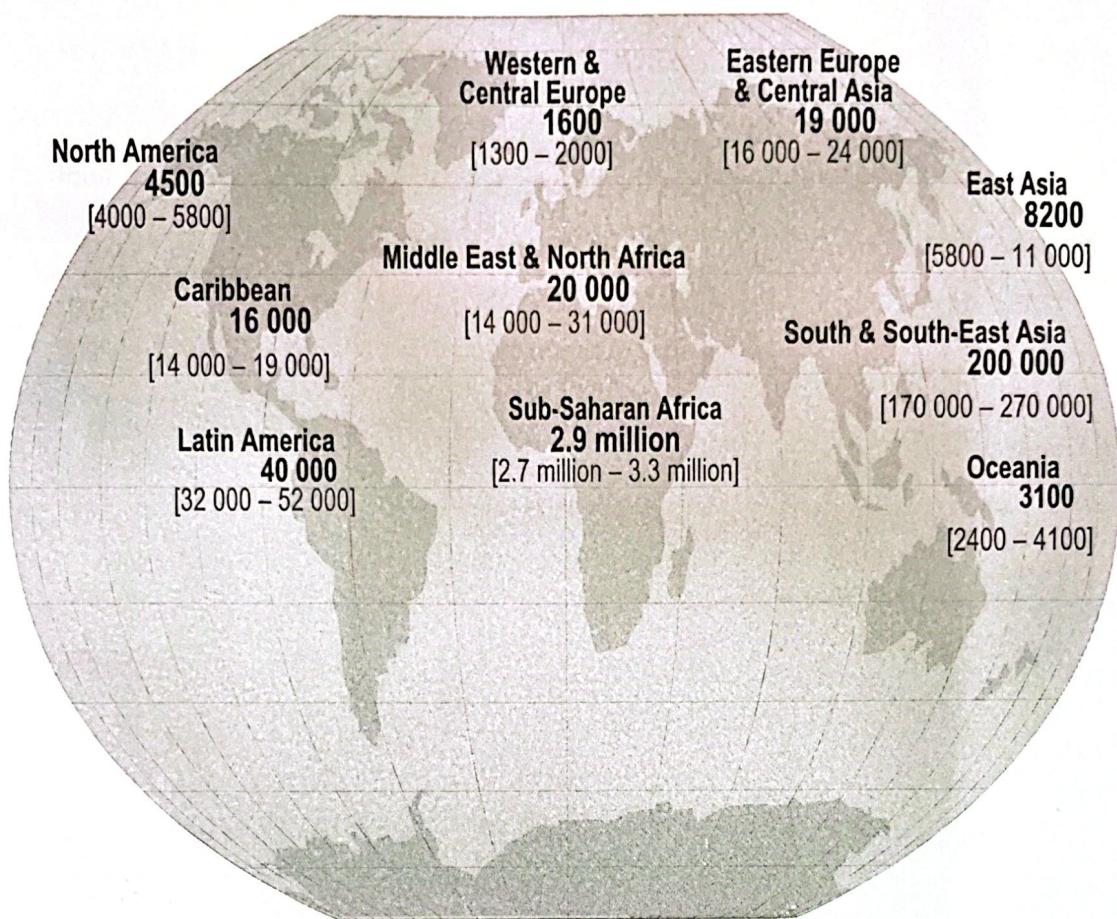


**Figure 3: Estimated adult and child deaths from AIDS 2012:**



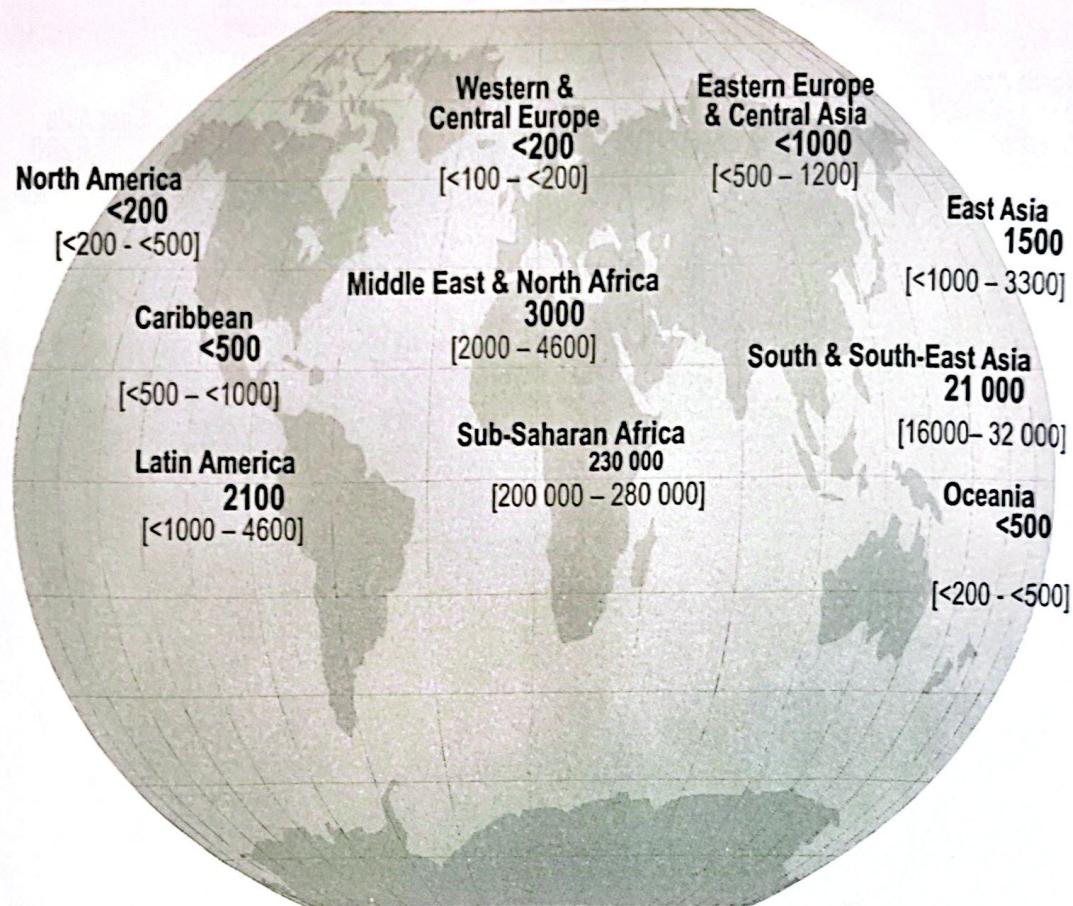
**Total: 1.6 million [1.4 million – 1.9 million]**

Figure 4: Children (<15 years) estimated to be living with HIV 2012:



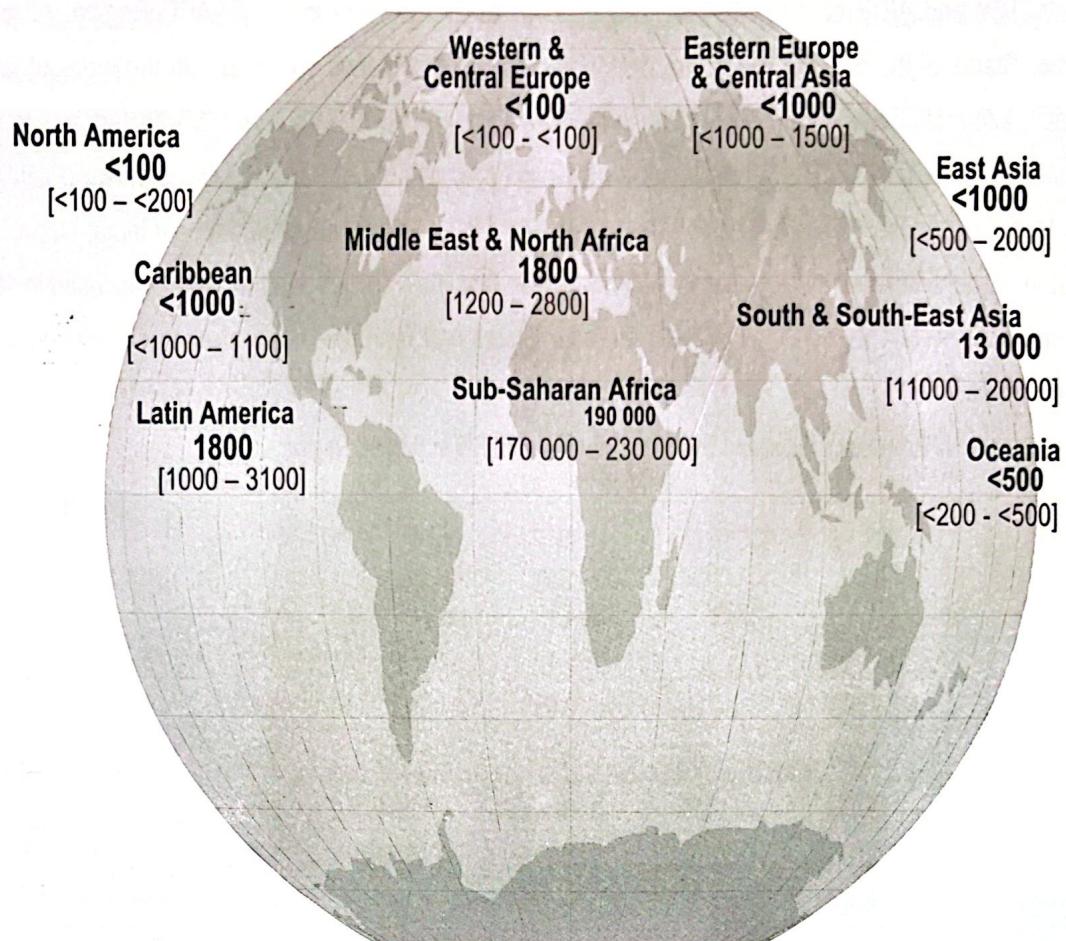
**Total: 3.3 million [3.0 million – 3.7 million]**

Figure 5: Estimated number of children (<15 years) newly infected with HIV 2012:



Total: 260 000 [230 000 – 320 000]

Figure 6: Estimated deaths in children (<15 years) from AIDS 2012:



**Total: 210 000 [190 000 – 250 000]**

Source: Joint WHO and UNAIDS core epidemiology slides, September 2013

### HIV & AIDS SITUATION IN THE SAARC REGION:

The HIV situation epidemic in SAARC region is a collection of diverse epidemics in countries, provinces & districts. HIV and AIDS continue to be a major public health problem in the SAARC Region. All eight Member States of the SAARC region are designated as low prevalence countries. On the basis of latest available information this region is home for an estimated number of 2.24 million HIV infected people and 1.56 lakh AIDS deaths in 2012. Table 02 shows the estimated number of People Living with HIV (PLHIV) in eight Member States of the SAARC Region in the year 2012. Three countries, namely India, Nepal and Pakistan account for majority of the regional burden. The first HIV infected persons were diagnosed in 1986 in India and Pakistan. By 1993, all SAARC Member States had reported the existence of HIV infection in their countries.

Table – 2: Adult HIV Prevalence Rates and Estimated Number of PLHIV in SAARC Region, 2012

Country	Estimated No. of PLHIV 2012 (all)	Estimated New HIV infections 15-49) HIV	Estimated Adult (ages 15-49) HIV	Estimated AIDS Deaths	Estimated Number of AIDS Deaths Detected	First HIV Positive Case (all ages)	in (Year)
Afghanistan	4592*	<1000	0.03*	295*	295*	1989	
Bangladesh	8000	<1000	< 0.1	< 500	< 500	1989	
Bhutan	1,100	<200	0.2	< 100	< 100	1993	
India**	2.09 million	1.16 lakh	0.27	1.48 lakh	1.48 lakh	1986	
Maldives	< 100	<100	< 0.1	< 100	< 100	1991	
Nepal	49000	1200	0.3	4100	4100	1988	
Pakistan	87000	19000	< 0.1	3500	3500	1986	
Sri-Lanka*	4,550*	<500	< 0.1	271*	271*	1987	
<b>Regional</b>	<b>2.24 million</b>				<b>1.56 lakh</b>		

Source: GLOBAL REPORT, UNAIDS report on the global AIDS epidemic 2013 \* Country Report, 2013 \*\* Annual Report 2012-13, NACO, India

The overall adult HIV prevalence in SAARC region remains below 1%. However, there are important variations existing between countries. Bangladesh, India, Nepal and Pakistan have reported concentrated epidemics among the key affected populations. Of the estimated number of 2.24 million PLHIV in SAARC region, 2.09 million were living in India in 2012.

**Table - 3: Estimated number of adults and children receiving and needing antiretroviral therapy, and coverage, 2012**

Country	Estimated number of adults needing ART	Reported 0-14 years	Estimated adults ART coverage (%)	Reported 12 months after receiving	Adults and children number of with HIV known to be on treatment	number of adults on ART initiation of ART (%)
Afghanistan	1200	150	9	8	100	
Bangladesh	2900	783	27	48	91	
Bhutan	< 500	33	11	5	....	
India	1 000 000	570 620	51	34 367	....	
Maldives	< 100	5	27	0	86	
Nepal	22 000	7168	33	551	....	
Pakistan	21 000	2996	14	139	....	
Sri Lanka	1100	363	35	24	76	
Regional	1 048 200	582 118	55	35 142		

Source: GLOBAL REPORT, UNAIDS report on the global AIDS epidemic 2013

On the basis of latest available information (Global Report, UNAIDS 2013), this region has 1.04 million estimated numbers of adults needing ART while in the region 0.58 million reported number of adults and 35142 numbers of children on ART in 2012. Table 03 shows three countries, namely India, Nepal and Pakistan account for majority of the regional burden.

**Table - 4: Number of HIV infected Female Adults, 2001-2012**

Country	2001	2012
Afghanistan	<1000	1400
Bangladesh	<1000	2700
Bhutan	<100	<500
India*	800 000	750 000
Maldives	<100	<100
Nepal	14000	14000
Pakistan	2400	24000
Srilanka	<500	<1000
Regional	816 400	792 100

Source: GLOBAL REPORT, UNAIDS report on the global AIDS epidemic 2013

Table 4 shows number of HIV infected female adults is in the slightly decreasing order in the year 2012 in comparison to 2001

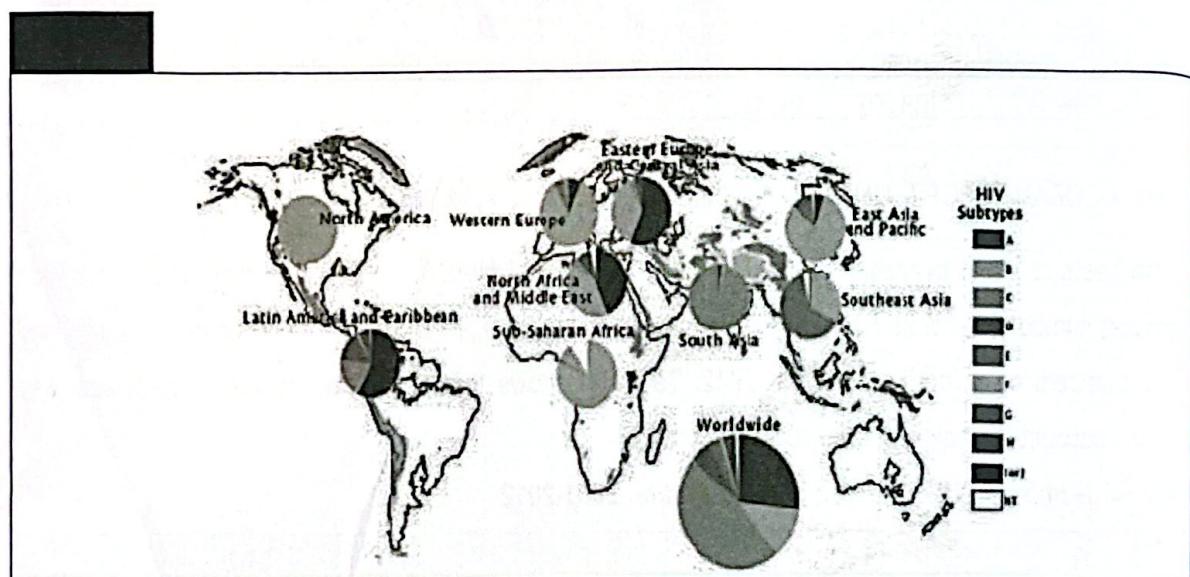
## Types and Subtypes of HIV

Two types of HIV are currently recognized: HIV-1 and HIV-2. Worldwide, the predominant virus is HIV-1. Transmission of both types of virus is through sexual contact, blood, and from mother to child, and they appear to cause clinically indistinguishable AIDS. However, HIV-2 is transmitted less easily, and the period between initial infection and illness is longer in the case of HIV-2.

### a. HIV-1

- Because of its high rate of replication, HIV-1 mutates rapidly into subtypes.
- We currently know of at least 10 genetically distinct subtypes of HIV-1 within the major group (group M), containing subtypes A to J.
- In addition, group O (Outliers) contains a distinct group of very heterogeneous viruses.
- These subtypes are unevenly distributed throughout the world.

Figure- 7: Estimated Prevalence of HIV-1 env Subtypes by Region (2000)



### What are the major differences among these subtypes?

The major difference is their genetic composition; biological differences observed in vitro and/or in vivo may reflect this. It may be that certain subtypes are associated predominantly with specific modes of transmission, for example: subtype B with homosexual contact and injecting drug use (essentially via blood) and subtypes E and C with heterosexual transmission (via a mucosal route).

- Many countries report a variety of subtypes.
- A person can be co-infected with different subtypes.

### **b. HIV-2**

- This is another human retrovirus, causing a similar immune deficiency through depletion of CD4 cells.
- Confined primarily to West Africa with some cases in southern and western India
- The first clinical case of HIV-2 was confirmed in Far Western Nepal in 2009.
- Compared to HIV-1, is less transmissible. It is also associated with a lower viral burden and a slower rate of both cell decline and clinical progression.
- Does not respond well to certain types of antiretroviral medications (NNRTI). It is important to consider the HIV type when prescribing antiretroviral therapy (ART).

### **c. Subtype of HIV-1**

- Subtype C may represent most infections, but data is currently lacking.
- Subtype C accounts for more than half of all new HIV infections worldwide.
- Subtype E is the primary subtype in Thailand and Southeast Asia.

## **HIV Transmission**

Geographic and socioeconomic factors influence the predominant mode of transmission. In some countries more than one of the modes of HIV transmission listed below is responsible for the HIV/AIDS epidemic.

### **a. Modes of transmission**

- Sexual contact: male-to-female, female-to-male, male-to-male, and female-to-female
- Parenteral: blood transfusion, injecting drug use through needle-sharing, needle stick injuries
- Perinatal: in utero, during labor and delivery, postpartum through breastfeeding

Worldwide, sexual transmission is the predominant mode. HIV cannot be transmitted by casual contact (for example, hugging or shaking hands), surface contact (for example, toilet seats) or from insect bites (for example, from mosquitoes).

### **b. Infectiousness of HIV related to the different mode of transmission**

#### **1. Chance per sexual encounter with vaginal intercourse:**

The heterosexual infectivity of HIV-1 is estimated to be approximately 0.001, or one transmission per 1000 contacts.

#### **2. Chance per sexual encounter with anal intercourse:** A metanalysis found a 1.4% chance of HIV transmission per act of receptive anal intercourse and 40.4% chance per partner. With insertive intercourse the risk per partner is slightly less at 39.9%.

- 3. Risk of HIV transmission with blood transfusion:** Ninety percent of recipients transfused with HIV antibody-positive blood are found to be HIV-infected at follow-up.
- 4. Risk from injecting drug use:** The estimated risk of transmission associated with sharing needles for injecting drug use is approximately 0.67% per needle-sharing contact.
- 5. Risk of a mother passing HIV to her baby:** The risk of transmission during pregnancy, delivery and breastfeeding without any interventions is 20-45%.
- 6. Risk from oral sex:** Oral intercourse is considered to pose a lower risk for HIV transmission, although good risk estimates are lacking. There are case reports of HIV infection in persons in whom the only reported risk factor was oral intercourse.
- 7. Pre-chewing food for children.** There have been a few documented reports of HIV transmission to children from HIV infected care takers who pre-masticate food for them. This may be common practice in parts of Nepal and should be included in counseling for parents of small children with HIV-infected family members.
- 8. Female to female transmission:** Among women having sex with women cases have been reported of transmission via oral-vaginal, oral-anal, sex toy-related and digital intercourse.
- 9. Human bites:** Bite injuries represent another potential means of transmitting HIV. However, HIV transmission by this route has been reported rarely.

#### **Other topics related to infectiousness:**

- 1. HIV survival outside of the body:** Once HIV leaves the body it dies within minutes. HIV does not survive well outside the body, making the possibility of environmental transmission remote.
- 2. HIV super-infection:** Super-infection occurs when someone with HIV later becomes infected with a different strain. Super-infection may lead to acquisition of a drug resistant strain and is also associated with accelerated disease progression.

#### **Biological factors affecting transmission**

##### *Factors that increase risk of transmission*

- Infectiousness of host
- High viral load during initial and more advanced stages of infection;
- Presence in semen and genital secretions;
- Exposure to blood, for example, genital ulcers, trauma during sexual contact, menstruation during sexual contact;
- Breastfeeding by HIV-positive mother;

- Susceptibility of recipient

- Inflammation or disruption of genital or rectal mucosa
- Lack of circumcision in heterosexual men
- Sex during menstruation
- Presence of an ulcerative or non-ulcerative sexually transmitted infection (STI)

### Viral properties

- Type of HIV virus (HIV-1 vs HIV-2): HIV-2 infection in children is rare. Compared with HIV-1, HIV-2 seems to be less transmissible from an infected mother to her child.
- Clade/Subtype of HIV-1: HIV 1 subtype (ie. A, B, C, D, E...) may influence the transmission of HIV.

### Factors that decrease risk

- Correct and consistent use of latex condoms
- ART may decrease the risk of HIV transmission.
- Antiretroviral medications have been shown to dramatically reduce vertical transmission from a mother to her fetus.
- Male circumcision: Randomized controlled trials from Africa show up to 60% reduction in HIV incidence amongst men who are circumcised.

### Socioeconomic factors facilitating transmission

- *Social mobility*

Global economy: more people traveling and working away from home

HIV follows the routes of trade and commerce

Men have sex with sex workers, contract HIV and return home to their wives, who contract HIV and pass it along to their infants in utero or through breast milk.

- *Stigma and denial*

Denial and silence regarding HIV are the norm. Stigma prevents people from speaking about or acknowledging HIV as a major cause of illness and death thereby preventing HIV-infected people from seeking care and from taking preventive measures.

- *People in conflict*

HIV is spread at times of instability, war, and violent struggles for power.

- *Cultural factors*

Cultural traditions, beliefs and practices affect people's understanding of health and disease and their acceptance of conventional medical treatment.

For example, in many cultures, domestic violence is viewed as a man's right reducing a woman's control over her environment. This means she cannot question her husband's extramarital affairs, cannot negotiate condom use and cannot refuse to have sex.

- *Gender*

Gender roles have a powerful influence on HIV transmission. In many cultures, men are expected to have many sexual relationships. There is social pressure for them to do so which increases their risk of becoming infected.

- *Poverty*

Poor people lack access to the information needed to understand and prevent HIV. Ignorance of the basic facts make millions of people worldwide vulnerable to HIV infection.

- *Drug use and alcohol consumption*

These lower inhibitions and impair judgment, which may result in risky behavior.

## **2. Basic Immunology and Natural History of HIV and AIDS**

### **PURPOSE:**

In this session, participants will learn about the basics of the normal immune system, how HIV damages and destroys the immune system, and how the disease progresses.

### **OBJECTIVES:**

By the end of this session, participants will be able to:

1. Explain the basics of the normal immune system.
2. Explain the HIV lifecycle and its effect on the immune system.
3. Understand the acute infection/seroconversion stage of HIV.
4. List the stages of disease progression.

### **1. The Normal Immune System**

- a. Protects the body by recognizing antigens on invading bacteria and viruses and reacting to them.
- b. Consists of lymphoid organs and tissues, including the bone marrow, thymus gland, lymph nodes, spleen, tonsils, adenoids, appendix, blood and lymphatic vessels.
- c. All components are vital in the production and development of lymphocytes or white blood cells.
- d. B-cells and T-lymphocytes (T-cells) are produced from stem cells in the bone marrow. B-cells mature in the marrow, but T-cells travel to and mature in the thymus gland.
- e. B-cells recognize specific antigen targets and secrete specific antibodies that coat the antigens by making them more vulnerable to phagocytosis or by triggering the complement system.

f. T-cells regulate the immune system and kill cells that bear specific target antigens. Each T-cell has a surface marker such as CD4, CD8 and CD3 that distinguishes it from other cells.

g. CD4 cells are helper cells that activate B-cells, killer cells (CD8) and macrophages when a specific antigen is present.

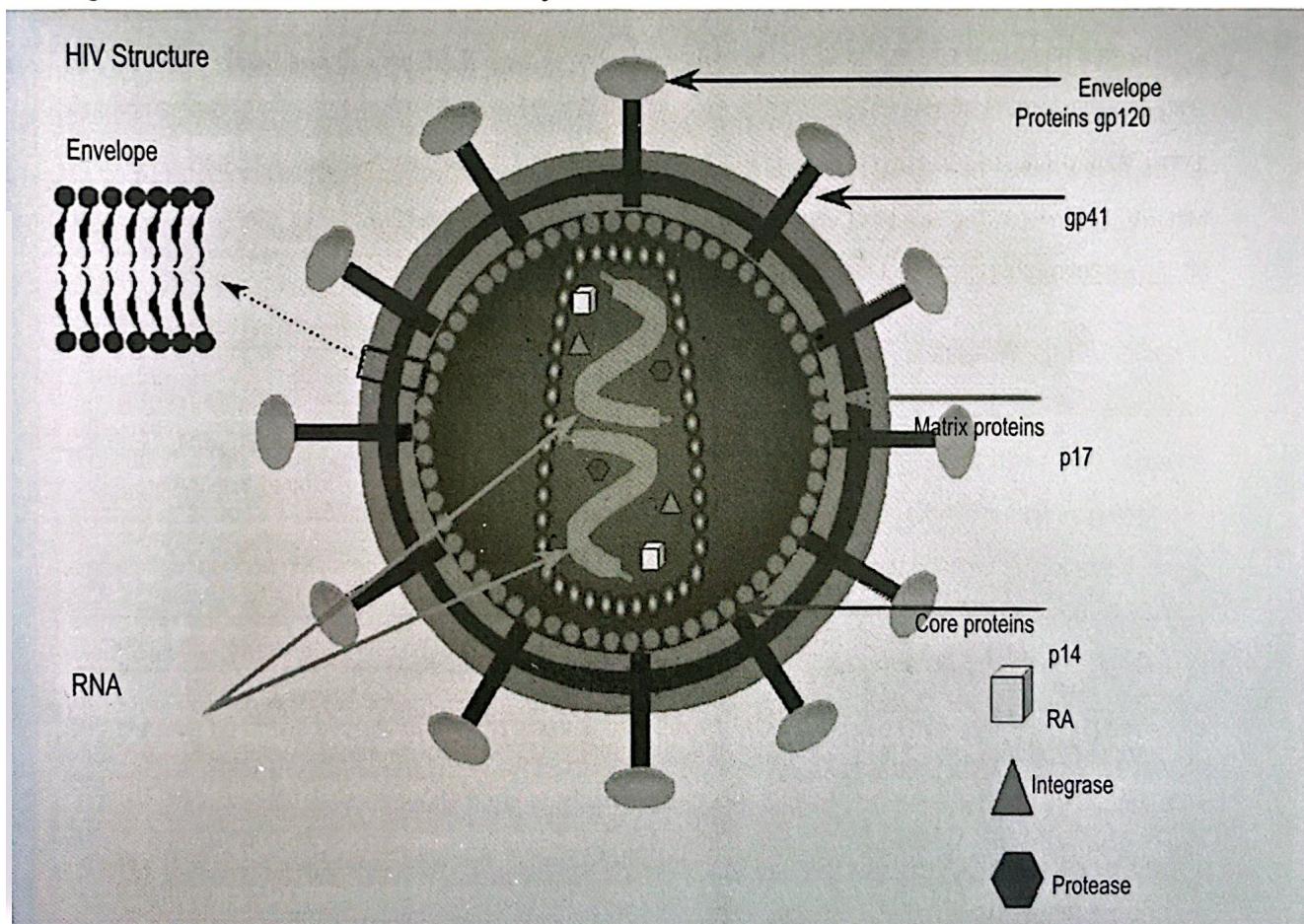
h. Phagocytes include monocytes and macrophages—large white blood cells that engulf and digest cells carrying antigenic particles.

i. The complement system consists of 25 proteins and is capable of inducing an inflammatory response when it functions with antibodies to facilitate phagocytosis or to weaken the bacterial cell membrane.

j. When the immune system is weakened or destroyed by a virus such as HIV, the body is vulnerable to opportunistic infections.

**2. The Human Immunodeficiency Virus (Source: Klatt EC. Human Immunodeficiency Virus. Pathology of AIDS. University of Utah; 1999. And Montero J, Nadler JP. Pathophysiology of HIV Infection. In HIV/AIDS Primary Care Guide. Crown House Publishing Limited; 2005:1-14.)**

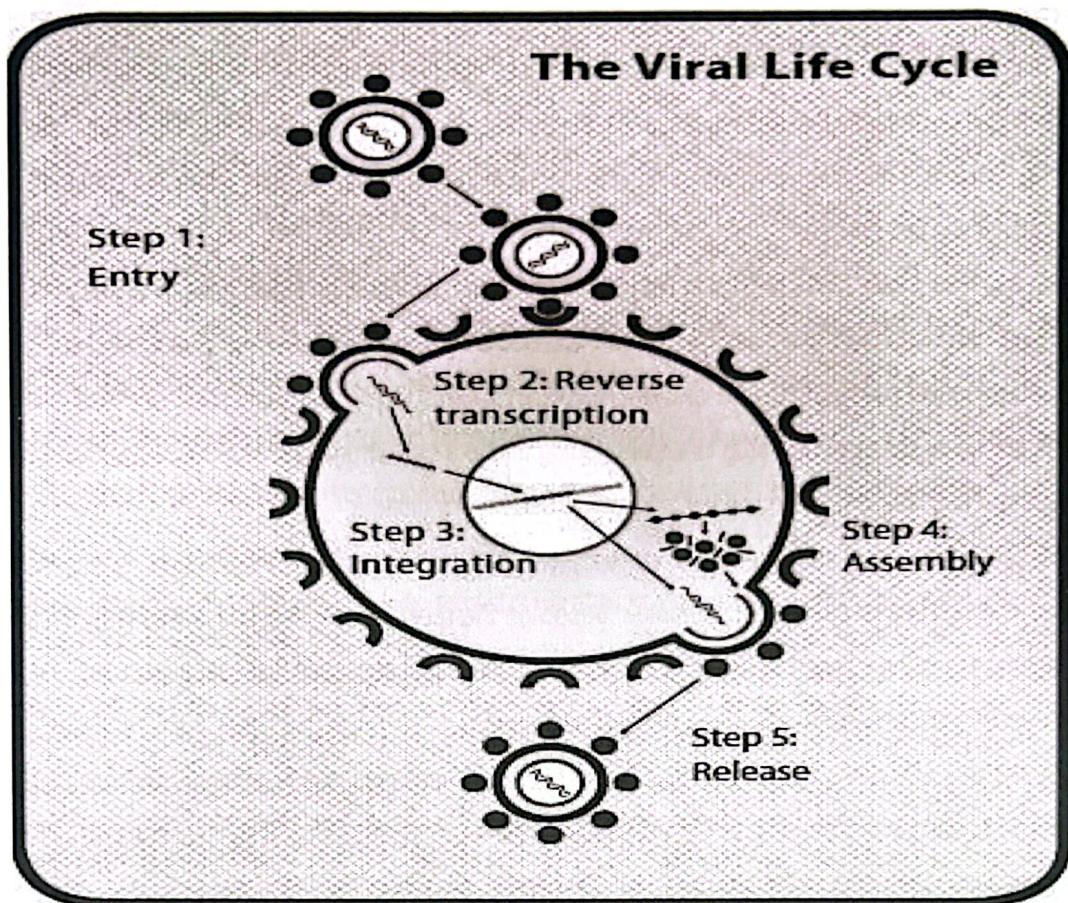
**Figure - 8: The Human Immunodeficiency Virus**



- a. It is a retrovirus which uses its ribonucleic acid (RNA) and the host's deoxyribonucleic acid (DNA) to make viral DNA. It has a long incubation period (clinical latency).
- b. It consists of a cylindrical center surrounded by a sphere-shaped lipid envelope. The center consists of two single strands of RNA.
- c. It causes severe damage to and eventually destroys the immune system by utilizing the DNA of CD4 lymphocytes to replicate itself. In the process, the virus destroys the CD4 lymphocyte.
- d. The HIV lifecycle
  - Host cells infected with HIV have a very short lifespan.
  - Therefore, HIV continuously uses new host cells to replicate itself.
  - Up to 10 million individual viruses are produced daily.
  - In the first 24 hours after exposure, the virus attacks or is captured by dendritic cells (a type of phagocyte) in the mucous membranes and skin.
  - Within five days of exposure, infected cells make their way to the lymph nodes and eventually to the peripheral blood, where viral replication becomes very rapid.
  - The five phases of HIV life cycle are: binding and entry, reverse transcription, replication, budding, and maturation.

**3. The Five Phases of the HIV Lifecycle** (Source: A Practical Guide to HIV Drug Treatment for People Living with HIV, Appendix A: The Viral Life Cycle and Antiretroviral Drugs, Available online at:  
<http://www.catie.ca/en/practical-guides/hiv-drug-treatment/appendices/a>)

Figure- 9: The viral life cycle



HIV cannot multiply by itself. Instead, it must get inside a cell to make copies of itself. When HIV infects a cell, it takes over the "machinery" of a cell and uses it to make new copies of itself (this is called viral replication). The newly created viruses leave the infected cell and go on to infect other cells. Experts estimate that up to 10 billion copies of HIV may be made every day in a person who is not on treatment.

Understanding how HIV replicates (the viral life cycle) allows us to understand how antiretroviral drugs work. The following illustrations show the distinct steps of the viral life cycle and the class of drugs that interfere with each step. (Appendix B lists all of the currently available drugs, by class.)

HIV is made up of two strands of genetic material called RNA. Along with the RNA, HIV contains three key enzymes:

- reverse transcriptase
- integrase
- protease

These enzymes are proteins that help the virus make copies of itself.

### **Step 1: Entry—HIV enters a cell:**

The outer surface of the virus is covered with proteins. Human cells also have proteins on their outer surface, called receptors. These receptors come in millions of different shapes. The HIV virus has proteins on its surface that fit perfectly into the receptors on the surface of certain cells, including CD4 cells, like a key in a lock. Once HIV attaches to these receptors, the virus can fuse with the cell. Then the contents of the virus are inserted into the cell.

Before HIV can infect a cell, it has to bind to not just one, but two receptors on the surface of the CD4 cell. One of these is called the CD4 receptor. The second is called a co-receptor. There are several different co-receptors, including two called CCR5 and CXCR4.

Many drugs are being developed to stop HIV from getting inside a cell. Drugs that stop HIV from joining to the CD4 receptor and fusing with the cell surface are called fusion inhibitors.

Drugs that block HIV from using a cell's co-receptors are called receptor blockers or co-receptor antagonists. They can have more specific names, based on the receptor they block. For example, CCR5 inhibitors interfere with the interaction between HIV and the CCR5 co-receptor on CD4 cells.

### **Step 2: Reverse transcription—HIV takes control of the cell:**

Once inside the cell, HIV takes control of the cell. One of the HIV enzymes, the reverse transcriptase (RT) enzyme, converts the genetic material of the virus (called RNA) into another kind of genetic material called DNA. Now the genetic material of the virus matches the genetic material of the "host" cell.

A class of drugs called reverse transcriptase inhibitors slow down or stop the action of the RT enzyme. These drugs come in two subtypes:

- nucleoside analogue reverse transcriptase inhibitors (NRTIs), commonly called nukes
- non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), commonly called non-nukes

Nukes were the first drugs approved for the treatment of HIV. Used in pairs, nukes continue to be a major part (the so-called "backbone") of most drug combinations. To make up an effective drug combination, the two-nuke "backbone" is paired with a drug (or sometimes more than one drug) from another class. This is usually a non-nuke or a protease inhibitor, but may also be an integrase inhibitor.

### **Step 3: Integration—HIV becomes part of the infected cell:**

At this point, a second viral enzyme called integrase inserts the newly converted viral DNA into the cell's own DNA. With the viral DNA integrated into the DNA of the cell, the virus has become part of the cell. This process has been compared to putting a bug in a computer software program. Drugs that stop, or inhibit, HIV from integrating into human cells are called integrase inhibitors.

**Steps 4 and 5: Assembly and release—HIV tricks the infected cell into making copies of itself:** An HIV-infected cell can remain inactive for a long time. If the infected CD4 cell becomes activated, it will start

making and releasing new virus. When a new copy of HIV is produced, it starts out as a single long chain of viral protein. The protease enzyme then works like scissors to snip these protein chains into smaller pieces. These newly cut pieces are then assembled into new virus particles, which "bud" from the host cell and go on to infect other cells.

Protease inhibitors (PIs) are drugs that interfere with the action of HIV's protease enzyme. They prevent protease from cutting the long chains of new viral protein. When PIs are used, new viruses can still be formed, but they are defective and cannot infect new cells.

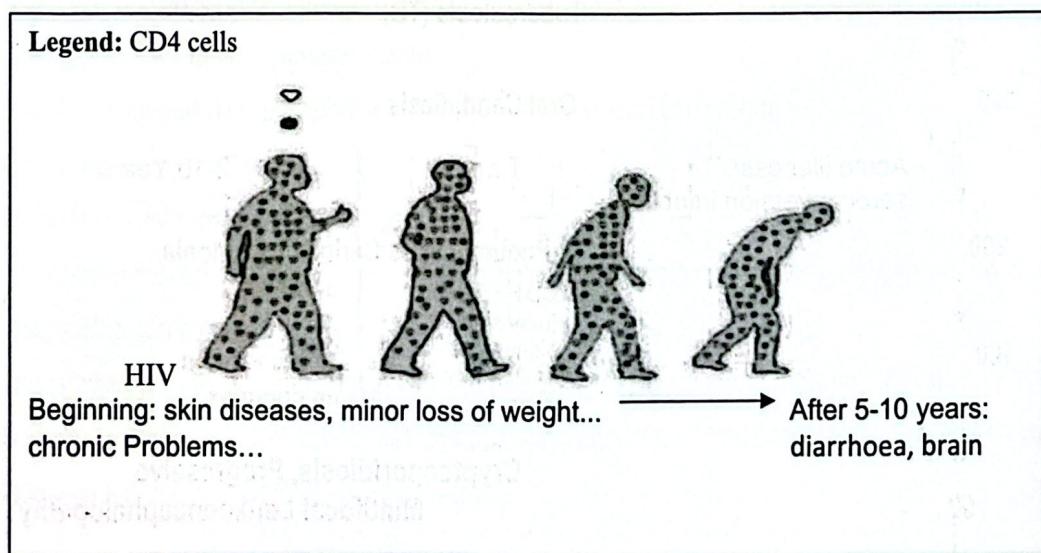
Researchers are working to develop new and different classes of drugs that interfere with the final steps of the viral life cycle, including the final assembly of the virus particles and budding from the cell.

#### 4. Patient Education - How to explain immunology and HIV to patients:

- Every healthy person has a strong body defense which defends the body against diseases. This defense system is called the immune system. White blood cells play an important role in defending the body against all kinds of different diseases.
- When a person gets infected with HIV, the virus will start to attack his/her immune system.
- During the first years, the immune system, although somewhat weakened by HIV, still functions well. The infected person may have no symptoms, or only minor symptoms, like skin diseases, small weight loss, and repeated sinusitis. Many people do not realize that they are HIV positive at this stage.
- After several years, the person's immune system becomes very weak and s/he is vulnerable to diseases which s/he could normally fight off.
- These diseases are called opportunistic infections because they take advantage of a weakened immune system to cause disease.
- Usually, it takes around 5-10 years after the initial infection before the person becomes very sick or is said to have AIDS, if s/he is not on ART.
- In our immune system, we have cells called CD4 cells which are a type of lymphocyte with a marker on its surface called CD4. HIV attacks mostly these CD4 cells. This is why the number of CD4 cells is a good way of checking how your immune system is working.

#### 4. Patient Education- How to explain CD4 and Disease Progression to patients:

Figure 10: Disease Progression in Patients



- As the CD4 levels decline, the risk of getting opportunistic infections increases.
- People with a good immune system have CD4 counts between 500-1500 cells/mm<sup>3</sup>.
- When the number of CD4 cells has decreased below 450 cells/mm<sup>3</sup> the person will start to get some opportunistic infections.
- When the CD4 count has decreased below 200 cells/mm<sup>3</sup> the person will have very serious opportunistic infections.

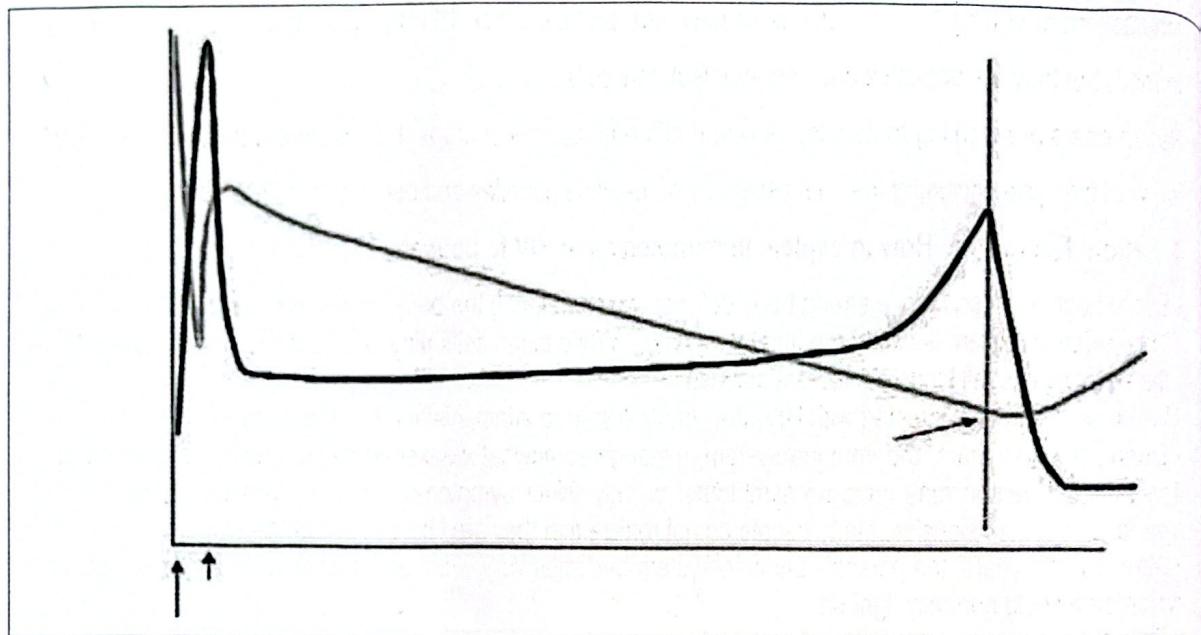


Figure 11: Natural History: The Chronology of HIV-Induced Disease

### 5. Stages of Disease Progression

The typical pattern of change of CD4 cell count and viral load over time, as well as the pattern of their response once ART is initiated.

CD4	OI	Start of Treatment
400	Herpes Zoster	
Viral Load	Tuberculosis (TB)	
300	Oral Candidiasis	
And		
CD4 Count		
200	Acute illness/	Time
	seroconversion infection	2-10 Years
100		CD4 Count
	Pneumocystis Carinii, Pneumonia	
50	CD4 = 350 (may start at higher level if AIDS-defining illness)	Viral Load
	andidiasis	
	cryptococcosis, im complex	
	Cryptosporidiosis, Progressive Multifocal Leukoencephalopathy	

### a. Acute HIV infection (seroconversion illness)

- After exposure, there is a 2-4 week period of intense viral replication before onset of an immune response and clinical illness.
- Acute illness lasts from 1-2 weeks and occurs in 53% to 93% of cases.
- Seroconversion illness manifests as a flu-like syndrome. General symptoms may include:
  - Acute onset of fever with or without night sweats
  - Myalgia is common; may be associated with muscle weakness
  - Lethargy and malaise are frequent and often severe, may persist for several months
  - Depressed mood
  - Pharyngitis/sore throat
  - Lymphadenopathy
  - Arthralgia
  - Anorexia/weight loss
  - Neurological symptoms
  - Gastrointestinal symptoms
  - Dermatological symptoms: Erythematous, non-pruritic, maculopapular rash is common
  - Lymphadenopathy

Clinical manifestations resolve as antibodies to the virus become detectable in the patient's serum.

First 1-2 weeks:

- Profound reduction in CD4 and CD8 lymphocyte counts.
- Followed by a peripheral lymphocytosis.
- Mild thrombocytopenia is common.
- C-reactive protein level and erythrocyte sedimentation rate are frequently elevated.
- Hemoglobin level usually remains stable.
- Elevated serum alkaline phosphatase and transaminase levels are common.

First 2-6 weeks:

- Antibodies to HIV may not yet be detectable.
- HIV antigen can be detected in serum before detecting antibodies; therefore, antigen testing is important in diagnosing seroconversion.
- The window period: Period in which HIV-positive patients may not test positive for anti - HIV antibodies. Generally limited to first 2-6 weeks, but repeat testing after 3 months is recommended. In rare cases, the window period may last as long as 6-12 months.

**b. Early immune depletion (CD4 cell count >500/ $\mu$ L)**

- During this stage, the level of the virus in the blood is very low.
- HIV replication takes place mostly within lymph nodes.
- Generally lasts for five years or more.
- Persistent Generalized Lymphadenopathy (PGL) without other symptoms may be noted.
- Usually symptom-free, but several autoimmune disorders may appear, such as:

Idiopathic thrombocytopenia (ITP)

Guillain-Barré syndrome

- Common conditions found in the general population occur, but may be more frequent.

**c. Intermediate immune depletion (CD4 cell count between 500 and 200/ $\mu$ L)**

- Immune deficiency increases.
- As the CD4 cell count drops, more infections appear.
- Less severe infections appear, particularly of skin and mucosal surfaces:

- Tinea
- Molluscum contagiosum
- Seborrheic dermatitis
- Bacterial folliculitis
- Warts
- Gingivitis

- Other infections begin to manifest:

- Oral candidiasis appears late in this phase.
- Reactivation of Herpes Zoster and Herpes Simplex may occur.
- Infection with Mycobacterium Tuberculosis occurs relatively early in this phase.
- Chronic sinusitis.

**d. Advanced immune depletion (CD4 cell count <200 cells/mm<sup>3</sup>)**

- Case definition of AIDS is having a CD4 cell count of less than 200 cells/mm<sup>3</sup> or AIDS-defining illness (ie. PCP pneumonia, Toxoplasmosis, Wasting Syndrome)

**3. Diagnosis of HIV and HIV-Specific Laboratory Investigations**

**PURPOSE:**

Clinicians and health care providers need to understand how to make a diagnosis of HIV in adults and children. Suspecting HIV based on clinical findings can be difficult and will be covered in the session on clinical presentation.

Participants will learn about the various serologic and laboratory tests available for diagnosing HIV infection, how they work and how they are used. But, the principles of HIV Testing and Counseling (HTC) are mentioned in separate chapter. This session will discuss the algorithm for HIV testing. In addition, other important HIV-related laboratory investigations will be addressed. There is a chance for discussion on some important ethical issues of HIV care related to testing and diagnosis.

**OBJECTIVES:**

By the end of this session, participants will be able to:

1. Describe the various diagnostic tests and how they work in HIV diagnosis.
2. Describe the algorithm for HIV testing.
3. Interpret the results of the tests and make a diagnosis.
4. Understand Early Infant Diagnosis (EID) and the algorithm for testing.
5. Describe baseline laboratory tests and CD4 and Viral Load testing.

**A. Laboratory Testing**

**1. Diagnostic tests**

**a. Rapid Tests**

- There are various tests available that provide results in about 10 minutes.
- Combinations of rapid tests are highly sensitive and specific.
- Useful in situations where immediate results are important to manage decisions.
- Laboratory with minimal set up will be sufficient.
- No separate visit required for results.
- Must use test kit approved by Ministry of Health.

**b. ELISA (enzyme-linked immunosorbent assay) / EIA (enzyme immunoassay)**

- An HIV antibody test detects antibodies formed by the immune system against HIV.
- Tests for a number of antibody proteins in combination.

- Positive samples should be tested by second ELISA test or confirmatory Western Blot.

**c. Western Immunoblot test**

- Used as a confirmatory test.
- Detects antibodies to a number of specific HIV proteins and is considered to be very specific.
- Samples yielding a negative result are reported as negative.
- Detects antibodies directed at specific HIV envelope and core proteins.
- Antibodies to only some viral proteins may yield an indeterminate Western Blot.
- Not commonly used in resource-limited settings.
- Expensive.

**d. DNA PCR (polymerase chain reaction)**

- A qualitative test used to detect intracellular virus.
- Able to detect a very small amount of virus.
- Useful for diagnosing infants prior to 18 months of age, when the maternal antibodies may still be present in child's blood.
- Also useful in cases of indeterminate serology.
- Provides a qualitative result: Positive or Negative.
- Also useful in diagnosis of acute infection, prior to the production of HIV-specific antibodies.
- Expensive test.

**e. P24 antigen test**

- Detects P24 antigen

**2. Testing strategy**

**a. Overview**

- All VCT sites must use test kits endorsed by the MoH.
- The use of two or more rapid tests based on different test principles is the minimum standard HIV test algorithm to be followed at all levels of the health care delivery system in government, private and NGO settings.
- Different "test principles" refers to different tests (brands) detecting antibodies to different antigens on the virus.
- All HIV testing should consist of an initial screening tests and then confirmation with another test, when the first test result is positive.
- Those testing negative by the second test (but positive by the first test) shall be subjected to a third test (a tie breaker). A third different rapid test need to be used.

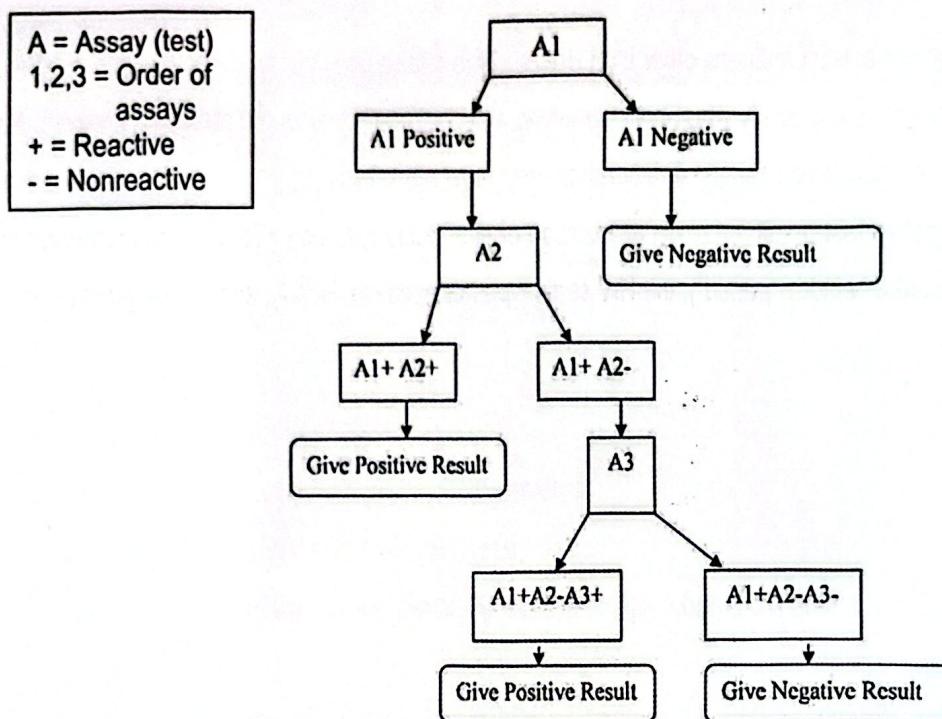
- The first test should be highly sensitive to provide reliable detection of antibodies. The second test should be highly specific to confirm that the specimen truly contains antibodies specific to HIV.

b. False Results

- Tests that can predict antigens other than HIV can give a false positive result (for example, ELISA). This is very rare, especially when both screening and confirmatory tests are reactive. However, the possibility of mislabeled sample or laboratory error must be considered.
- False negative test results may occur because of time delay following infection and production of antibodies (the "window period"), the HIV strain type (for example, HIV-2), and the reagents used.

Strategy (Venous Blood Sample or Finger Prick)

Figure 12: Serial Testing for HIV Diagnosis



Algorithm: All serum/plasma is first tested with one rapid assay, which is highly sensitive (A1).

- Serum that is non-reactive on the first test is considered HIV antibody negative (A1-).
- Any serum found reactive on the first assay is retested with a second highly specific rapid assay based on a different antigen and/or different test principle.
- Serum that is reactive on both tests is considered HIV antibody positive (A1+A2+).
- Any serum that is reactive on the first test but non-reactive on the second test should be retested with a third different rapid test/tiebreaker test or ELISA at a central laboratory.
- If the result is reactive, then it should be considered HIV antibody positive (A1+A2-A3+).
- If the result is non-reactive, then it should be considered HIV antibody negative (A1+A2 - A3 -).

d. The Window Period:

- The body may require some time to produce antibodies against HIV.
- If someone had a risky exposure in the 3 months prior to testing negative, they should return for repeat testing in 3 months.
- This is true for adults and children over 18 months of age.

## Small Group Activity

### Case Study 2:

An HIV positive woman delivers a healthy baby boy. He is tested for HIV using an ELISA test just after birth and is found to be HIV positive.

#### Questions

- Was this the correct test to use?
- When is the optimal time to first test this baby and by what method?
- Is this baby HIV-infected?

## D. HIV Diagnosis in Children

### 1. Children under 18 months of age

- Babies less than 18 months old cannot be diagnosed as HIV positive using antibody based tests alone (ie. Rapid tests, ELISA or Western Blot).
- Mother's antibody may be present in baby's blood until 18 months of age.
- HIV DNA PCR testing is needed to diagnose a baby between 6 weeks to 18 months age as being HIV-infected.
- This then allows babies to start antiretroviral therapy earlier.

### 2. Protocol for Early Infant Diagnosis (Babies < 18 months of age)

- a. HIV-exposed babies from 6 weeks to 18 months should undergo HIV testing.
- b. Babies from 6 weeks to <9 months of age should have HIV DNA PCR done drawn to reveal HIV status.
- c. Babies >9 months, should first have a Rapid test for screening.
  - If Rapid test is negative, they do not need PCR. They are negative.
  - If Rapid test is positive, a PCR should be sent to differentiate the baby's infection from the mother's antibodies.
- d. Breastfeeding status must be considered during HIV testing of infants.
  - The breastfeeding window period is 6 weeks with both PCR and rapid tests.
  - Test should be repeated 6 weeks after stopping breastfeeding.
  - Exclusive breastfeeding should be encouraged until 6 months of age for all HIV-exposed infants with continued breastfeeding until 12 months after introduction of complementary feeds at 6 months.
- e. Dried Blood Spot (DBS) Collection
  - Special PCR DBS paper allows mailing of specimen from remote locations.
  - Collection of sample can be by blood draw or heel stick.

f. Confirmation of single positive DNA PCR sample on child less than 18 months. If possible, confirm all positive DNA PCR with second virologic sample (DNA PCR or RNA PCR). However, do not delay ART initiation while awaiting results.

g. 18 month confirmation: All babies should be retested by standard adult protocol at 18 months for confirmation of any results before 18 months (regardless of testing positive or negative).

Note: Sick babies under 18 months of age without known DNA PCR result should start ART if they meet presumptive Clinical Diagnosis of severe HIV disease criteria. This may be in areas without access to DNA PCR or while awaiting testing results. See the Pediatric ART chapter for details.

#### **E. Baseline laboratory tests**

After diagnosis is confirmed, a baseline laboratory evaluation is needed to establish the stage of the disease and risk of HIV-related diseases, as indicated by the CD4 count.

##### **1. Baseline laboratory evaluation to establish stage of disease and risk of HIV-related diseases:**

- CD4 cell count

Other recommended baseline tests include:

- Complete Blood Count (CBC)
- Serum Chemistry Panel (ALT/SGPT, Creatinine, Blood Urea)
- Syphilis serology
- Chest X-ray
- Pap smear
- Serology for Hepatitis B, Serology for Hepatitis C
- Sputum for AFB
- Urine for pregnancy test, in females of childbearing age
- Urinalysis to assess for proteinuria

##### **2. CD4 lymphocyte count**

###### **a. Immunological assessment (CD4 count)**

- The pathogenesis of HIV infection is largely due to the decrease in the number of T cells (a specific type of lymphocyte) that bear the CD4 receptor (CD4+).
- The immune status of a child or adult living with HIV can be assessed by measuring the absolute number (cells/mm<sup>3</sup>) or percentage of CD4+ cells, and this is regarded as the standard way to assess and characterize the severity of HIV-related immunodeficiency.
- Progressive depletion of CD4+ cells is associated with progression of HIV disease and an increased likelihood of opportunistic infections and other clinical events associated with HIV, including wasting and death.

- Absolute CD4 counts (and less so CD4%) fluctuate within an individual and depend on intercurrent illness, physiological changes or test variability. Measuring the trend over two or three repeated measurements is more informative than a single value.

**b. CD4 lymphocyte count in adults and adolescents**

- Normal range: 500-1500 cells/mm<sup>3</sup>
- In general, the CD4 count progressively decreases as HIV disease advances.
- CD4 depletion is the most consistent and notable laboratory abnormality observed in HIV disease.
- CD4 of <200 cells/mm<sup>3</sup> signifies severe immunodeficiency in adults and children over 5 years of age.
- This is the most useful test for assessing immune function and is of vital importance in patient assessment.
- Recommendations for ART and prophylaxis against OIs are based on the CD4 count and degree of immunosuppression.
- The CD4 count usually increases in response to effective ART, although this may take many months.

**c. CD4 in children**

- The absolute CD4 cell count and the CD4% in healthy infants who are not infected with HIV are considerably higher than those observed in uninfected adults and slowly decline to adult values by the age of about six years. Age must therefore be taken into account when considering CD4 counts in children.
- For children younger than five years of age, the absolute CD4 count tends to vary more than the CD4%. Currently, therefore, the measurement of the CD4% is thought to be more valuable in younger children.
- However, if limited access to CD4%, an absolute count is still useful to help care for a child younger than 5 years.

**3. Viral Load**

- Measures the number of virus particles per ml of blood by quantifying HIV RNA.
- In resource-constrained settings, viral load should not be obtained in patients not yet taking ART. It should be reserved for those on ART only.
- Initiation decisions should be based on clinical staging and CD4 count.
- 50-1,000,000 HIV copies per ml can be detected, depending on which assay is used.
- Current assay detects down to 72 copies of HIV. Therefore a report of <72 copies/ml is UNDETECTABLE and signifies that ART is working.
- Viral load should only be obtained on patients taking ART and is not required at baseline.

- All people living with HIV (PLHIV) suspected of failing ART by clinical or immunologic criteria should have viral loads checked.
- Also, viral load testing is recommended every 6 months for those on ART starting 6 months after treatment initiation, if resources allow.
- In addition, viral load should be checked in pregnant women on ART/ARVs at 36 weeks of gestation to determine need for elective caesarian section, in babies starting nevirapine (NVP) containing ART <12 months of age after exposure to prevention of mother to child transmission (PMTCT) NVP (or EFV), and in some women starting ART after PMTCT NVP or EFV exposure (see PMTCT section).
- Persistent viral load of 5,000 usually requires a change to second-line ART.
- Expensive test

#### **4. Resistance Testing**

- There are two types of resistance testing: genotyping and phenotyping.
- The most common type is genotype testing, which is the primary type performed in clinical care.
- Genotyping involves elucidating the genomic sequence of the main circulating virus. Results will predict which ARV drugs are likely to work well for the patient (sensitive) and which are unlikely to be useful (resistant).
- It is a very expensive test.
- It should only be considered in the case of second-line failure when there are no clear choices of ARV options. The hope is that some ARVs can be “recycled” if the patient’s virus is still sensitive to them.
- The viral load must be at least 1,000 copies/mL in order to run the test.
- Patients should ideally be taking their latest ART regimen at the time of blood draw for resistance testing. After one month of stopping ARVs, resistance mutations may fade, be archived and not show on genotype testing, although they are still present in the patient.

#### **5. Clinical Presentation and WHO staging**

##### **PURPOSE:**

There are several different ways to define HIV infection and AIDS. In this session, participants will learn about the clinical presentation and overview of the WHO classification system of HIV. Many signs and symptoms of HIV infection can be general and/or similar to those found in other diseases. Participants will therefore also learn about diseases with a similar presentation to HIV and about the differential diagnosis of HIV infection.

##### **OBJECTIVES:**

By the end of this session, the participants will be able to:

1. List the presentation of acute/primary HIV infection.
2. List to the differential diagnosis for acute/primary HIV infection.
3. Classify stage of HIV infection based on the WHO staging systems.

#### **A. Patient Clinical Presentation**

##### **Introduction:**

A good clinical examination and thorough interview of the patient is needed to diagnose and stage HIV disease.

Common findings to look for on physical examination include:

- Oral thrush
- Macular rash on palate as a sign of Kaposi sarcoma
- Herpes zoster scarring
- Florid nature of skin manifestations, a hallmark of HIV
- Condition of the pectoralis, temporalis, biceps, gluteus and shin cover muscles as a clue to wasting
- Lymphadenopathy, usually not  $>2.5$  cm

#### **B. Acute - Primary HIV Infection and Seroconversion**

##### **Primary HIV Infection and Seroconversion**

###### **a. Clinical features**

- After exposure, there is a 2-4 week period of intense viral replication before onset of an immune response and clinical illness.
- Acute HIV usually presents as an acute febrile illness 2-4 weeks after infection which lasts from 1-2 weeks and occurs in 53% to 93% of cases.
- Clinical manifestations resolve as antibodies to virus become detectable in patient serum.
- Patients then enter a stage of asymptomatic infection lasting months to years.

###### **b. Seroconversion illness**

- Manifests as a flu-like syndrome. General symptoms may include:
  - Acute onset of fever with or without night sweats
  - Myalgia is common, may be associated with muscle weakness
  - Lethargy and malaise are frequent and often severe, may persist for several months
  - Depressed mood
  - Pharyngitis/sore throat
  - Maculopapular rash
  - Orogenital ulcers
  - Lymphadenopathy

- Arthralgia
- Anorexia/weight loss
- Neurological symptoms
  - Headache
  - Photophobia
  - Retro-orbital pain
  - Early infection of central nervous system frequently results in aseptic meningoencephalitis with symptoms. HIV is readily isolated from the cerebrospinal fluid during primary infection
- Other more unusual features include:
  - Myelopathy
  - Peripheral neuropathy
  - Brachial neuritis
  - Facial palsy
  - Guillain-Barré syndrome
  - Meningoencephalitis
- Gastrointestinal symptoms
  - Mucocutaneous ulceration is a distinctive feature
  - Ulcers are generally small, round or oval. Surrounding mucosa looks normal.
  - Pharyngeal edema is common.
  - Oral/oropharyngeal candidiasis
  - Nausea/vomiting
  - Diarrhea
- Dermatological symptoms
  - Erythematous, non-pruritic, maculopapular rash is common.
  - Roseola-like rash
  - Diffuse urticarias
  - Desquamation of palms and soles
  - Alopecia
- Lymphadenopathy
- Laboratory findings

First 1-2 weeks:

- Lymphopenia with profound reduction in CD4 and CD8 lymphocyte counts.
- Followed by a peripheral lymphocytosis.

- Mild thrombocytopenia is common.
- C-reactive protein level and erythrocyte sedimentation rate are frequently elevated.
- Hemoglobin level usually remains stable.
- Elevated serum alkaline phosphatase and transaminase levels are common.

First 2-6 weeks:

- Antibodies to HIV may not yet be detectable.
- HIV antigen can be detected in serum before detecting antibodies; therefore, antigen testing is important in diagnosing seroconversion.
- The window period: Period in which HIV-positive patients may not test positive for anti -HIV antibodies. Generally limited to first 2-6 weeks, but repeat testing after 3 months is recommended. In rare cases, the window period may last as long as 6-12 months.

**Note:** In high prevalence, high incidence settings such as STI or sex worker clinics, as many as 5% of those testing HIV antibody negative will actually be in the window phase and are really infected with HIV. People in these settings who test HIV negative should be counseled strongly to return in three months for repeat testing.

#### **Differential diagnosis of acute/primary HIV infection**

- The more general signs and symptoms of acute HIV are common to many infections.
- Patients may have acquired both HIV and other sexually transmitted or blood-borne diseases at the same time.
- Be sure to consider HIV testing when testing for other infections that have a similar presentation.
- The following diseases have a similar presentation to acute/primary HIV infection, and you should consider them when making a differential diagnosis:
  - a. Epstein-Barr virus mononucleosis
  - b. Cytomegalovirus (CMV) mononucleosis
  - c. Toxoplasmosis
  - d. Rubella
  - e. Syphilis
  - f. Viral hepatitis
  - g. Primary herpes simplex virus (HSV) infection
  - h. Disseminated gonococcal infection
  - i. Other viral infections

- Management

- Clinical management is primarily symptomatic.
- The goal at this stage is to give appropriate counseling and education to prevent further spread.

- Issues to consider:

- The physical distress of the illness
- Tentative nature of the diagnosis before serodiagnosis is made
- Patient's psychological state
- Implications for the patient's lifestyle
- Contact tracing should be attempted to identify the source. Contact person may be unaware of their infection; may also be seroconverting; may be unaware of safer sex or safer injecting practices.

Note: In high prevalence, high incidence settings such as STI or sex worker clinics, as many as 5% of those testing HIV antibody negative will actually be in the window phase and are really infected with HIV. People in these settings who test HIV negative should be counseled strongly to return in three months for repeat testing.

### **C. Clinical presentation of Chronic HIV**

- a. Chronic HIV is usually asymptomatic for many years. The only indication of infection is a positive HIV laboratory test.
- b. HIV progresses clinically as immunodeficiency develops.
- c. Some PLHIV remain clinically well until very advanced immunosuppression has developed, while others become ill, while CD4 is still relatively high.
- d. The discussion on WHO Staging will review most common presenting illnesses of PLHIV.

### **D. Follow-up visits after testing HIV positive**

- a. After being informed about their test results, patients may need close follow-up (weekly or monthly).
- b. An accessible system of referrals is important
- c. Once the relationship has been established, and the patient understands his or her situation and is in stable condition, you may extend the interval.
- d. Clinical Management of HIV SOPs recommend that adults return:
  - Every 1 month for those eligible, but not starting ART
  - Every 1 month for those requiring cotrimoxazole prophylaxis
  - Every 3 months for those not yet medically eligible for ART
- e. The subsequent visits should include:
  - Ongoing education about HIV/AIDS and positive living

- Positive prevention methods
- Questions about pregnancy or unmet family planning needs at each visit
- Ongoing psychosocial counseling or referrals
- Those medically eligible for ART, but not yet initiated require intensive patient treatment literacy education and recruitment of family member or other treatment supporter
- Diagnosis, treatment and prevention of opportunistic infections
- WHO Clinical staging at every visit
- CD4 counts every 6 months
- TB Screening using questionnaire at every visit.

#### **E. WHO Staging (Clinical and Immunological)**

**Overview of staging in HIV infection. (Ref: WHO Staging guidelines 2007)**

- a. WHO clinical staging is used once HIV infection has been confirmed by laboratory testing.
- b. For babies less than 18 months with no PCR results, presumptive clinical diagnosis of severe HIV disease can be made.
- c. The clinical stage is useful for assessment at baseline (first diagnosis of HIV infection) or entry into HIV care and in the follow-up of patients in care and treatment programmes.
- d. Staging should be used to guide decisions on when to start cotrimoxazole prophylaxis and other HIV-related interventions, including when to start ART.
- e. The clinical stages have been shown to be related to survival, prognosis and progression of clinical disease without ART in adults and children.
- f. Where laboratory monitoring is available, CD4 cell count is essential in determining immunological status.

Details of immunologic staging are covered in the diagnosis and laboratory session.

**Table 5: WHO clinical staging of established HIV infection**

<b>HIV-associated symptoms</b>	<b>WHO clinical stage</b>
Asymptomatic	1
Mild symptoms	2
Advanced symptoms	3
Severe symptoms	4

#### **The WHO Clinical Staging System**

- WHO has also developed a staging system to categorize immunosuppression based on which clinical illnesses the patient has had.
- This staging system helps predict morbidity and mortality.

- Clinical markers fall into four stages of prognostic significance and form the basis of the WHO Clinical Staging System.
- There is a separate Clinical Staging system for pediatric use, with subtle but important differences.

### WHO immunological classification

1. WHO has developed a laboratory staging system to categorize the immunosuppression by CD4 count.
2. The likelihood of disease progression to AIDS or death without ART increases with increasing immunodeficiency (decreasing CD4).
3. Opportunistic infections and other HIV-related conditions are increasingly likely with CD4 counts below 200 cells/mm<sup>3</sup>.
4. Response to ART is affected by the immune stage at which it is started. So people beginning ART with advanced immunodeficiency (CD4 >200–350) appear to have better virological outcomes than those who commence with more severe immunodeficiency.
5. Adults starting ART with CD4 <50 have a much greater risk of death.

### Case Studies:

#### Case Study 1:

A 35 year old truck driver comes to the clinic complaining of persistent diarrhea that started 5 months ago. Stool exam reveals cryptosporidium.

**In what WHO Stage is this patient?**

#### Case Study 2:

A young woman comes to the clinic complaining of unexplained fever and weakness for over a month. From her previous record you see that six months ago she weighed 54kg. She now weighs 46 kg. She has a history of herpes zoster and a positive HIV antibody test.

**Based on symptoms and history what clinical stage is she in?**

**Introduction of the “Continuity patients”** - We will follow these three patients throughout the remainder of the course.

#### Case Study 3:

A 22-year-old woman. She is HIV positive. She thinks she got HIV when she was a teenager after being forced to go to HIV prone areas for work. She has repeated middle ear infections, and lost some weight, but not a lot. She has no other clinical signs.

**What clinical stage is she in now?**

**Answers:** Stage 2 (recurrent otitis media)

#### Continuation of Case Study 3

That woman comes to the consultation with blisters on one side of the chest. It is really painful. It started 2 days ago. In the mean time, her family makes plans to marry. She would like to have children in the future, but not now. She is using oral contraception. She wants some treatment for her very painful blisters.

- All persons with symptomatic HIV (Stage 2, 3, 4)

OR

- Asymptomatic individuals who have a CD4 count of 350 or less starts to have an itchy rash on his arms and legs.

In what clinical stage is he?

**Case Study 5:**

Mr. A person is a businessman. He is 40 years old. He has a nice house and lives in capital city. His wife died 2 years ago. He has 2 young children ages 4 and 6 years, who are in good health. He has a new wife. Now, his weight has dropped from 75 kg to 73 kg, and he starts to have an itchy rash on his arms and legs.

What could you suggest to Mr. A person?

In what clinical stage is Mr. A person?

**WHO Clinical Staging of HIV for Adults and Adolescents**

**Clinical Stage 1**

- Asymptomatic
- Persistent generalized lymphadenopathy

**Clinical Stage 2**

- Unexplained moderate weight loss (<10% of presumed or measured body weight)<sup>a</sup>
- Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections

**Clinical Stage 3**

- Unexplained<sup>b</sup> severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhea for longer than one month
- Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than 1 month)
- Persistent oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10<sup>9</sup> per litre) and/or chronic thrombocytopenia (<50 × 10<sup>9</sup> per litre)

**Clinical Stage 4**

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacterial infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis)
- Recurrent septicaemia (including non-typhoidal Salmonella)
- Lymphoma (cerebral or B-cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy or symptomatic HIV-associated
- Cardiomyopathy

a. Assessment of body weight in a pregnant woman needs to consider the expected weight gain of pregnancy.

b. Unexplained refers to where the condition is not explained by other causes.

c. Some additional specific conditions can also be included in regional classifications (such as penicilliosis in Asia).

## 5. Overview of HIV-Related Disease and Cotrimoxazole Prophylaxis

### PURPOSE:

In this session HIV-related opportunistic infections (OIs) will be generally described. It also briefly describes the indications and protocols for Cotrimoxazole prophylaxis in adults and children.

### OBJECTIVES:

By the end of this session, the participants will be able to:

1. Define the term opportunistic infection.
2. Describe why PLHIV are susceptible to OIs.
3. Understand the most common OIs in SAARC region.
4. Describe the prophylactic use of Cotrimoxazole.
5. Describe the recommendations for Cotrimoxazole preventive therapy.
6. Understand when to prescribe preventive therapy, to whom, and which regimen to use.

### A. Brief Overview of Opportunistic Infections

**Definition of an Opportunistic Infection (OI):** An infection caused by an organism that would not cause disease in a person with a well-functioning immune system. People with HIV are especially susceptible to OIs.

#### This is the result of:

- a. Suppression of the immune system
- b. Psychological stress, which can influence the immune system
- c. Depletion of nutritional status
- Co-infections with pathogens such as TB and malaria increase the HIV viral burden and thus accelerate the disease progression. Therefore, preventing other infections such as STIs, malaria and TB can be of clinical benefit for PLHIV.
- Many PLHIV first learn they have HIV through diagnosis with an OI.
- The natural history of HIV involves a progressive loss of CD4 lymphocytes. As the CD4 level declines, the risk of contracting OIs increases.
- Usually it takes around 10 years after infection before the person becomes very sick (AIDS), if s/he is not taking ART.
- OIs may be bacterial, viral, fungal or protozoal.

#### Most Common OIs in Asia

1. **India:** The spectrum of HIV-related diseases in India includes a wide variety of endemic diseases prevalent within each region
  - Pulmonary tuberculosis is the most commonly reported OI in India

- Large number of reports of mucocutaneous candidal infections. There are reports that 50-100% of PLHIV have oropharyngeal candidiasis
- Parasitic infections like Cryptosporidiosis, Microsporidiosis, Isosporiosis, Cyclosporiasis and Strongyloides have been well documented in Indian patients
- *Penicillium marneffei*, one of the emerging AIDS-defining infections, has been reported only from North Eastern State
- The spectrum of bacterial infection is changing towards conventional pathogens.
- *Pneumocystis jiroveci* pneumonia (PCP) is rarely documented in India. This may be due to a lack of available diagnostic investigations.
- Eastern India: 88% of immunocompromised HIV-positive patients had oral candidiasis, 57% tuberculosis, 47% vibrio cholera, 45% cytomegalovirus, 43% cryptosporidiosis and 42% *E. coli* infections.
- Mangalore, Karnataka: Tuberculosis was the most common infection followed by candidiasis, cryptosporidiosis and cryptococcal meningitis.
- Northern India: In this retrospective study of 421 subjects, the predominant OI was tuberculosis (47%, 189 cells/ $\mu$ l), followed by parasitic diarrhea (43.5%, 227 cells/ $\mu$ l) and oral candidiasis (25.2%, 189 cells/ $\mu$ l).

A different investigator reports the spectrum of OIs in India as follows:

- Pulmonary TB is the number one diagnosis
- Oral Candidiasis is very common
- HSV, Extra pulmonary TB, Herpes Zoster were fairly common
- PCP was seen, but less commonly
- CNS disease was most commonly caused by Cryptococcal meningitis, followed by Toxoplasmosis, then TB meningitis. CNS lymphoma was very rare. AIDS Dementia Complex was rarely reported, but may have been under recognized.
- Diarrhea was most commonly caused by Isospora followed by Cyclospora

## 2. Most common Opportunistic Infections in Nepal

- *C. parvum* is among the most prevalent parasitic pathogen found in PLHIV patients with diarrhea in Nepal. A study done in Kathmandu in 2004 found that 10.7% of HIV infected patients and 30.8% of AIDS patients had laboratory proof of Cryptosporidium on stool samples. All those with cryptosporidium had clinical diarrhea.
- A published report from Pokhara, Nepal in 2005 showed that fever was the most common symptom encountered (43.6%) in PLHIV. After this cough and dyspnea (36.5%), weight loss (36.5%) and TB (21.6%) were also prevalent. The most common pathogen isolated in OI patients was mycobacterium TB (60%), followed by cryptosporidiosis (13%) and then candida (11%).

• At Manipal Teaching Hospital in Pokhara in 2008, the most common OIs were as follows:

- Tuberculosis (30%) (70% Pulmonary, 30% Extrapulmonary)
- EPTB cases included CNS, pleural and abdominal TB.
- Candidiasis (14%) (Both oral and esophageal)
- Pneumocystis jiroveci pneumonia
- Cryptosporidiosis
- Disseminated cryptococcosis
- Pneumococcal pneumonia
- Bacteremia
- Dermatophytosis
- Hepatitis

• In 2009, Sashi et al reported that out of 150 HIV-infected clients the most common clinical symptoms included: loss of appetite, continuous fever, weight loss, headache and diarrhea.

The most common OI diagnoses included:

- Oral Candidiasis
- Pneumonia
- Salmonella
- Cryptosporidiosis
- Tuberculosis

### 3. Less common OIs in Nepal, but some cases identified:

Lymphoma (non-CNS), CNS Lymphoma, Possible PML, TB of the abdomen, TB osteomyelitis or joint infections

### 4. Common symptoms (often with no definitive diagnosis made):

Diarrhea, Fever

### 5. Diseases not common in Nepal:

Penicilliosis, Kaposi Sarcoma- very rare

## B. Cotrimoxazole Prophylaxis in Adults and Adolescents (Ref: WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, June 2013)

### 1. When to start cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis should be initiated to decrease morbidity and mortality from PCP, toxoplasmosis, bacterial infections and malaria.

The need for cotrimoxazole prophylaxis should be assessed at each visit.

Give cotrimoxazole to all HIV-infected adults and adolescents as below:

### **Cotrimoxazole (Trimethoprim-Sulfamethoxazole) dosing:**

- 1 double strength (DS) tablet once daily (DS = TMP160mg/ SMX 800mg) OR
- 2 single strength (SS) tablets once daily (SS = TMP 80mg / SMX 400mg)

### **Timing of cotrimoxazole prophylaxis initiation in relation to ART initiation**

- The most common initial side effect of cotrimoxazole and ART (especially nevirapine) is a rash. Start cotrimoxazole prophylaxis first and initiate ART two weeks later if the individual is stable on cotrimoxazole and has no rash.
- Do NOT start cotrimoxazole and ART at the same time.

### **2. When to stop cotrimoxazole prophylaxis:**

- a. Do not stop, but continue lifelong, if NOT on ART.
- b. If on ART and the CD4 is >350 on two consecutive samples 6 months apart, cotrimoxazole can be discontinued.
- c. Stop prophylaxis for severe cutaneous reactions, such as Stevens-Johnson syndrome, renal and/or hepatic failure, and severe hematological toxicity. Substitute alternative drug. See below.

### **3. Follow-up of clients on cotrimoxazole prophylaxis every month:**

- a. Monitor for toxicity, clinical events and adherence.
- b. Lab tests of hemoglobin and white blood counts, only as indicated.
- c. Adherence counseling for cotrimoxazole can be useful to help prepare clients for ART in the future and problem-solve barriers to medication adherence.
- d. Use an alternative antibiotic for treating breakthrough bacterial infections, while continuing cotrimoxazole.
- e. For toxoplasmosis and PCP infections, prophylaxis should be held and full active treatment initiated.

Cotrimoxazole prophylaxis should be restarted after the treatment course.

### **4. Side Effects from cotrimoxazole:**

- a. Fixed drug reaction: one or several dark areas on the skin. They disappear when stopping the drug. They reappear on the same location when restarting the drug.
- b. Stevens Johnson reaction: a very severe drug reaction that can be fatal if not recognized.

There is involvement of the eyes and mucosa of the mouth. The skin lesions can look like burns with blistering and peeling. Patients lose fluids (as they do with burns) and can go into shock. These patients need to have cotrimoxazole stopped and should be referred urgently to hospital.

- c. Other new generalised drug rashes: If the patient has peeling or involves the eye or mouth or are associated with fever, stop and refer. If there is no peeling, no fever and no eye or mouth involvement, stop the drug. Follow-up the next day.

- d. Liver failure: Jaundice, yellow color of the white of the eyes, can appear. Stop all drugs.
- e. Haematological failure: in rare cases, cotrimoxazole can suppress the bone marrow. This can present in several ways:
  - Severe anemia (pallor or low haemoglobin), and/or
  - Decrease in white blood cells (lymphopenia) (leading to infections) and/or
  - Thrombocytopenia- easy bleeding due to a decrease in blood platelets

#### 5. Alternatives to cotrimoxazole if side effects occur:

Dapsone 100 mg once daily is the first choice.

OR

In cases of non-life threatening adverse reactions: stop treatment for two weeks; then re- challenge the client with TMP/SMX in a gradually increasing dose of an oral suspension of TMP/SMX. After desensitization under surveillance, up to 70% may again tolerate TMP/SMX.

#### 6. Cotrimoxazole in Pregnancy and Lactation

- a. Cotrimoxazole should be given in pregnancy at any trimester for prophylaxis.
- b. Theoretical concerns about first and third trimester exposure are greatly outweighed by the documented benefits of cotrimoxazole prophylaxis for women. Women who are breastfeeding should continue to receive cotrimoxazole prophylaxis.

#### 7. Restarting cotrimoxazole

If prophylaxis has been stopped because of rising CD4, cotrimoxazole (or Dapsone) should be restarted if the CD4 cell count falls below 350 or if new or recurrent WHO clinical stage 2, 3 or 4 conditions occur.

**Table 6: Protocol for cotrimoxazole desensitization among adults and adolescents**

Step	Dose
Day 1	80 mg SMX + 16 mg TMP (2 ml oral suspension)
Day 2	160 mg SMX + 32 mg TMP (4 ml oral suspension)
Day 3	240 mg SMX + 48 mg TMP (6 ml oral suspension)
Day 4	320 mg SMX + 64 mg TMP (8 ml oral suspension)
Day 5	One single-strength SMX-TMP tab (400 mg SMX + 80 mg TMP)
Day 6	Two single-strength SMX-TMP tabs or one double strength tab (800 mg SMZ + 160 mg TMP)

a Cotrimoxazole oral suspension is 40 mg trimethoprim + 200 mg sulfamethoxazole per 5 ml.

#### 6. Cotrimoxazole in Pregnancy and Lactation

- a. Cotrimoxazole should be given in pregnancy at any trimester for prophylaxis.
- b. Theoretical concerns about first and third trimester exposure are greatly outweighed by the documented benefits of cotrimoxazole prophylaxis for women. Women who are breastfeeding should continue to receive cotrimoxazole prophylaxis.

## 7. Restarting cotrimoxazole

If prophylaxis has been stopped because of rising CD4, cotrimoxazole (or Dapsone) should be restarted if the CD4 cell count falls below 350 or if new or recurrent WHO clinical stage 2, 3 or 4 conditions occur.

## 8. Cotrimoxazole in HIV-Infected Children: Indications

**Table 7: Cotrimoxazole Prophylaxis for HIV infected children: When to start and stop**

Situation	Start	Discontinue
All HIV-infected infants <12 months of age	Regardless of CD4 count or clinical status	Until age 5 yrs and then reassess as below
1-5 years	1. All Symptomatic (WHO Stage 2, 3 or 4) regardless of CD4 count 2. Any WHO stage and CD4 <25%	Until age 5 yrs and then reassess as below
When CD4 count not available >5 years.	All Symptomatic (WHO Stage 2, 3 or 4)	If not on ART, do not discontinue. If on ART: *restart cotrimoxazole prophylaxis if the CD4 count falls below the initial threshold or if new or recurrent WHO clinical stage 2, 3, or 4 conditions occur - Absence of clinical symptoms after at least 1 year of ART - With good adherence and secure access to ART
When CD4 count available >5 years.	Any WHO clinical stage and CD4 <350/mm <sup>3</sup> Or WHO clinical stage 3 or 4, irrespective of CD4 level	If not on ART, do not discontinue If on ART: * -CD4 > 350 cells /mm <sup>3</sup> after at least 6 months of ART*
If history of PCP (secondary prophylaxis)	At initial visit	Do not discontinue
Presumptive symptomatic HIV disease	At any age	Until HIV infection can be excluded

\*Restart Cotrim prophylaxis if the CD4 count falls below the initial threshold or if new or recurrent WHO clinical stage 2, 3, or 4 conditions occur

## 9. Initiation of cotrimoxazole prophylaxis in HIV-exposed children

CTX prophylaxis is universally indicated, starting at 6 weeks after birth and maintained until cessation of risk of HIV transmission and exclusion of HIV infection.

**Table 8: CTX formulations & dosage for HIV-infected/exposed infants and children**

Recommended daily dosage	Suspension syrup (5 ml)	Paediatric tablet (100 mg/20 mg) 200 mg /40 mg)	Single adult tablet (400 mg/ 80 mg)	Strength adult tablet (800 mg/ 160 mg)	Double strength adult tablet (800 mg/ 160 mg)
< 6 months	2.5 ml	One tablet	¼ tablet, possibly mixed with feeding	—	—
6 months – 5 years	5 ml	Two tablets	Half tablet	—	—
> 6 – 14 years	10 ml	Four tablets	One tablet	Half tablet	—
> 14 years	—	—	Two tablets	One tablet	—

## **6. Comprehensive Care for People Living with HIV**

### **PURPOSE:**

To provide an opportunity for participants to explore issues and strategies involved in providing comprehensive care and treatment services.

### **OBJECTIVES:**

By the end of the session participants will be better prepared to:

1. Describe the purpose and components of a comprehensive care and treatment program.
2. Understand the HIV continuum of care.
3. Understand the management of HIV as a chronic disease.
4. Describe the importance and elements of standards of care.
5. Understand the opportunities within care and treatment programs to promote prevention (Positive prevention)
6. Understand HIV programmatic issues.

### **1. Background**

Care, treatment and support programs should be designed to respond to the needs and demands of people living with HIV and their families or households. This often requires considering a context of stigma, fear, neglect and impoverishment that complicates the clinical picture. Access to ART can help mitigate the effect of this context.

The purpose of HIV care, treatment and support programs is to:

- Assure equitable access to diagnosis, medical care, pharmaceuticals and supportive services.
- Reduce morbidity and mortality from HIV and related complications.

- Promote prevention opportunities within care, treatment and support clinical encounters.
- Improve the quality of life for adults and children living with HIV and their families.

## **2. Components of comprehensive care, treatment and support**

Providing comprehensive care to PLHIV and to their families requires a broad range of services that include not only medical care and pharmaceuticals, but also supportive services to assure adequate nutrition; psychological, social, and daily living support; and prevention messages wherever the opportunity arises.

Comprehensive HIV care includes the following components:

- **Medical and nursing care**

- Counseling and testing for screening and diagnostic purposes
- Prophylaxis for OI
- Management of HIV-related illnesses, including OI
- TB control
- STI management
- Management of HIV disease with ART
- Palliative care
- Access to HIV-related drugs, including drugs for OI, ARV and traditional therapies
- Interventions to reduce parent-to-child transmission of HIV
- Clinical HIV care for mothers and infants
- Support systems such as functional laboratories and drug management systems
- Nutritional support
- Health education
- Adequate universal precautions in clinical settings and post-exposure prophylaxis (PEP)

- **Psychological support**

- Community services to meet the emotional and spiritual needs of positive individuals and their families, including support through post-test clubs and peers

- **Socioeconomic support**

- Material and social support within communities to ensure that nutritional and daily living needs are met
- Support for children affected by HIV/AIDS (CABA)

- **Involvement of HIV-positive individuals and their families** in service planning and delivery to ensure that the HIV care, treatment and support programs intended for them, address their needs and rights.

- **Respect for human rights and legal needs**

- Services that address stigma and discrimination issues in health facilities, in communities and in the workplace as well as promote equal access to care

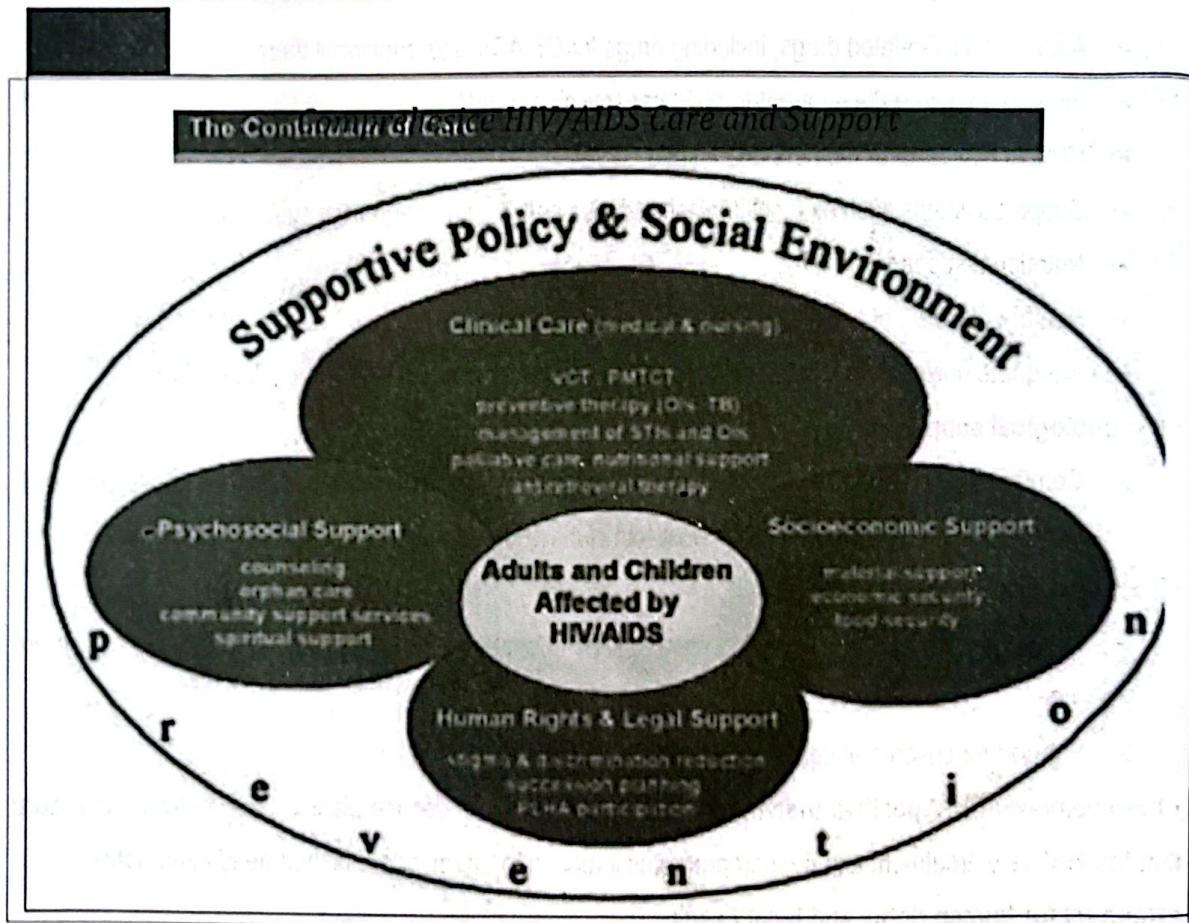
**Figure 13: below illustrates the main domains and elements of HIV comprehensive care.**

In this comprehensive approach, each service is linked to and reinforces other services.

### 3. Continuum of HIV care, treatment and support

Multiple providers or programs may offer the range of care, treatment and support services in different locations. However, partnership and collaboration are essential to make timely patient access to the appropriate services possible. The HIV Care Continuum (figure on following page) illustrates how these linkages should function in a referral system. Care providers at any service point should know who provides other services within comprehensive care, where the services are located, and when and how to make a referral.

**The HIV care of continuum**



In the medical domain, referrals need to be made to higher level services and discharge planning to community oriented services, for example, community care centers (CCC) and community home based care (CHBC) teams. Home care providers should be able to assess risk situations for referrals to both medical and support services. Referrals at all levels must be explicit to ensure that social, legal, human rights, and peer support needs are being met. Peers from PLHIV support groups play a major role and should be involved in shaping the delivery of care in communities.

#### 4. HIV care requires a chronic disease management approach

In resource-constrained settings, chronic disease management has been relegated to the background. Priority has been given to acute illnesses, for example, respiratory illnesses and malaria. But chronic disease management is essential, especially once life-prolonging treatment for HIV is available, creating a demand for long-term care.

Principles of chronic disease management that are pertinent to HIV care are as follows:

a. The patient and health providers work as a team to foster the patient's self-management skills, the health care provider's application of technical knowledge and skills, and assistance from social services. This demands a steady relationship between patient and health care team members. At a minimum, the team includes a clinician authorized to prescribe medications (a doctor or health assistant), a nurse and a counselor. Supporting this collaboration are community service organizations providing services to meet the patient's many non-medical needs. There should be regular interdisciplinary care team meetings to discuss care issues, review treatment protocols, express concerns, and support colleagues.

b. Continuing care involves regularly scheduled visits with clinical and support staff on a predetermined schedule to:

- (1) monitor disease status and treatment effect, including labs;
- (2) provide rapid response to emerging health and socioeconomic issues; while at the same time
- (3) maintain up-to-date, easily retrievable documentation.

The result is that continuing care always tries to avoid or reduce disease-related exacerbations that require acute management.

c. Support for care team members is essential in order to provide quality care, and avoid frustration and burnout.

d. Currently, available treatment is life-long. It is to be expected that motivation to maintain wellness and adhere to treatment will fluctuate during the course of the disease.

## **5. Standards of care**

- a. Setting standards of care for HIV-infected persons is intended to promote delivery of the highest possible quality of care and establish measures to evaluate and improve client services. This requires deciding how to achieve the standards, applying them in clinical practice and then evaluating whether they have been achieved (what is needed/process issues/desired outcomes).
- b. There will be different standards for a comprehensive care package at each level of the health care system—that is, referral hospital, district or peripheral hospital, primary health center, health post, sub-health post and community. Developing practice standards and then monitoring the quality of their implementation are both important to delivering appropriate HIV care.
- c. Clinical services include affordable and standardized practices based on international and national guidelines: preventive therapies, management of HIV-related conditions and OI, laboratory services, secure supply of prescribed medications, ART, PEP for occupational injuries and rape, STI management and palliative care.
- d. Standards of care and recommendations continue to change as research and programmatic experience guide countries to improve the care provided.

## **6. Comprehensive Care Small Group Session**

- Discuss management of HIV as a chronic disease in your locality
- Discuss Comprehensive Care:
  - What services are in place?
  - What services are needed?
  - How do you make successful referrals?
  - What linkages to community groups exist?
  - Do standards of HIV care in your community exist?
  - How can you develop them?
  - Present synopsis to large group

## **7. Prevention as a part of care and treatment**

Prevention must not be neglected as PLHIV receive care and treatment. In some countries, there has been a tendency to relax prevention behaviors, such as condom use, once many with HIV are treated. This can be a tragic consequence of what is perceived as an enhanced program for PLHIV. At each point in the process of providing care and treatment, opportunities exist to introduce or reinforce prevention messages.

## 8. Respiratory Manifestations of HIV

### PURPOSE:

In this session, participants will learn about respiratory problems, including common etiological agents, clinical presentation, recommended diagnostics and common findings, management and treatment.

### OBJECTIVES:

By the end of this session, participants will be able to:

1. List the various etiological agents that cause respiratory infections.
2. Describe the clinical presentation of specific respiratory infections.

### Introduction

#### a. Overview

The respiratory manifestations of HIV disease are a major cause of morbidity and mortality. Preventable and treatable respiratory infections are seen in up to two-thirds of all HIV-infected individuals.

#### b. The differential diagnosis of respiratory infections in HIV includes the following pathogens:

- **Mycobacterial infection:** M. tuberculosis, M. avium complex
- **Protozoal infection:** Toxoplasmosis gondii
- **Bacterial infection:** Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Moraxella cattharalis, Klebsiella pneumoniae, Pseudomonas aeruginosa
- **Fungal infection:** Pneumocystis jiroveci, Penicillium marneffei, Cryptococcus neoformans, Histoplasmosis, Coccidioidomycosis, Aspergillosis
- **Helminthic infection:** Strongyloides stercoralis, Paragonimus westermanii

The pattern of pulmonary infections that emerge with falling CD4 counts is shown below:

Table 9: Association of pulmonary infections with CD4 counts in PLHIV

Infection	CD4 cell count
<i>Mycobacterium tuberculosis</i>	<400
Bacterial pneumonia	Can occur at any CD4
Suppurative lung and sinus disease	<100
<i>Pneumocystis jiroveci</i> pneumonia	<200
<i>Mycobacterium avium</i> complex	<100
Cytomegalovirus	<100

(Ref: Guidelines for Prevention and Management of Common Opportunistic Infections/Malignancies among HIV-infected Adults and Adolescents NACO India 2007)

### A. Bacterial Pneumonia

#### a. Common etiological agents:

- *Streptococcus pneumoniae*
- *Hemophilus influenzae*
- *Staphylococcus aureus*

#### b. Clinical presentation:

- Abrupt onset with fever
- Cough
- Production of purulent sputum
- Dyspnea
- Pleuritic chest pain

#### c. Recommended diagnostics:

- Chest X-ray
- Blood culture
- FBC
- Grams stain of sputum
- Sputum culture and sensitivity
- Common findings: X-ray may show pneumonic consolidation, infiltrates, or pleural effusion; leukocytosis; blood cultures may be positive

#### d. Management and treatment:

##### • Mild pneumonia:

Amoxycillin, Erythromycin or Doxycycline

- **Moderate to Severe pneumonia:**

Amoxycillin/Clavulanic Acid

2nd or 3rd generation cephalosporin (Cephaclor, Cefuroxime or Ceftriaxone)

PLUS

Coverage for atypical (Azithromycin or Doxycycline)

Staph pneumonia: Cloxacillin, Flucloxacillin, Amox-Clav, Cefuroxime and Clindamycin

### **B. Pneumocystis jiroveci pneumonia (PCP)**

- a. Etiological agent: *Pneumocystis jiroveci* (*classified as fungal*)

- b. Clinical presentation:

- Dry cough
- Progressive shortness of breath
- Fever
- Few chest signs: Often nonspecific and insidious

- c. Recommended diagnostics: Chest X-ray. Generally a clinical diagnosis in Nepal Chest x-ray shows bilateral lace-like interstitial infiltrates extending from the perihilar region or may be normal

- d. Management and treatment:

TMP-SMX high dose PO or IV x 21 days (Cotrimoxazole 15mg/kg divide into 3 or 4 times per day:

- 2 SS tab qid if <40kg
- 3 SS tab qid if >40kg

If hypoxic, add Prednisone 40 mg bid for 5 days, then taper

## **8. Neurological Manifestations of HIV**

### **PURPOSE:**

In this session, participants will learn about neurological disorders related to HIV, including common etiological agents, clinical presentation, recommended diagnostics and common findings, management and treatment. This session will also cover the clinical features, management, and treatment of AIDS dementia complex, painful sensory and motor neuropathies and primary CNS lymphoma.

### **OBJECTIVES:**

By the end of this session, participants will be able to:

1. Describe the various etiological agents that cause neurological disorders.
2. Describe the clinical presentation of specific neurological disorders.
3. List the recommended diagnostics and common findings of some common neurological disorder.
4. Understand the treatment and management of common neurological disorders.

## Introduction

### a. Overview

- Reported incidence of neurological abnormalities on clinical examination varies greatly, from 16 to 72 percent among hospitalized patients.
- A wide range of neurological manifestations is reported including cognitive defects, focal deficits such as hemiplegia and acute peripheral facial palsy, painful feet syndrome and encephalopathy.
- Some of these manifestations are caused directly by HIV itself; others result from OIs caused by different pathogens or drugs.

### b. The differential diagnosis of OIs involving the brain includes the following pathogens:

• <b>Protozoal infection:</b>	Toxoplasmosis gondii
• <b>Mycobacterial infection:</b>	M. tuberculosis
• <b>Bacterial infection:</b>	Strep Pneumoniae, Neisseria meningitis
• <b>Fungal infection:</b>	Cryptococcus neoformans, Candida species (rare)
• <b>Viral infection:</b>	Cytomegalovirus, Herpes simplex
	Virus, varicella zoster virus, JS virus
	(PML)

**Table 10: Neurological Involvement in HIV Infection**

(Ref: Guidelines for Prevention and Management of Common Opportunistic Infections/Malignancies among

HIV related	OI related
Acute aseptic meningitis	Cryptococcal meningitis
Chronic meningitis	Cerebral toxoplasmosis
HIV encephalopathy (AIDS dementia)	CMV retinitis and encephalitis
Vacuolar myopathy	Progressive multifocal leukoencephalopathy (PML)
Peripheral neuropathy (sensory)	Primary CNS lymphoma
Myopathy	TB Syphilis

HIV infected Adults and Adolescents NACO India 2007)

**A. Cerebral Toxoplasmosis**a. Etiological agent: *Toxoplasma gondii*

b. Presenting Symptoms and signs

- Headache (severe, localized)
- Fever, Confusion, Myalgia, Arthralgia
- Focal neurological deficits, e.g., seizures, hemiparesis, hemiplegia, cerebellar tremor, cranial nerve palsies, hemisensory loss, visual problems or blindness
- Personality changes
- Cognitive disorders
- Clinical symptoms may evolve in less than two weeks.

c. Diagnostics

• CSF values: Normal: 20-30%, Protein: 10-150/ml, WBC: 0-40 (monos), toxoplasma Ag positive PCR

• CT scan:

- Lesions: Multiple ring-enhancing lesions 1-2 cm
- Location: Basal Ganglia and Cortex
- Enhancement: Prominent
- Edema/Mass Effect: Less than lymphoma

d. Management and Treatment

• Provide physiotherapy as necessary

• Start anti-convulsant treatment: Phenytoin or Carbamezepine

• Start treatment for acute phase:

Pyrimethamine + folic acid + sulfadiazine or Trimethoprim/Sulfamethoxazole for 4 weeks

or

Clindamycin + pyrimethamine + folinic acid

e. Unique features, Caveats

- One of the most common HIV-related neurological complications
- Usually occurs when CD4<100
- Monitor blood count regularly as relatively high doses of drugs can lead to toxicities
- Leukopenia, thrombocytopenia and rash are common. Folic acid reduces the risk of myelosuppression.
- During treatment, patients should maintain a high fluid intake and urine output
- Patient needs maintenance therapy to prevent recurrence. Consider discontinuation if CD4 sustained above 200 for >6 months

Secondary prophylaxis after a case of Toxoplasmosis

- Preferred regimen for suppressive therapy: Pyrimethamine + folinic acid + sulfadiazide
- If allergic to sulfa: Dapsone or Clindamycin

*An HIV-infected individual presenting with typical signs and symptoms and normal CSF findings should be put on treatment for toxoplasmosis.*

**B. Cryptococcal meningitis**

a. Etiology: *Cryptococcus neoformans*

b. Presenting symptoms and signs

- Usually nonspecific at onset.
- Symptoms can be present for >1 month.
- Protracted headache and fever may be the only signs.
- Nausea, vomiting, and stiff neck may be absent and focal neurological signs uncommon.
- Extraneuronal symptoms: skin lesions, pneumonitis, pleural effusions and retinitis
- Fever, malaise and nuchal pain signify a worse prognosis, and nausea and vomiting and altered mental status occur in terminal stages

c. Diagnostics

- CSF values: Normal 20%, Protein 30-150/dl, WBC: 0-100 (monos), Glucose decreased: 50-70mg/dl, Culture positive: 95-100%, India ink positive: 60-80%, Crypt Ag >95% sensitive and specific

- Blood: Serum Crypt Ag 90% sensitive (very useful)

d. Management and Treatment

- Preferred initial regimen: Amphotericin B IV, + flucytosine po x 14 days
- Alternative initial regimen: Amphotericin B IV alone x 14 days

- Continuation regimen: Fluconazole po for 8-10 weeks (Preferred) or Itraconazole po for 8 weeks

- Maintenance therapy: Fluconazole po for life

e. Unique features, Caveats

- Most common life-threatening fungal infection in HIV/AIDS patients.
- The most common cause of meningitis in patients with HIV/AIDS in Africa and Asia.
- If untreated, it is slowly progressive and ultimately fatal
- Evolution occurs in less than 2 weeks
- Usually when CD4<100
- Headache is secondary to fungal accumulation, so the headache increases gradually over time, goes away and then comes back and is harder to get rid of. It then becomes continuous, and this is what the patient reports.
- Requires lifelong suppressive treatment unless immune reconstitution occurs.
- Characteristically involves the retinal vessels.
- There is minimal or no accompanying uveitis.
- Rare but devastating illness in resource poor settings.
- Treatment is very expensive and usually not available.

### C. Painful Sensory and Motor Peripheral Neuropathies

a. Presenting symptoms and sign

- Burning pain and numbness in toes and feet, ankles, calves, fingers in more advanced cases paraplegia
- Autonomic dysfunction
- Poor bowel/bladder control
- Dizziness secondary to postural hypotension
- Contact hypersensitivity in some cases
- Mild/moderate muscle tenderness, muscle weakness
- Later: Reduced pinprick/vibratory sensation; reduced or absent ankle/knee jerks
- Sweating

b. Diagnostics

- Electromyography/nerve conduction velocities show predominantly axonal neuropathy
- CPK usually elevated
- CSF - look for CMV or HSV infections
- Serum B12 and TSH

c. Management and Treatment

- Exclude neurotoxic drugs, alcoholism, diabetes, B12 deficiency, thyroid problems and treat underlying causes.
- Discontinue presumed neurotoxic medication
- Provide proper nutrition and vitamin supplements
- Nutrition counseling and psychological support

#### Pain control

- Ibuprofen or codeine for modest symptoms
- Amitriptyline at night
- Phenytoin or carbamazepine especially for episodic shooting pain. Can combine antidepressants with anti-convulsants
- Morphine for severe symptoms
- Lidocaine ointment topically
- Physiotherapy may be helpful, but may be hampered by pain

#### D. HIV-associated dementia complex (HAD)

##### a. Presenting Signs and Symptoms

- In up to 10% of patients, this is the first manifestation of HIV disease
- Afebrile; general lethargy
- Triad of cognitive, motor and behavioral dysfunction
- Early stages- concentration and memory deficits, inattention, motor-uncoordination, ataxia, depression, emotional lability
- Late stages - global dementia, paraplegia, mutism

##### b. Diagnostics

- CT scan: Lesions: Diffuse ill-defined hyperintensities
- Location: White matter
- Enhancement: None
- Edema/Mass Effect: None
- Prominent Atrophy

##### c. Management and treatment

- Possible benefit from antiretroviral regimens with agents that penetrate the CNS (AZT, d4T, ABC, nevirapine)
- Benefit of AZT at higher doses for mild or moderately severe cases is established; monitor therapy with neurocognitive tests
- Anecdotal experience indicates response to ART, if started early

- Sedation for those who are agitated and aggressive—use smaller doses initially to avoid over-sedation
- Close monitoring:
  - to prevent self-harm
  - to ensure adequate nutrition
  - to diagnose and treat OIs early
- Psychological support for caregivers—looking after demented patients is exhausting; caregivers need regular breaks and may need counseling

d. Unique features, caveats

- Frequency in AIDS patients 10-15%
- CD4 <200
- Prevalence increases with improvement of general management of various OIs because patients live long enough to develop severe immune suppression.
- Patients present with a demeanor similar to Parkinson's disease and may even be misdiagnosed as such.

## 9. Gastrointestinal Manifestations of HIV

### PURPOSE:

In this session, participants will learn about oral lesions, dysphagia, odynophagia, acute and chronic diarrhea, and other conditions of the gastrointestinal system, including common etiological agents, clinical presentation, recommended diagnostics, common findings, management, and treatment.

### OBJECTIVES:

By the end of this session, the participants will be able to:

1. List the various etiologies that cause oral lesions, dysphagia and odynophagia.
2. List the various infectious agents that cause acute and chronic diarrhea.
3. Describe the clinical presentation of these diseases.
4. Explain the recommended diagnostics and common findings for each.
5. Explain management and treatment for these illnesses.

### 1. Oral and Esophageal Manifestations

#### a. Overview

- Patients with AIDS have many different conditions involving the oral cavity.
- An examination of the mouth needs to be part of the physical exam of every patient suspected of HIV infection even in the absence of complaints. Oral lesions and difficulty swallowing can develop rapidly.
- Often it is the presence of oral thrush that raises the suspicion of HIV infection.
- Oral lesions may be debilitating because they interfere with eating and contribute to weight loss.

- Esophageal complaints are common especially when CD4 is less than 200 and are frequently misdiagnosed as a peptic ulcer.
- Incidence is higher in patients with CD4<200
- Empiric approach to treatment is reasonable.

b. Differential diagnosis includes the following pathogens:

• <b>Bacterial infection:</b>	Aerobic infections causing gingivitis
• <b>Fungal infections:</b>	Candida albicans
• <b>Viral infections:</b>	Epstein-Barr virus (hairy leukoplakia), HSV, CMV
• <b>Oncologic conditions:</b>	Kaposi sarcoma

#### A. *Candida albicans*

a. Presenting signs and symptoms

Oral (thrush):

- Pseudomembranous white/yellow colonies or clusters appearing anywhere in the oral cavity. May be quite discrete or extensive and can be easily removed by wiping
- Erythematous: red patches on mucosal areas; if tongue is involved it may lose its usual surface texture
- Hyperplastic similar to pseudomembranous, but usually adheres to the tissue
- Angular cheilitis: fissuring at corners of mouth with or without visual colonization.

Esophageal:

Pseudomembranous lesions extend into lower pharynx and esophagus, causing difficulty swallowing, nausea and retrosternal and epigastric pain.

b. Diagnostics

Oral candidiasis

- Typical clinical appearance on physical examination
- Microscopic examination of scrapings show pseudohyphae on KOH preparation

Esophageal candidiasis

- Typical clinical presentation and response to antifungals.
- Endoscopy if available.

c. Management and treatment

Oral (thrush)

- Nystatin (500,000 IU) gargled 4–5 times daily x 7–14 d
- Clotrimazole troche 5 times daily 7–14 d
- Fluconazole 100 mg/day PO x 7–14 days

### **Esophageal candidiasis**

- Fluconazole 200mg/day x 14– 21 days.
- Use intermittent therapy for as long as possible to delay the emergence of resistant candidiasis

#### **d. Unique features, caveats**

#### **Oral candidiasis**

- Rare condition in a healthy person, but is frequently the first indication of immune impairment in PLHIV.
- Recurrent episodes of oral candidiasis usually occur in patients with CD4 <300.
- Suppressive therapy generally is not recommended unless patients have frequent/severe recurrences.

#### **Esophageal candidiasis**

- Develop in 10– 20% of PLHIV with CD4 <100 and is the most common cause of dysphagia.

Refer to Annex IV for differential diagnosis of oral lesions in HIV.

### **B. Oral hairy leukoplakia**

#### **a. Presenting Signs and Symptoms**

- Non-removable whitish plaques with vertical folds, mostly on the lateral surface of the tongue.

#### **b. Diagnostics**

- Clinical Diagnosis: White lesion that is hairy, shaggy or furry that will not scrape off (unlike candida) or persists after antifungals

#### **c. Management and treatment**

- No need to treat

#### **d. Unique features, caveats**

- It is a sign of immune suppression.
- Caused by the Epstein-Barr virus (EBV).
- More common with with CD4<200
- Neither dangerous nor painful and does not require any treatment

## **2. Diarrhea**

#### **a. Overview**

- Chronic diarrhea is a very frequent and frustrating problem with HIV infection; at least 50 percent of PLHIV experience it at some time.
- More frequent with disease progression.
- Often accompanied by nausea, weight loss, abdominal cramps and dehydration.
- Often an intermittent watery diarrhea, without blood or mucous.

- Diarrhea is more likely to be severe, recurrent, persistent and associated with extra-intestinal manifestations in HIV disease.
- Wherever possible, establish the cause and give specific treatment. Failing this, management is symptomatic: give antidiarrheals such as codeine phosphate.
- The key to good management is rehydration with potassium-containing low sugar solution.
- High energy and protein intake reduces the degree of muscle wasting.
- Prevention consists of attention to personal hygiene, hand washing, drinking boiled water and eating only thoroughly cooked meat and vegetables.

b. An infectious agent can be identified in about 50 percent of patients with HIV-associated diarrhea.

c. Differential diagnosis includes the following causes:

- **Bacterial infection:** *Campylobacter, Shigella, Salmonella, enterohemorrhagic E. coli, enteroinvasive E. coli, C difficile, V. cholerae, Yersinia, Aeromonas*
- **Parasitic infection:** *Cryptosporidium species, Giardia lamblia, Isospora belli, Entamoeba histolitica, Microsporidium species, cyclospora*
- **Mycobacterial infection:** *M. tuberculosis, M. avium complex*
- **Viral infection:** *Rotavirus, Astrovirus, Calicivirus, picornavirus, adenovirus, Herpes virus, Cytomegalovirus*
- **Helminthic infection:** *Strongyloides stercoralis*
- **Drug-associated diarrhea:** *Certain ARVs especially protease inhibitors*
- **HIV enteropathy**
- **Non-infectious disorders:** *Kaposi Sarcoma, lymphoma*

#### *Bacterial Causes of Diarrhea*

- It is clinically impossible to distinguish the different types of bacterial gastroenteritis without a stool culture
- If empiric therapy with TMP/SMX is not effective in patients with bacillary dysentery, fluoroquinolones can be tried
- If symptoms of bloody diarrhea persist, erythromycin can be given

#### *A. Campylobacter*

a. Presenting signs and Symptoms

- Fever and general malaise
- Sometimes without GI symptoms
- GI symptoms can include bloody diarrhea

- Abdominal pain and weight loss

**b. Diagnostics**

- Campylobacter bacilli found in stool culture

**c. Management and Treatment**

- Erythromycin (Fluoroquinolones may be effective, but resistance rates of 30-50%)

***B. Salmonella***

**a. Presenting signs and symptoms**

- Fever; general malaise

- May have no GI symptoms, or present with bloody diarrhoea, abdominal pain and weight loss.

**b. Diagnostics**

- Stool culture/ Blood culture: *Salmonella* bacilli may be found

- Serology: positive Widal test with increasing titres

**c. Management and treatment**

- If signs of sepsis, IV Ciprofloxacin 500 mg bid or ofloxacin 400 mg bid or ceftriaxone 1 g IV for 7–10 days.

- Mild-moderate disease: Ciprofloxacin 500mg orally bid for 5-7 days. Alternative is Azithromycin 1gm first day then 500mg for 6 days

**d. Unique features, caveats**

- *Salmonellosis* is a frequent cause of bacteremia in PLHIV. Transmission is through contaminated food or water or oral-anal contact and from cattle and poultry, raw eggs or unpasteurized milk products.

***c. Shigella***

**a. Presenting signs and symptoms**

- High fever

- Abdominal pain

- Bloody diarrhoea

**b. Diagnostics**

- Stool microscopy— fresh examination and after concentration. Multiple stool samples may be needed.

*Shigella* bacillus found in stool

**c. Management and treatment**

- Ciprofloxacin 500 mg bid for 5 days

**• Alternatives:**

- Azithromycin 1gm first day then 500mg for 6 days Or

- TMP/SMX 1 DS po bid for 5 days

**d. Unique features, caveats**

- In many developing countries, resistance of *Shigella* (and *Salmonella*) to TMP/SMX has increased

**D. Toxin induced: *E. coli***

a. Presenting Signs and Symptoms

- Diarrhea
- Fever

b. Diagnostics

- Stool microscopy and culture

c. Management and Treatment

- Treatment based on culture and sensitivities results
- Start Fluoroquinolone while awaiting results

**E. *Clostridium difficile***

a. Presenting Signs and Symptoms

- Diarrhea and fever

b. Diagnostics

- Stool microscopy and culture

c. Management and Treatment

- Metronidazole
- May be difficult to make the diagnosis. Hospitalization and previous antibiotics increase risk.
- 5-30 percent of patients with *C. difficile*-associated diarrhea experience relapse.

**F. *Entamoeba histolytica***

a. Presenting Symptoms and signs

- Colitis, bloody stools, cramps, can be asymptomatic

b. Diagnostics

- Stool for ova and parasite exam

- No fecal WBC's

c. Treatment

- Metronidazole 800mg tid for 7 days.

- For invasive or organ infection give Metronidazole for 10 days followed by Paromycin 500mg tid for 7 days.

d. Unique features, caveats

- *E. histolytica* may be recurrent or more severe in HIV patients

## 10. Dermatological Manifestations of HIV

### PURPOSE:

In this session, participants will learn about skin lesions and infections, including common etiologies, clinical presentation, management and treatment.

### OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the various etiological agents that cause skin lesions in HIV infection.
2. Describe the clinical presentation of common skin lesions or infections.
3. Explain the treatment and management of common skin conditions.

### 1. Introduction

#### a. Overview

- Many patients with HIV infection (80 to 100 percent) develop dermatological conditions at some point in the course of the disease.

- Skin conditions may be very disabling, disfiguring and even life-threatening.

#### b. Differential diagnosis includes the following etiologies:

- Bacterial infection: *Streptococcus aureus, streptococcus species, treponema pallidum, bartonella species*

- Mycobacterial infection: *M. tuberculosis, M. avium complex*

- Viral infection: *Herpes simplex and zoster virus, molluscum contagiosum,*

- condylomata accuminata*

- Infestations: *Scabies*

- Fungal infection: *Seborrheic dermatitis, tinea corporis, pityriasis*

- versicolor, penicillium marneffei, cryptococcus*

- neoformans, histoplasma*

#### c. Clues from presentation

- Warm, inflamed, painful and/or fluctuant-a bacterial infection

- Discolored skin patches-a fungal infection or Kaposi's sarcoma

- Localized eruptions or localized pimple-like swellings-a viral infection

- Prurigo/urticaria, macular, maculopapular or scaly lesions-classified as other skin conditions, including drug eruptions, seborrhea, psoriasis, and scabies

## **A. Herpes zoster**

### **a. Presenting symptoms and signs**

- Painful cluster of vesicles on an erythematous base in dermatomal distribution
- Lesions can become necrotic and extensive

### **b. Diagnostics**

#### **• Clinical**

- Herpes zoster in a young person is highly predictive of HIV infection
- Almost 25 percent of PLHIV experience recurrences

### **c. Treatment**

- Analgesics and local lesion care with Gentian Violet or antiseptics
- Lidocaine gel locally for pain
- Calamine lotion
- Stronger analgesics for more severe pain (codiene)
- Oral acyclovir for ophthalmic or disseminated zoster
- Antibiotics for secondary infection

### **Post-herpetic neuralgia**

- Phenytoin or Carbamezepine

## **B. Papular pruritic eruption (PPE)**

### **a. Presenting Symptoms and signs**

- Itching
- Generalized maculopapular rash
- Erythroderma
- Excoriated hyperkeratotic hyperpigmented papules on extremities & lower back
- Severe itch
- Worse with CD4 less than 200
- Refractory to treatment

### **b. Diagnostics**

- Clinical
- No specific OI is known to be the cause.
- A generalized pruritic maculopapular rash due to eosinophilic folliculitis is common in HIV

### **c. Management and Treatment**

- Topical corticosteroids, high potency
- Topical calamine lotion (not very effective)

- Oral antihistamine (such as diphenhydramine, chlorpheniramine or promethazine)
- Antibiotics (if secondarily infected)
- UV light
- ART is effective

### C. Drug eruption

#### a. Common causative drugs

Sulfonamide (Cotrimoxazole, Sulfadiazine), Pentamidine, Acyclovir, Anti -tuberculous drugs (INH, RFP, Thioacetazone), Dapsone, Ofloxacin, Fluconazole, Carbamazepine, Antiretrovirals (especially Nevirapine, Efavirenz, and Abacavir)

#### b. Presenting Signs and Symptoms

- Generalized skin eruption and/or inflamed mucus membranes
- Morbilliform reaction
- Lichenoid drug eruption
- Urticaria
- Photoallergic reaction
- Exfoliative dermatitis
- Stevens-Johnson Syndrome (mucus membrane involvement)
- Toxic Epidermal Necrolysis (extensive involvement)

#### c. Diagnostics

##### • Clinical

#### d. Treatment

- Withdraw Drug
- Local Lesion Care
- Give oral antihistamine
- Systemic corticosteroids are immune-depressing and should only be given in life-threatening situations.

### D. Kaposi sarcoma

#### a. Presenting symptoms and signs

- Dark, patchy, painless swelling or nodules
- Maculopapular, nodular or plaque-like lesions
- Red or purple
- Lymphedema of face, genitals, or limbs from lymphatic infiltration
- May present with abdominal pain/distension, obstruction or GI bleeding from visceral KS
- Pulmonary KS: shortness of breath or cough with frothy or blood-stained sputum

**b. Diagnostics**

- Mainly clinical
- Can be confirmed by biopsy

**c. Management and Treatment**

- Discrete solitary or few lesions: No treatment

- Otherwise: cryotherapy (topical liquid nitrogen), intralesional vinblastine or surgical excision.

- If lesions are disseminated or extensive and if treatment is envisaged, do a biopsy.

- Radiotherapy: for intraoral or pharyngeal KS, painful cutaneous KS, and lymphedema

- Often regresses with ART

**d. Unique features, caveats**

- Oral KS can be aggressive

- KS can occur at any CD4, but more common and aggressive at lower CD4 counts

- Lesions can be stable for a long time

- Association with HHV Type 8

- Often disseminated involving many organs- skin, lymph nodes, mouth, lungs, GI, liver and spleen.

## **11. Lymphadenopathy and Fever in HIV**

**PURPOSE:**

In this session, participants will learn about lymphadenopathy and fever, including common etiological agents, the clinical presentation and diagnostic criteria for most common causes in PLHIV.

**OBJECTIVES:**

By the end of this session, participants will be able to:

1. Describe the various etiologies that cause lymphadenopathy.
2. Describe the clinical presentation of persistent generalized lymphadenopathy (PGL).
3. Describe features of lymph nodes that indicate further evaluation.
4. Describe the various etiologies of fever.
5. Explain the recommended diagnostics and describe the common findings for these tests.
6. Provide management and treatment for bacteremia/septicemia.

### **1. Introduction to Lymphadenopathy**

**a. Overview**

- Swelling of lymph nodes is a symptom often encountered.
- You should carry out a careful history and physical examination.
- The cause often becomes obvious, but in more complicated cases, laboratory tests and lymph node biopsy may be necessary to establish a definitive diagnosis.

b. Differential diagnosis includes the following pathogens:

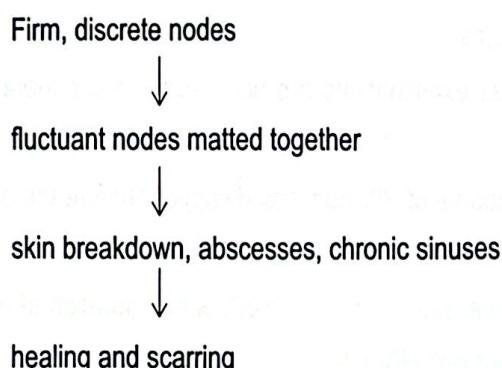
- HIV-related: Persistent generalized lymphadenopathy (PGL)
- Opportunistic infections: Tuberculous lymphadenitis, CMV, toxoplasmosis, infections with nocardia species, fungal infections (histoplasmosis, penicilliosis, cryptococcus, etc.)
- Reactive lymphadenopathy: Pyomyositis, pyogenic skin infections, ear, nose, and throat (ENT) infections
- STI: Syphilis, inguinal lymphadenopathy resulting from donovanosis, chancroid or lymphogranuloma venereum (LGV). See WHO guidelines.
- Malignancies: Lymphoma, Kaposi sarcoma

You should differentiate these etiologies from other causes of lymphadenopathies: carcinomatous metastases, brucellosis, visceral leishmaniasis (kalaazar), sarcoidosis, trypanosomiasis, ricketisial disease, infectious mononucleosis and drug reactions (for example, phenytoin hypersensitivity).

#### A. Tuberculosis lymphadenopathy

##### a. Signs and symptoms

- Cervical nodes most commonly involved.
- One of the most common forms of extra-pulmonary TB in HIV patients.
- Usual course of lymph node disease is as follows:



- Fluctuant nodes without significant inflammation or tenderness suggest M. TB, atypical mycobacteria, or cat scratch disease.
- In severely immunocompromised patients, TB lymphadenitis may resemble acute pyogenic disease.
- If generalized lymphadenopathy, consider miliary TB.

b. Diagnostics: Fine-needle aspiration of the involved lymph node with AFB stains. In smear negative pulmonary TB, aspirate extra-thoracic lymph nodes.

c. Treatment: Follow concerned country TB Guidelines

#### Characteristics of lymph nodes that require further evaluation

- Large (>4cm)

- Rapidly growing nodes
- Tender/painful nodes not associated with local infection
- Matted/fluctuant lymph nodes
- Obvious constitutional symptoms (fever, night sweats, weight loss)
- Suspicion of Pulmonary TB
- Evidence of abscesses

### **B. Persistent Generalized Lymphadenopathy (PGL)**

#### **a. Signs and symptoms**

- Lymph nodes  $> 1.5$  cm in  $> 2$  extrainguinal sites of  $> 3$  months duration
- Non-tender, symmetrical, and often with posterior cervical, axillary, occipital, and epitrochlear nodes

#### **b. Diagnostics:**

- CBC and chest x-ray to rule-out other cause.
- CXR: Hilar or mediastinal nodes

#### **c. Treatment:**

- No specific treatment for PGL

#### **d. Unique features of PGL**

- Develops in up to 50% of PLHIV
- Up to one-third have no other symptoms
- PGL is a clinical diagnosis. No further examinations are necessary, unless there are features of another disease
- PGL may slowly regress during the course of HIV and may disappear before the onset of AIDS

### **2. Fever of Unknown Origin**

Defined as a recurrent or persistent fever (temperature  $> 38.0^{\circ}\text{C}$ ) with a duration of more than four weeks as the only clinical presentation in a patient with HIV infection.

#### **a. Differential diagnosis includes the following etiologies:**

- **Protozoal infection:** Malaria
- **Bacterial infection:** Pyogenic infections of the chest, CNS, urinary tract, etc  
  - Bacteremia due to Borreliosis, salmonella, streptococcus
  - pneumonia, H. influenzae
- **Mycobacterial infection:** Mycobacterium tuberculosis, atypical mycobacteria (MAC)
- **Fungal infection:** Systemic fungal infections (penicilliosis, cryptococcosis)
- **Viral infection:** Upper respiratory tract infections, cytomegalovirus, EBV, HIV infection itself

- **Malignancies:** Lymphomas
- **Other:** Drug reaction

b. Work-up:

- History taking
- Physical Examination
- Laboratory Evaluation (if appropriate and available):

- CBC
- Malaria smear
- Blood culture for bacteria
- Widal test for salmonella
- Typhoid serology
- Liver function tests
- Rheumatologic work-up: Rheumatoid Factor, ANF, ds DNA
- K39 for kala-azar
- Urinalysis
- Sputum AFB
- CSF examination
- India ink of CSF
- Skin scraping
- Tuberculin skin test (PPD)
- BM aspiration

- Radiologic Evaluation (if appropriate and available):

- Chest X-Ray
- Ultrasound

Question remains of what to do if patient is still febrile after empiric treatment. It may be a case of Mycobacterial Avium Complex.

#### **A. Bacteremia/Septicemia**

##### **a. Common etiological agents:**

- Pneumococcal
- meningococcal

##### **b. Clinical presentation:**

Fever (intermittent), chills at onset, pulse weak and rapid, skin eruptions (petechial or purpuric most common), headache, anorexia, vomiting, diarrhea, delirium, shock, hypotension, vascular collapse, renal failure, death

c. Recommended diagnostics:

- Urinalysis for albumin, erythrocytes, leukocytes
- Blood cultures for aerobic and anaerobic organisms
- Blood counts for anemia

Common findings:

- Urine may be positive for albumin, etc.
- Blood cultures may be positive
- Patient may be anemic

d. Management and treatment:

- Amoxicillin 500mg tid po and Gentamycin (3-5mg/kg day) IV
- Ciprofloxacin 750mg bid for 7 day
- Cetirizone 2gm IV qid
- Cotrimoxazole 1 DS tablet bid for 7 –14 days
- Supportive measures: Adequate nutrition and fluid intake maintain electrolyte balance with IV fluids
- Requires vigorous treatment, including hospitalization

## B. Fungal infections (histoplasmosis, penicilliosis, cryptococcosis)

a. Presenting symptoms and signs

- Fever, lymphadenopathy, often skin lesions or lung lesions

b. Diagnostics:

- Biopsy for histology and culture of skin lesions or lymph nodes often reveals the diagnosis

c. Management and Treatment

### Histoplasmosis and Penicilliosis

- Amphotericin B for moderate-to-severe cases
- Itraconazole is the preferred lifelong maintenance therapy
- If itraconazole is not available, use ketoconazole

### Cryptococcosis

- Amphotericin B (IV) for 14 days, then fluconazole for 8-10 weeks.
- After that, maintenance therapy with fluconazole

## 12. Sexually Transmitted Infections and Gynecological Manifestations of HIV Disease

### PURPOSE:

Participants will learn about the common gynecological problems associated with HIV including common etiologies, clinical features, management and treatment. In addition they will learn about sexually transmitted infections, including presentation in men who have sex with men.

### OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe common manifestations of gynecological problems and the various etiological agents that cause them.
2. Describe the clinical features of each infection.
3. Describe the treatment and management of gynecological problems and STIs
4. Describe the diagnosis and management of STIs in men who have sex with men.

### 1. Gynecological Problems and STIs

#### Introduction:

Gynecological problems are common among women living with HIV and may be the presenting sign of immunosuppression in women. HIV contributes to the frequency and severity of many gynecological infections, including vaginal candidiasis, herpes simplex, pelvic inflammatory disease and genital warts. Treatment for many of these infections is relatively inexpensive, but women living with HIV often require higher doses and longer courses of therapy; they may also suffer from more frequent recurrences.

#### A. Vaginal discharge

##### a. Etiology

- Gonococcal infection
- Chlamydia trachomatis
- Trichomonas vaginalis
- Bacterial vaginosis
- Candidiasis

##### b. Management and treatment

- General: Follow the country specific STI Case Management Guidelines. Ensure treatment of partners.
- Candidiasis: Patients often get recurrent attacks (even after treatment), and these may become persistent as the HIV disease worsens. If recurrence is very frequent, you may consider regular intermittent treatment.

#### Treatment includes:

- In reality there often will not be a specific diagnosis in the case of vaginal discharge.
- Without laboratory findings to guide:

- Vaginitis treatment should include:

- Tinidazole/Metronidazole

PLUS

- Fluconazole/Clotrimazole

- Cervicitis treatment should include:

- Azithromycin

PLUS

- Cefixime/Ceftriaxone

Note: Avoid fluconazole during pregnancy because of teratogenicity.

## **B. Lower abdominal pain and fever (Pelvic Inflammatory Disease- PID)**

### **a. Signs and Symptoms**

- Pain in lower abdomen- episodic or continuous
- Fever low or high grade
- Vaginal discharge
- Tenderness in lower abdomen
- Fever >38C

### **b. Etiology**

- Gonococcal infection
- Chlamydia trachomatis
- Anaerobic bacteria

### **c. Recommended Treatment**

- Outpatient Treatment (for mild or moderate PID):

- Cefixime 400mg single oral dose or Ceftriaxone 250mg IM single dose PLUS
  - Doxycycline 100mg bid for 14 days PLUS
  - Metronidazole 400mg tid for 14 days

Follow-up at 3-7 days or sooner, if necessary. Should be referred to hospital for admission, if condition does not improve.

- Inpatient PID Treatment (severe PID):

- Ceftriaxone 250mg IM daily or other third generation cephalosporin (IV only) PLUS
  - Doxycycline 100mg bid for 14 days PLUS
  - Metronidazole 400mg tid for 14 days

- Four "C's"

- Compliance

- Counseling/ Client Education
- Contact Tracing
- Condoms

- If STI is suspected to be the cause, follow the country specific STI Case Management Guidelines; ensure treatment of partners.

Exclude acute conditions (for example, appendicitis or ectopic pregnancy)

If patient does not respond to treatment, refer to exclude pelvic abscess or TB.

You may find huge pelvic abscesses in immunosuppressed patients following pelvic infection or surgical procedures.

Drainage and appropriate antibiotic therapy to cover aerobic and anaerobic organisms is necessary.

### **C. Genital sores (ulcers or blisters)**

#### **a. Etiology**

- Syphilis (*Treponema pallidum*)
- Genital herpes (*Herpes simplex virus*)
- Chancroid (*haemophilus ducreyi*)
- Granuloma inguinale (*Klebsiella granulomatis*)
- Mycobacterium TB

#### **b. Management and treatment**

- If an STI is suspected to be the cause, follow the country specific STI Case Management Guidelines; ensure treatment of partners.

#### **• Herpes simplex:**

Recurrent genital herpes ulcers are very common in patients with HIV; they tend to be more severe and may spread to buttocks and abdomen.

In late HIV disease, lesions become persistent, extensive and extremely painful.

#### **• Treatment:**

- Give supportive treatment: pain relief and gentian violet.
- First clinical episode-Acyclovir 200mg orally 5 times a day for 5 days
  - Note: in severe cases, you may need to extend treatment for 2-3 weeks.
- Recurrences: Acyclovir 200mg 5 times a day for 5 days
- For suppressive therapy of frequent outbreaks (>6/yr): Acyclovir 200mg bid continuously
  - for 6 months to one year
- In case of secondary infection, give antibiotics: cloxacillin 250 mg qid x 5 days

Note: Oral acyclovir is usually not used to prevent perinatal HSV transmission

#### **D. Genital warts**

##### **a. Etiology**

- *Condyloma acuminata*. This should be distinguished from:

i. *Condylomata lata* (from secondary syphilis)

ii. *Molluscum Contagiosum*

##### **b. Management and treatment**

- Tend to be more common and severe in persons with HIV

- Treat with:

- Topical podophyllin 10-25% in tincture of benzoin, applied carefully to warts. Wash off after 4 hours. Retreat at weekly intervals. Treat <10cm per session. Do not use in pregnancy.

OR

- Trichloracetic acid (30-50%): Applied to warts. Repeat at weekly intervals. Can be used in pregnancy.
- If caused by secondary syphilis, follow the country specific STI Case Management Guideline; ensure treatment of partners.
- Counsel on prevention of transmission to partner.

#### **E. Malignancies**

##### **Cervical cancer, CIN:**

Caused by Human Papilloma Virus (HPV): More HPV and more oncogenic strains of HPV in women with HIV. A continuum from dysplasia to invasive cancer

##### **a. Symptoms:**

- Often asymptomatic, vaginal discharge, vaginal bleeding, pelvic pain

##### **b. Diagnosis:**

- pap smear or visual inspection with acetic acid for screening, colposcopy and biopsy.

- Consider the diagnosis if resistant STI after empiric treatment

##### **c. Treatment:**

- Dysplasia can be treated with cryotherapy, LEEP excision or Cone biopsy, depending upon age and severity. Treatment for invasive cancer include Hysterectomy,

Chemotherapy, Radiotherapy

- If HIV positive patients have a severely compromised immunological status, they often do not respond well to cancer surgery, radiotherapy and chemotherapy.

- A vaccine to HPV, the most common underlying cause of cervical cancer is becoming available. This is ideally given to young women prior to first sexual intercourse to prevent primary HPV infection and hence future cervical cancer.

- Kaposi sarcoma- Can also be seen in genital area

## **F. Amenorrhea and intermenstrual bleeding**

### **a. Etiology**

- In general, HIV positive women with menstrual disturbances (such as oligomenorrhea menorrhagia) often suffer from chronic ill health.

- May be linked to general deterioration and weight loss due to HIV disease

### **b. Management and treatment**

- Exclude other causes such as pregnancy, perimenopause, uterine fibroid, genital tract infections, cervicitis, PID, TB and cancer.

- Menses and fertility may return after treatment of other infections, improvement in overall status from antiretroviral therapy and weight gain.

- Best management is to provide counseling and reassurance.

- If the woman is sexually active and not using an effective method of contraception consistently, do a pregnancy test.

- Counsel about potential return to fertility with weight gain.

- Consider individual reproductive goals and contraception.

## **2. Management of STIs among Male Sex Workers (MSW)/ Men who have sex with men**

### **(MSM) and Third Gender**

#### **A. Definitions**

- a. MSM may have receptive, insertive and /or oral sex. They might self-identify as heterosexual, bisexual or homosexual. Some may choose not to identify themselves as any of these sexual orientations. They might have a locally known identity.

- b. Third genders are men or women who feel different about their gender identities regardless of their biological sex. The risk of STIs (including HIV) is more in male to female third-genders.

- c. Characteristics of MSM/TG: Many MSM/TG has sex with the opposite sex. Common sexual practices include receptive and or insertive anal sex, receptive and or insertive oral sex, insertive vaginal sex, mutual masturbation.

- d. Some MSM/TGs also have other risks e.g., alcohol or drug use, needle sharing for drug use.

- e. MSM/TG has high rates of partner change and low rates of condom use.

f. Many infections remain unnoticed in this group. The primary syphilis chancre is painless. In the anal region it may not be reported. Gonococcal and chlamydial infections of the rectum are commonly asymptomatic.

**B. Laboratory tests for MSM/TG where microscopy is available.**

a. Screening for syphilis, gonococcus, HIV, Hepatitis B and Hepatitis C should be done after appropriate counseling and consent.

b. Specimens should be taken from rectum and urethra

**C. Treatment**

a. The drug treatments and duration to treat STIs are the same as in other people with STIs

b. On anoscopy, if there is macroscopic pus or if there are  $>5$  pmns/HPF on gram stain of rectal swabs treat MSM for both gonorrhea and chlamydia as above.

**D. Counseling**

a. Client counseling and education is needed

b. Emphasize condom use with water based lubricants during sex

c. Regular follow-up, partner notification (contact tracing), treatment and counseling are important risk reduction activities.

### **13. Ophthalmologic Manifestations of HIV**

**PURPOSE:**

In this session, participants will learn about common ophthalmologic disorders related to HIV, including common etiological agents, clinical presentation, recommended diagnostics and common findings, management and treatment.

**OBJECTIVES:**

By the end of this session, participants will be able to:

1. List some of the common ophthalmologic disorders related to HIV.

2. List the common HIV related etiological agents involved in ophthalmologic disorders and their clinical presentation.

**Introduction**

There are numerous ophthalmic manifestations of HIV infection. It is important to recognize OI involving the eye early so that appropriate therapy can be started.

Due to the potentially devastating and rapid course of retinal OI, it is suggested that all PLHIV should undergo routine ophthalmologic evaluations. Any HIV-infected person who experiences ocular symptoms also should be seen by an ophthalmologist. In patients with early-stage HIV disease (CD4 count  $>300$  cells/ $\mu$ L), ocular syndromes associated with immunosuppression are uncommon. Nonetheless, eye

infections associated with STIs such as herpes simplex virus, gonorrhea, and chlamydia may be more frequent in PLHIV; therefore, clinicians should screen for HIV in the presence of these infections.

### **Cytomegalovirus retinitis**

CMV retinitis is the most common retinal infection in patients with HIV, occurring in 15-40% of patients with advanced HIV. CMV is a DNA virus classified in the herpes group of viruses. CMV retinitis tends to occur usually once the CD4 cell count has fallen below 50 cells/ml. The combination of ART and effective anti-CMV drugs, has vastly improved the visual prognosis for patients with CMV retinitis, and has dramatically reduced the risk of developing bilateral blinding disease.

With the introduction of effective ART, the incidence of CMV retinitis has been noted to decrease by about 75 per cent. However, the incidence of CMV, especially new or recurrent CMV retinitis, remains high during the first few months of ART, consistent with the delay in immune recovery following initiation of ART. In patients with a history of CMV who subsequently receive ART, immune reconstitution may result in inflammatory retinal lesions, vitritis, or uveitis.

### **Clinical Presentation CMV Retinitis**

- Usually unilateral, but may be bilateral (up to 30 to 50 per cent of patients). Presents unilaterally and giving CMV treatment almost always prevents the onset of retinitis in the other eye
- Peripheral retinitis may be asymptomatic, or may present with floaters and peripheral visual field defects.
- Central retinal lesions or lesions impinging on the macula are associated with decreased visual acuity or central field defects.
- Painless
- Floaters are common

### **Diagnosis**

- It is uncommon to find CMV retinitis in HIV-infected patients with a CD4 count >40 cells/ $\mu$ L, and a CD4 count >50-100 cells/ $\mu$ L in an individual with retinitis should prompt a reconsideration of the diagnosis of CMV retinal infection.
- Retinitis: Creamy yellow-white opacified lesions, hemorrhagic retinal detachment.

### **Treatment**

#### **• Gancyclovir:**

- Induction dose: Gancyclovir IV 5 mg/kg 12 hourly x 14-21days
- Followed by:
- Maintenance: Gancyclovir IV 5 mg/kg/day
- Alternative maintenance: Valgancyclovir 900mg orally od

- Valgancyclovir is equally effective and is now the preferred treatment. It is more expensive, but reduced needs for hospitalization may off-set this cost.

- Dose is:

Valgancyclovir 900mg bid for 21 days then reduce to maintenance dose of 900mg od

- Drug interaction: Gancyclovir (or Valgancyclovir) and Zidovudine both can cause bone marrow suppression.

#### Small Group activity:

Divide into 2 groups. Using the information contained in the session each group should complete 2 rows of the matrix of other causes of eye complaints related to HIV (as indicated below). These should include: Name of disorder, clinical presentation, diagnosis, treatment, prognosis/other important facts. Information can be obtained from text that follows. See example of CMV Retinitis.

Groups should present these.

**Table 11: Ophthalmological manifestations**

Name of Disorder	Clinical Presentation	Diagnosis	Treatment	Prognosis/other important facts
CMV Retinitis	<p><b>Clinical Presentation</b></p> <p><b>CMV Retinitis</b></p> <ul style="list-style-type: none"> <li>• Usually unilateral, but may be bilateral.</li> <li>Asymptomatic, or may present with floaters, or peripheral visual field defects.</li> <li>• Central retinal or macular lesions associated with decreased visual acuity or central field defects.</li> <li>• Painless</li> </ul>	<p><b>Diagnosis</b></p> <ul style="list-style-type: none"> <li>• CD4 usually &lt;50.</li> <li>Almost always &lt;100</li> <li>• Retinitis: Creamy yellow white opacified lesions, haemorrhagic, retinal detachment.</li> <li>• Negative IgG Ab means CMV is unlikely. Patients with advanced immune-suppression might sero-revert to anti-body negative.</li> <li>• Positive IgG Ab is not diagnostic.</li> <li>Most PLHIV are positive without active infection</li> </ul>	<p><b>Treatment</b></p> <ul style="list-style-type: none"> <li>• Gancyclovir: Induction dose Gancyclovir IV 5 mg/kg 12 hourly x 14-21days</li> <li>• Followed by Maintenance Gancyclovir IV 5 mg/kg/day</li> <li>• Alternative maintenance Valgancyclovir 900mg orally od</li> <li>• Valgancyclovir is now preferred treatment.</li> <li>• Dose is: Valgancyclovir 900mg bid for 21 days then reduce to maintenance dose of 900mg od</li> <li>• Drug interaction:</li> </ul>	<ul style="list-style-type: none"> <li>• Treatment of unilateral disease almost always prevents the onset of retinitis in the other eye. Hence Preventing blindness.</li> <li>• Can have CMV retinitis Immune Reconstitution Inflammatory Syndrome (IRIS)</li> </ul>

Gancyclovir (or  
Valgancyclovir) and  
ZDV both can cause  
bone marrow  
suppression.

### **Herpes Zoster Ophthalmicus**

Herpes zoster ophthalmicus (HZO) is characterized by a vesiculobullous rash over the ophthalmic branch of the trigeminal nerve and may be associated with keratitis, conjunctivitis, blepharitis, and uveitis. HIV infection is associated with more severe corneal involvement and postherpetic neuralgia.

Acyclovir may diminish ocular sequelae of herpes zoster ophthalmicus. Adults with an acute, moderate to severe skin rash may receive acyclovir orally and bacitracin in ointment form for skin lesions. In the presence of uveitis, topical prednisolone and a cycloplegic should be applied. In cases of retinitis, choroiditis, or cranial nerve involvement, intravenous acyclovir and oral prednisone are indicated.

### **Herpes Simplex Keratitis**

Herpes simplex virus (HSV) can cause painful and often recurrent corneal ulcerations with a characteristic branching or dendritic pattern on slit lamp exam. HSV keratitis often is associated with corneal scarring and iritis, appears to require a prolonged course of treatment, and recurs frequently. Treatment consists of trifluorothymidine and cycloplegic drugs, with debridement of the ulcer using a cotton tip applicator. Oral acyclovir (400 mg twice daily for 1 year) decreases the risk of recurrent HSV keratitis by 50%.

## **Section – B: Anti retroviral (ARV) Treatment delivering Preparedness**

### **PURPOSE:**

Participants will learn about the preparedness of Anti-retroviral (ARV) treatment delivering which includes country preparedness, community preparedness, site preparedness and linkage and referral system among the HIV/AIDS clinical setting across the country.

### **OBJECTIVES:**

By the end of this session, participants will be able to:

1. Describe commitment, participation and national ART guideline in relation to country preparedness.
2. Explain importance of formative research in the community and stakeholders involvement including PLHA.
3. Describe in this section regarding ART centers, eligible criteria for setting up ART center, feasibility assessments for ART center and site preparedness (clinical, laboratory, pharmacy).
4. Describe the identification of organizations and facilities dealing with HIV/AIDS/PLHA, mapping of such organizations, consultation for setting up linkages and referral systems including procedures and schedules; and evolving formats for referrals and feedbacks.

## **Operational Aspects on Anti retroviral (ARV) Treatment**

### **Anti retroviral (ARV) Treatment delivering Preparedness**

1. Country Preparedness
2. Community Preparedness
3. Site Preparedness
4. Referral Systems and Linkages

#### **1. Country Preparedness**

- a. Commitment and participation
- b. National ART guidelines

##### **a. Commitment and participation**

In principle, government leaders should plan and commit to integrate ARV treatment into existing HIV services which would have great potential benefits for individuals, families and overall social and economic development. Leaders need to consider relevant questions before treatment could be introduced in a safe, effective and equitable manner facing the myriad challenges and complexities associated with treatment.

It is necessary to develop or review National ART policies and treatment guidelines, and select first- and second-line drug regimens, most appropriate to the local context. Another major task is defining the roles of donors, government authorities at all levels, and technical partners. It is essential to establish mechanisms (on Task forces, steering committees etc) to elicit and manage broad participation. The intent should be integration of treatment programs within national, provincial, district and municipal structures to increase the potential for sustainability of services.

#### **Steering Committee:**

The committee's role is to monitor overall implementation of ART program. The members must be from national, provincial, district and community stakeholders, as well as representatives from donor partners and the technical advisory partners. The committee addresses barriers to service provision and expansion, fosters a climate conducive to comprehensive care and support for PLHA, determines cost-sharing mechanisms and levels, ensures coordination and collaboration among stakeholders, monitors progress and makes recommendations to improve the program. The committee may meet twice annually, has a mix of medical and non-medical members.

#### **Scientific Committee:**

The committee's role is to establish and maintain a realistic framework for administering, monitoring and evaluating ART services. The members will be from Staff of Ministry of Health, NACP, the technical advisory partners and other agencies. Among its other responsibilities, it establishes quality assurance mechanisms, discusses health professionals on management of difficult cases, ensures effective and

appropriate use of data, and advises the Steering Committee, National ARV Task Force and Ministry of Health. The committee may meet quarterly.

#### **Operational Management Committee:**

The committee's role is to ensure open communication, clearly defined work plans and synchronized action to meet program objectives. The committee will review standard operating procedures (SOPs), clinical algorithms and other relevant guidelines, supervises health providers at their sites, identifies and responds immediately to problems, ensures a minimum standard for data management at health facilities, and updates the Steering and Scientific committees on program progress. The committee may meet as often as needed, but not less than monthly.

#### **b. National ART guidelines and drug selection:**

Care and treatment guidelines —including those relating to ART — generally reflect the knowledge and treatments available around the time of publication, and therefore require periodic review and updating.

Addressing different questions in relation to delivery of ART services is necessary early —when integrating ART into existing HIV care and support services. Delaying the process can delay procurement, which has grave implications for people with late-stage AIDS. It is best to select regimens based on scientific data, adapt from national guidelines and then undertake a process to register the most appropriate drugs for that setting.

### **2. Community Preparedness**

- a. Formative research in the community
- b. Stakeholder involvement, including PLHA
- a. **Formative research in the community**

Community institutions —local governments, traditional leadership, churches and mosques, schools, media etc— are tremendously influential in shaping attitudes and norms, including those related to treatment-seeking behavior. Many cultural traditions, beliefs and practices promote health and well-being, while others inhibit people from accessing the information, services and support they need to live healthy lives. In the context of HIV/AIDS, negative perceptions among family members, neighbors, health workers and others can lead PLHA to discontinue medical and psychosocial services or refuse to seek them. Where stigma and discrimination are pervasive, PLHA who are *clinically* eligible to participate in ART programs may find it difficult to visit a health facility regularly, be contacted at home or to disclose HIV-positive status to a relative or friend who can support adherence to medications. Thus, preparing communities for ART introduction was a key component of the programs, carried out concurrently with work at the national level. In addition to assessing and addressing stigma and discrimination, the programs should also educate communities about the benefits and limitations of ART, the challenges for involvement of Community

leaders, including representatives of PLHA groups, play an important role in formative assessments and planning activities, and join the steering committees formed to guide program implementation and monitoring and evaluation. Community groups continue to provide services that make safe & effective ART delivery possible.

There is an importance of community-specific information in designing, implementing and promoting HIV/AIDS services. There should be advocacy and sensitization activities, develop communication messages and improve services. Formative research will help program staff to understand issues related to service utilization, improve health worker-patient interaction, and design services that respond to the needs of users and the communities where they live.

#### **Stakeholder Involvement, Including PLHA**

Work with local stakeholders and community members, including PLHA groups, to design, support and evaluate clinic and community services.

Consideration of HIV as a chronic condition is a relatively new concept to most people in the target communities. As a result, rumors and misinformation about ART begin to circulate along with word of the planned programs. It is imperative that program staff gather local stakeholders — PLHA, district and municipal officials, traditional leaders, health workers, media and others — to discuss ART, explain the planned interventions, forge partnerships and develop plans for joint action.

Mobilizing community organizations, including PLHA groups, is an important step in ART planning and implementation. Their involvement helps correct misconceptions about ARV drugs — for example, that they are a treatment, not a cure — and help to reinforce overall HIV prevention, care and support messages in the community.

### **3. Site Preparedness**

- a. ART Centers
- b. Eligible criteria for setting up ART center
- c. Feasibility assessments for ART center
- d. Site preparedness (clinical, laboratory, pharmacy)

#### **a. ART Centers**

The main objective of Anti-retroviral Therapy (ART) is to provide comprehensive services to eligible persons with HIV/AIDS.

The *specific objectives* of an ART center are to:

- i. Identify eligible persons with HIV/AIDS requiring ART through laboratory services (HIV testing, CD4 Count and other required investigations)
- ii. Provide free ARV drugs to eligible persons with HIV/AIDS regularly without any interruptions

- iii. Provide counseling services before and during treatment for ensuring drug adherence
- iv. Provide treatment for prevention and treatment of opportunistic infections
- v. Educate persons and escorts on nutritional requirements, hygiene and measures to prevent transmission of infection
- vi. Refer patients requiring specialized services or admission.
- vii. Provide comprehensive package of services including condoms and prevention education

#### **Site selection for ART Centers**

ART sites will be selected based on strong government commitment to provide and sustain treatment, well-established national AIDS programs and the presence of ongoing prevention and care interventions. Government leaders will select the sites based on community need, existence of other HIV services (testing and counseling, preventive therapy and treatment for opportunistic infections, home-based care), capacity to deliver ART, level of infrastructure, and local willingness to participate in a treatment initiative. Subsequently, program staff and partners conducted in-depth assessments to begin preparing sites (clinics, laboratories, pharmacies) to deliver comprehensive HIV services, including treatment, in line with national and international guidelines.

#### **b. Eligibility criteria for setting-up ART center**

All countries should finalize the criteria to set up ART center according to country context.

The following criteria could be used to set-up ART centers in Public and Private organizations:

- i. High HIV/AIDS burden compared to other places
- ii. Availability of existing ART services in the vicinity (district, state, region/provinces)
- iii. Efficient Services provided with adequate human resources available in the site
- iv. Availability of adequate space for setting up ART center within the site area
- v. Willingness to assign minimum one faculty from Departments of Medicine and/or Microbiology to support ART center on a daily basis
- vi. Agreeing to follow NACP technical and operational guidelines prescribed by Government
- vii. Commitment to regularly furnish information on facilities, services and outcomes in prescribed formats to NACP

#### **c. Feasibility Assessment for ART centers**

A feasibility assessment team comprising of officers from Ministry of health, NACP and independent referees/ consultants would visit identified sites before sanctions are issued for setting up new ART centers. The team would assess feasibility on the basis of check-list on parameters related to ART services prepared according to country context.

**d. Site preparedness (clinical, laboratory, pharmacy)**

**Preparedness of ART Centers**

Once an ART center has been sanctioned, The ART team of 10 members consisting of faculty members from the Departments of Medicine, Pediatrics, Obstetrics & Gynecology and Dermatology is selected by the hospital /site headed by the in charge of ART center as the Nodal Officer. This is followed up by training of all team members, faculty members and other contractual staff appointed to the ART center.

**Location and Access to ART center**

The ART center should be located ideally in the Medicine OPD. If this is not feasible, the hospital in consultation with the NACP should choose a place within the same campus which is accessible to patients and keeping in mind cross-referral to and from various departments.

**Space for ART center**

It should have adequate number of rooms for the following services: examination room, counseling room, Pharmacy, Laboratory, Office Space and Waiting Area

**General equipment for ART center**

The ART center should be furnished adequately with general medical equipments. These equipments if inadequate can be procured from the grant provided for the ART center.

**CD 4 machines**

Each ART center should have access to CD4 tests either directly or by a clear linkage mechanism for conducting regular uninterrupted CD4 counts at a designated center. The center must follow the instructions on collection and transport of samples (and not patients) from testing site to the Identified site where the test is to be conducted. The reagents and other consumables needed for CD4 test would be procured by NACP and supplied to the centers. The machines should be utilized optimally to ensure that there is minimal waiting period for CD4 test.

All those patients who are screened for ART or are on ART will have their CD4 count done free of cost to a maximum of two tests per year (According to feasibility in country context).

**Human Resources**

The ART team should consist of trained faculty from the Department of Medicine and Departments commonly linked with care and support of PLHA (Microbiology, Obstetrics & Gynecology, Pediatrics, Dermatology and Venereology). In addition, the team should also have dedicated staff sanctioned for the ART centers and appointed through redeployment or on contractual basis. The appointment of contractual staff should be done by the steering committee in the institution. During the appointment of contractual staff, NACP representative should be invited as a special invitee.

A sense of ownership should prevail in the Department of Medicine of which the ART center is an integral part.

### **Pharmacy Services**

Take steps very early to ensure a secure, uninterrupted supply of ARV drugs.

Attention to drug procurement must come very early in the program and precede training and other program interventions. This is increasingly important as the lag time between ordering and receipt of product increases as pharmaceutical firms face exponential increases in ARV orders worldwide. To guarantee drug supply and avoid stock-outs, it is essential to define protocols for drug forecasting, ordering, dispensing and tracking at both the national and health-facility levels. Pharmacy staff requires training on ART, related protocols, functional record-keeping of drug procedures, and systems to minimize drug theft and diversion. Before an ART program begins, it is important to consider infrastructure needs, such as secure, air-conditioned storage space and confidential counseling areas. Records (bin cards, forms and patient records), labels and bottles/cartons are also essential to an effective pharmacy function. Involve pharmacy staff at the site and national levels in identifying system strengths and weaknesses.

### **ARV Drugs:**

All ART centers are provided with ARV drugs directly by NACP/Logistic Management. The number of patients for which drugs are supplied is estimated in consultation with the ART center concerned.

**Stavudine (d4T) is now recommended at the dose of 30 mg twice daily for all adult and adolescent patients regardless of body weight (A-III)**

Based on available evidence, the GDG has concluded that the 30 mg formulation of stavudine, dosed twice daily, should be used for all adult and adolescent patients, irrespective of body weight. (*GDG: Guideline Development Group*)

#### **Programmatic implications:**

- 1) All new patients with weight over 60 kg being prescribed a Stavudine - containing regimen should be started on d4T 30 mg only. No patients already receiving d4T 30 mg should be stopped up to d4T 40 mg
- 2) All patients receiving d4T 30 mg or 40mg with evidence of Stavudine related toxicity (even with no signs of treatment failure) should be moved to a non- Stavudine containing regimen, according to current WHO ART guidelines
- 3) All patients receiving d4T 40 mg without evidence of Stavudine toxicity should be moved to d4T 320 mg, as soon as possible, considering the programme feasibility.
- 4) Any new procurement orders of Stavudine in either single or fixed dose combinations should only include d4T 30 mg.
- 5) Any new procurement orders of d4T 40 mg in either single or fixed dose combinations should to the extent possible be cancelled and replaced with d4T 30 mg containing products.

### **Drugs for opportunistic infections (OIs):**

Requirement of different drugs used for prevention and treatment of Opportunistic Infections may vary from country to country. Bulk supplying all drugs may lead to expiry of uncommonly used drugs and shortage of more frequently used drugs. There should be adequate drugs supplied for management of OI's in ART centers along with ART drugs.

### **Linkages and Referrals**

Mechanisms for establishing linkages and referral systems are necessary to meet immediate and long-term needs of the persons enrolled in a comprehensive HIV care program. People living with HIV/AIDS (PLHA) would need a wide range of services through out their life span, which may be different during the course of HIV infection and stage of the disease.

These needs are related to:

- Physical health
- Psychological health
- Psycho-social health
- Nutritional status
- economic status and concern for financial stability/security
- Quality of life

Age and gender of the PLHA are also important as they are critical determinants of access to services. In the present health care delivery system, many of these services cannot be provided under one roof. There is, therefore, need to develop linkages and referral systems to take care of these needs.

Following steps would help in establishing linkages:

- Identification of organizations and facilities dealing with HIV/AIDS/PLHA
- Mapping of such organizations in the district/region;
- Consultation for setting up linkages and referral systems including procedures and schedules; and
- Evolving formats for referrals and feedbacks.

Looking at the various needs of the PLHA, linkages and referral system need to be set up with other departments within the institution where ART center is located and with service providers and organizations outside the institution.

A functional, formal referral system is an integral component of comprehensive HIV services. Such a system fosters communication and coordination between care and support services, both within health facilities and between health facilities and community support agencies/groups. Collaboration between services is essential to comprehensive care and support for PLHA. Primary services include: HIV testing and counseling, Prevention of Mother to Child Transmission (PMTCT), HIV clinical care, nutrition and food support; home-based care; palliative care; end-of-life care; psychosocial support, including PLHA groups, socioeconomic support and human rights and legal support.

Creating a directory of services available at health facilities and in the community is a first step in educating providers and patients. A standard referral note or slip for patients to present at the referred site is a valuable tool.

#### **4. Monitoring and Evaluation**

##### **PURPOSE**

To discuss record keeping, flow charts and organizational systems to provide services with a high standard of care in participant's local setting.

Regular **monitoring and supervision** of all activities carried out at all the ART centers (Government, Non-Government Sector) are important for monitoring effectiveness and quality of services. To facilitate a uniform and systematic monitoring, it is necessary to develop common monitoring tools and systems.

The standardized recording and reporting tools used for data collection and supervision includes:

<b>Care and Treatment Records</b>	
1.	Pre-ART Register
2	ART Enrollment Register
3	Patient Treatment Record
4	Patient ID Card
<b>Drug Dispensing and Stock Management Registers</b>	
5..	Antiretroviral Drug Stock Register
6	Antiretroviral Drug Dispensing Register
<b>Programme Performance Monitoring Reports</b>	
7.	Monthly ART Centre Report
8.	Quarterly ART Center Reports
9.	Cohort Analysis Report
<b>Supervision, Quality Assurance and Feedback Forms</b>	
10.	ART Treatment Centre Appraisal Form
11.	ART Centers Supervisory Checklist
12.	Summary Recommendations of Supervisory Visit

The National ART Programme should use a paper-based as well as computerized monitoring system consisting of registers, records and forms. The purpose of maintaining various registers and forms is to record relevant information in an easily retrievable manner and for different purposes.

**a. Reporting, Data Transmission and Analysis:**

Information from the prescribed records and registers is compiled and used in filling up various monitoring reports, which are forwarded to NACP. Monthly reports should be forwarded by 2<sup>nd</sup> working day of every month to NACP. It is intended to use electronic means of data recording and reporting.

**b. Increase in coverage of ART**

To ensure high coverage of eligible HIV infected adults and adolescents, who should receive ART, active identification of eligible patients and linkages with various facilities need to be established. To facilitate this task, following activities need to be organized in a systematic manner:

**Public Awareness**

There is evidence to show that level of general awareness towards HIV/AIDS has increased the health care seeking behaviour in the population. However, knowledge and utilization about various services available for prevention, counseling, testing, care and treatment is low in the communities. This has resulted in sub-optimal utilization of various services. It should publicize availability of services offered in details through various means of communication (TV, radio, Newspapers, and Brochures). Channels and newspapers should be selected based on the target audience and the coverage.

**4. Referral System and Linkages**

There is lack of adequate linkage and referral system between ART centers and other facilities. People found to be HIV+ should be referred to ART centers and if CD4 count is less than critical level, should be put on ART. There should be linkages between other relevant health facilities and ART centers.

# **PART - II**

## Module-II: Antiretroviral Treatment

### Section – A: ART in Adults and Adolescents

#### PURPOSE:

In this session, participants will learn about the goal of antiretroviral therapy (ART), management considerations and guidance on scaling up ART in resource-constrained settings. They will also learn about the drug mechanisms of the major anti-retro virals (ARV), including how and when to take them, their form, dosage and how to store them. They will learn the current thinking on why, how and when to start ART. They will discuss clinical evaluation, lab tests for initiation and monitoring purposes.

#### OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the goals of ART.
2. List key considerations in the management of chronic HIV illnesses in resource-constrained settings.
3. Explain the vast collateral benefits of ART, the obstacles for ART programs in resource-poor countries and the prerequisites for scaling up.
4. Discuss the prerequisites for scaling up, the pros and cons of ART and what comprises optimal ART.
5. Describe how the different classes of ARVs work.
6. Describe dosages and administration of ARVs.
7. Explain the rationale and timing for ART initiation, including the pros and cons of different approaches to this issue.
8. Describe the objectives of the clinical evaluation for ART.
9. Explain the country specific ART guidelines on when to initiate ART in adults.

#### 1. Goals and Principles of ART

##### 1. The goals of ART are to:

- a. Reduce the viral load as much as possible, for as long as possible, in order to halt disease progression and prevent or reduce resistant variants.
- b. Restore and preserve immune function. The body's defense system gets a chance to recover and less opportunistic infections occur.
- c. Reduce HIV-related morbidity and mortality.
- d. Improve the quality of life for PLHIV.
- e. Prevention of mother-to-child transmission.
- f. Post-exposure prophylaxis of HIV.

## **2. Benefits of ART**

- a. Prolongs and improves quality of life
- b. Increases HIV testing and uptake
- c. Increases motivation of health care workers, since they feel that they can do more
- d. Increases access to health facilities
- e. Decreases expenses for palliative and OI care
- f. Decreases number of orphans
- g. Keeps households and businesses intact
- h. Has the potential to enhance prevention
  - Behavioral: access to prevention education during care encounters
  - Biological: decreased transmission because of lowered viral load (including mother-to child)

## **3. Obstacles for ART programs in SAARC region**

- a. Inadequate infrastructure
- b. Inadequate laboratory monitoring (i.e., LFT unavailable in many settings, no resistance testing)
- c. Inadequate trained doctors and nurses
- d. Rapid staff turnover
- e. Stigma (amongst health care workers and in community)

## **4. Prerequisites for starting ART**

- a. Availability of adherence and counseling with follow-up services
- b. Medical services capable of managing common HIV-related infections including opportunistic infections and STIs.
- c. Routine laboratory services, preferable with access to CD4 lymphocyte count and PCR for viral load count. Lack of viral load testing and even CD4 testing should not preclude initiation of ART.
- d. Access to antiretroviral drugs and other drugs to treat OI and other associated diseases.

## **5. National ART Guideline**

Follow Country specific ART guideline for prescribing ART.

## **6. Optimal ART**

- a. Prolongs and improves quality of life
- b. Suppresses viral load and decreases chance for resistance
- c. Achieves immune reconstitution
- d. Preserves future therapeutic options
- e. Good side effect profile
- f. Good tolerability

g. Tailored to individual needs for adherence

h. Inexpensive

i. Minimum chance of drug interactions

## 2. Antiretroviral Drug Mechanisms

### 1. Antiretroviral therapies: Mode of action

a. The six groups of approved Antiretroviral drugs (ARVs):

- Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTI: divided into NsRTI and NtRTI)
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
- Strand Transfer Integrase Inhibitors (INSTI)
- Protease Inhibitors (PI)
- Fusion Inhibitors (FI)
- CCR5 Entry Inhibitors

b. The first four groups act on HIV by interfering with its reproductive cycle. The main stages of the cycle where these drugs act to inhibit replication of the virus are:

- Inhibit the reverse transcriptase enzyme to interrupt the production of proviral DNA. ARVs prevent the formation of proviral DNA. NRTI and NNRTI act here.
- Inhibit maturation of the virion by interrupting the protein processing and virus assembly.

During this stage protease enzymes are required.

c. Fusion and CCR5 Entry Inhibitors act by inhibiting fusion and entry of the virus with/into the target cells.

d. Nucleoside reverse transcriptase inhibitors (NRTIs):

- Lead to premature termination of the production of the HIV DNA chain;
- Are active against both HIV 1 and 2;
- Resistance develops rapidly if given solely as single drugs (monotherapy);
- Tenofovir (TDF) is the first nucleotide RTI with durable activity against some nucleoside resistant strains of HIV. It has a favorable safety profile. Tenofovir is a good choice if baseline levels of cholesterol or triglycerides are high. (Expensive)
- Do not use the following drugs together:

- AZT + d4T
- d4T + ddI (unless no other choice exists, due to high rates of toxicity)
- TDF + ddI

Table 11: Nucleoside reverse transcriptase inhibitors

Nucleoside reverse transcriptase inhibitors			
Acronym	Generic	Unit Dose	Daily Dose
AZT (ZDV)	Zidovudine	300 mg	1 pill twice a day
ddl	Didanosine	250 mg 400 mg	Wt < than 60 kg 250mg od Wt > than 60 kg 400mg od
d4T	Stavudine	30 mg	1 pill 30 mg twice a day (see below)
3TC	Lamivudine	150 mg	1 pill twice a day (Can give as 2 pills once day)
AZT + 3TC (combination tablet)	Zidovudine + Lamivudine	300mg/150mg	1 pill twice a day
ABC	Abacavir	300 mg	1 pill twice a day
D4T+3TC (combination tablet)	Stavudine + Lamivudine	30mg/150mg	1 pill twice a day
TDF	Tenofovir	300 mg	Once daily

e. Nonnucleoside reverse transcriptase inhibitors (NNRTIs):

- NNRTIs do not work in HIV-2 and HIV-1 group O infection.
- Rapid resistance will develop if NNRTIs are used as single agents.
- Interaction with some drugs occurs because of induction and/or inhibition of cytochrome P450 enzymes.

Table 12: Non-nucleoside reverse transcriptase inhibitors

Non-nucleoside reverse transcriptase inhibitors			
Acronym	Generic Name	Unit Dose	Daily Dose
NVP	Nevirapine	200 mg	1 pill once a day for the first 14 days After 14 days one pill twice a day
EFV	Efavirenz	600mg	1 pill once a day in the evening

f. Protease inhibitors (PIs)

- The HIV protease enzyme is responsible for cleaving various polyproteins in the process of producing mature infectious viroids. PIs interfere with the production of HIV protease enzyme; this leads to a reduction of the virus in the body.

- PIs are associated with multiple drug interactions because of their inhibition of cytochrome P450 enzymes. For example, PIs increase the metabolism of rifampicin and decrease its effectiveness in treating TB.
- Although not a recommended regimen, indinavir should be taken with plenty of water to prevent kidney stones.
- If a patient develops diabetes during PI treatment, it is best to stop the PI if there is an alternative.

**Table 13: Protease inhibitors**

Protease inhibitors			
Acronym	Generic Name	Unit Dose	Daily Dose
LPV/RTV Co-formulated combination	Lopinavir/Ritonavir	200mg LPV with / 50 mg RTV	2 pills twice daily
IDV/RTV*	Indinavir with Ritonavir boost	400 mg IDV 100 mg RTV	2 IDV pills 2 times daily Together with ritonavir 100mg twice daily
SQV /RTV	Saquinavir HG with Ritonavir boost	200 mg SQV / RTV 100mg	5 pills 2 times a day Together with ritonavir 100mg twice daily
ATV/RTV	Atazanavir with Ritonavir boost	(200 + 100mg tabs) ATV / RTV 100mg	300mg once daily Together with ritonavir 100mg once daily

**Administration and storage of ARVs:**

a. Take on an empty stomach—1h before or 2h after a meal

• Didanosine

b. Take with food

• Atazanavir/ritonavir

• Indinavir/ritonavir

c. Take with or without food

• Zidovudine

• Stavudine

• Lamivudine

• Nevirapine

• Efavirenz, but avoid taking with or after high fat meal

• Lopinavir/ritonavir

• Abacavir

• Saquinavir/ritonavir

d. Storage of ARVs in the refrigerator

- Ritonavir
- Didanosine suspension

**Short Role Play:**

Patient: You are HIV-positive and come to your provider asking for a refill of ARV medications. You obtained your medications from a family member abroad. Show the doctor/ nurse your medicines.

Doctor/Nurse: He/she shows you Zidovudine (ZDV) and Lamivudine (3TC) pills and says that is all he is taking.

- How do you counsel him?
- What do you say?

- Stavudine solution
- Lopinavir/ritonavir suspension
- e. Storage of ARVs in glass jars
- Zidovudine syrup and Stavudine syrup

**3. Why do we have to use the combination of 3 ARVs?**

Combination therapy makes sense for lots of reasons. Here are the most important ones:

- **It takes a lot of force to stop HIV.** HIV makes new copies of itself very rapidly. Every day, many new copies of HIV are made. Every day, many infected cells die. One drug, by itself, can slow down this fast rate of infection of cells. Two drugs can slow it down more, and three drugs together have a very powerful effect.
- **Anti -HIV drugs from different drug groups attack the virus in different ways.** Different ARVs attack HIV at different steps of the process of making copies of itself (first when entering the cell, and then when new copies want to leave the cell). Hitting two targets increases the chance of stopping HIV and protecting new cells from infection.
- **Combinations of anti -HIV drugs may overcome or delay resistance.** Resistance is the ability of HIV to change its structure in ways that make drugs less effective. HIV has to make only a single, small change to resist the effects of some drugs. For other drugs, HIV has to make several changes. When one drug is given by itself, sooner or later HIV makes the necessary changes to resist that drug. But if two drugs are given together, it takes longer for HIV to make the changes necessary for resistance. When three drugs are given together, it takes even longer.

The powerful combination of 3 different ARVs is called HAART: Highly Active Antiretroviral Therapy. This is the standard of good therapy, and has the greatest benefits for the longest time.

## WRITTEN EXERCISE:

Participants should complete this written exercise on their own unless time allows completion during the session. Answers should be distributed after completion.

1. Write the generic name of each of the drugs used in the first-line regimens, their abbreviation and the category of medication.
2. Write the generic name of each of the drugs used in second-line regimens and the category of medication.

### 3. When to start ART

#### a. When and how to start ART

- A patient needs ART only when he or she is symptomatic and/or there is evidence of significant immune system damage.
- *Do not start ART if:*
  - The patient is unmotivated
  - Without intensive counseling
  - If treatment cannot be continued
  - The patient is asymptomatic and no CD4 count is available
  - Laboratory monitoring is not possible
  - There is no ability to diagnose and treat OIs
  - In the presence of terminal incurable disease, serious clinical or psychosocial condition

#### b. Objectives of clinical evaluation before initiation of ART

##### a. Conduct a clinical evaluation to:

- Establish presence of HIV infection by means of:
  - History of possible exposure and pertinent medical and family history
  - Voluntary counseling and testing (results from patient seeking a test while not hospitalized or seeking clinical care)
  - Counseling and testing for diagnostic purposes
- Do a baseline clinical assessment and prepare the patient
- Psychosocial assessment
  - Psychosocial history
  - Essential demographic characteristics
  - Family economic status
  - Coping
  - Disclosure status

- Length of time since diagnosis of HIV infection, current medications and symptoms
- Baseline medical history
  - Past medical history including major illnesses (for example, TB), hospitalizations, surgeries,
  - past medications and allergies
  - For women, pregnancy history (gravida), current or planned pregnancy and access to family planning services
  - Review of systems (respiratory, cardiac, neurological, genitourinary etc...)
- Baseline physical exam:
  - Vital signs
  - Weight
  - Physical exam, documenting abnormalities:
    - General physical status including body weight and height
    - Eyes: fundoscopic exam, if possible
    - Oropharynx
    - Lymph nodes
    - Lungs
    - Heart
    - Abdomen
    - Extremities
    - Nervous system
    - Genital tract
    - Skin
- Establish status of HIV disease, for example, whether OIs are present and assign WHO Clinical Stage.
- Identify co-existing medical conditions and treatments that may influence the choice of therapy.
- Discuss and decide the need for ART.
- Determine when to start and what to use.
- Discuss adherence and other issues.

b. Obtain baseline laboratory tests including:

- TC, DC, Hb%, Platelets
- ALT/SGPT – If needed LFT (Liver function test)
- Serum creatinine – If needed kidney function test (Urea, Electrolytes)
- Blood sugar level
- Chest X ray

- Sputum for AFB
- Hepatitis B and Hepatitis C Serology
- Urine pregnancy test as indicated in female
- Urinalysis to assess for proteinuria
- CD4 cell count
- For women, cervical pap smear or other method of cervical cancer screening, if available.

c. In preparation for initiation, review:

- Expected benefits of the regimen
- Potential side effects of the regimen
- Possible drug interactions
- Partnership between patient and caregiver
- Lifelong commitment to treatment
- Need to maintain safe sex practices to prevent HIV transmission
- The critical importance of medication adherence!

Early treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level. The 2013 Guidelines Development Group recommends that national HIV programmes provide ART to all people with a confirmed HIV diagnosis with a CD4 count of 500 cells/mm<sup>3</sup> or less, giving priority to initiating ART among those with severe/advanced HIV disease (see Annex1) or a CD4 count of 350 cells/mm<sup>3</sup> or less. It is also recommended to initiate ART in people with active TB disease and HBV co-infection with severe liver disease, all pregnant and breastfeeding women with HIV, all children younger than five years living with HIV and all individuals with HIV in serodiscordant relationships, regardless of CD4 cell count (below table).

**Table 14: Summary of recommendations on when to start ART in adults, adolescents, pregnant and breastfeeding women and children**

Population	Recommendation
Adults and adolescents (≥10 years)	<p><b>Initiate ART if CD4 cell count ≤500 cells/mm<sup>3</sup></b></p> <ul style="list-style-type: none"> <li>• As a priority, initiate ART in all individuals with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm<sup>3</sup></li> </ul> <p><b>Initiate ART regardless of WHO clinical stage and CD4 cell count</b></p> <ul style="list-style-type: none"> <li>• Active TB disease</li> <li>• HBV coinfection with severe chronic liver disease</li> <li>• Pregnant and breastfeeding women with HIV</li> <li>• HIV-positive individual in a serodiscordant partnership (to reduce HIV transmission risk)</li> </ul>
Children	<b>Initiate ART if CD4 cell count ≤500 cells/mm<sup>3</sup></b>

<b>≥5 years old</b>	<ul style="list-style-type: none"> <li>• As a priority, initiate ART in all children with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count <math>\leq 350</math> cells/mm<math>^3</math></li> </ul>
	<ul style="list-style-type: none"> <li>Initiate ART regardless of CD4 cell count</li> <li>• WHO clinical stage 3 or 4</li> <li>• Active TB disease</li> </ul>
<b>Children 1-5 years old</b>	<ul style="list-style-type: none"> <li>Initiate ART in all regardless of WHO clinical stage and CD4 cell count</li> <li>• As a priority, initiate ART in all HIV-infected children 1-2 years old or with severe/advanced HIV disease (WHO clinical stage 3 or 4) or with CD4 count <math>\leq 750</math> cells/mm<math>^3</math> or <math>&lt;25\%</math>, whichever is lower</li> </ul>
<b>Infants &lt;1 year old</b>	Initiate ART in all infants regardless of WHO clinical stage and CD4 cell count

### When to start ART in adults and adolescents

#### New recommendations

- As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count  $\leq 350$  cells/mm $^3$  (*strong recommendation, moderate-quality evidence*).
- ART should be initiated in all individuals with HIV with a CD4 count  $>350$  cells and  $\leq 500$ /mm $^3$  regardless of WHO clinical stage (*strong recommendation, moderate-quality evidence*).<sup>a</sup>
- ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations:
  - Individuals with HIV and active TB disease (*strong recommendation, low-quality evidence*).
  - Individuals co-infected with HIV and HBV with evidence of severe chronic liver disease (*strong recommendation, low-quality evidence*).
  - Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (*strong recommendation, high-quality evidence*).
  - Pregnant and breastfeeding women with HIV.

a. *There is insufficient evidence and/or favorable risk-benefit profile to support initiating ART at a CD4 cell count  $>500$  cells/mm $^3$  or regardless of CD4 cell count or WHO clinical stage in the following situations: individuals with HIV older than 50 years, individuals with HIV-1 infected or co-infected with HIV-2, individuals with HIV co-infected with HCV and key populations with HIV with a high risk of transmission (such as people who inject drugs, men who have sex with men, transgender people and sex workers). ART*

initiation in these populations should therefore follow the same principles and recommendations as for other adults with HIV.

There is insufficient evidence and/or favorable risk-benefit profile to support initiating ART in everyone co-infected with HIV and HBV with a CD4 count  $>500$  cells/mm<sup>3</sup> or regardless of CD4 cell count or WHO clinical stage. Initiating ART regardless of CD4 count is therefore recommended among people with evidence of severe chronic liver disease, who are at greatest risk of progression and mortality from liver disease. For people without evidence of severe chronic liver disease, ART initiation should follow the same principles and recommendations as for other adults.

Table 15: Summary of when to initiate ART in adults and adolescents with HIV

Target population	Recommendation
Severe advance HIV infection	Initiate ART in all individuals regardless of CD4 cell count
HIV infection ( WHO clinical stage 1 or 2	Initiate ART if CD4 $\leq 500$ cells/mm <sup>3</sup> (CD4 $\leq 350$ cells/mm <sup>3</sup> as a priority)
TB disease	Initiate ART in all individuals with active TB disease regardless of CD4 cell count <i>(Unchanged from 2010 recommendations )</i>
Hepatitis B Co-infection	Initiate in all individuals with CD4 $\leq 500$ cells/mm <sup>3</sup> and regardless of CD4 cell count in the presence of severe chronic liver disease
HIV-serodiscordant couples	Provide ART to all partners infected with HIV regardless of CD4 cell count (to reduce the risk of HIV transmission to the negative partner) <i>(Existing 2012 recommendation)</i>

*TB treatment should be initiated first, followed by ART as soon as possible afterwards (and within the first eight weeks of initiating TB treatment). For those with a CD4 count less than 50 cells/mm<sup>3</sup> ART should be provided within two weeks of starting TB treatment*

*Severe chronic liver disease includes cirrhosis and end-stage liver disease and is categorized into compensated and decompensated stages. Decompensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy) or liver insufficiency (jaundice).*

## Background

Since 2002, WHO guidelines on ART have evolved as the body of evidence to support the earlier initiation of ART has progressively increased. The 2010 WHO guidelines for adults and adolescents recommended initiating ART for all individuals (including pregnant women) with a CD4 count  $\leq 350$  cells/mm<sup>3</sup> regardless of WHO clinical stage and for those with severe or advanced HIV disease (WHO clinical stages 3 or 4) regardless of CD4 count. This strong recommendation was based on moderate-quality evidence from randomized controlled trials and observational studies showing that initiating ART at or below this CD4 threshold reduced mortality, disease progression (including TB), vertical HIV transmission and serious adverse events. Mathematical modelling simulations also suggested that initiating ART earlier could impact on both sexual and vertical HIV transmission if there is high treatment coverage and full adherence. For people with active TB disease or HBV coinfection requiring HBV treatment, the 2010 guidelines recommended initiating ART regardless of CD4 cell count. Global ART coverage for those eligible according to the 2010 recommendations (CD4  $\leq 350$  cells/mm<sup>3</sup>) had reached 54% – or more than 8 million people – by the end of 2011, but coverage varies across regions, ranging from 15% to 68%. Only 9 low- and middle-income countries have reported coverage exceeding 80% and 68 countries have reported coverage of less than 50%. Nevertheless, policy changes in countries have been significant. A recent survey in 92 countries showed that more than 90% had adopted the CD4 threshold for initiating ART of 350 cells/mm<sup>3</sup> or less, and several other countries have moved their CD4 threshold above 350 cells/mm<sup>3</sup>. The median CD4 count at the time ART is initiated, although increasing, has been far lower than 350 cells/mm<sup>3</sup> in almost all settings, including high-income countries, and late presentation for treatment is associated with high early mortality rates and poor retention in care. Increasing knowledge of HIV status, strengthening links between testing and care and ensuring optimal long-term retention and adherence remain significant challenges in many settings.

## Rationale and supporting evidence

Since 2010, evidence and programmatic experience have continued to shift the risk benefit ratio towards initiating ART earlier. Increasing evidence also indicates that untreated HIV may be associated with the development of several non-AIDS-defining conditions (including cardiovascular disease, kidney disease, liver disease, several types of cancer and neurocognitive disorders) and that initiating ART earlier reduces such events and improves survival. Recent evidence also shows that ART substantially reduces sexual transmission in HIV-serodiscordant couples, but not all studies have reported survival benefits. At the same time, more convenient and less toxic regimens have become more widely available, and ARV costs have continued to fall. How early ART should be started is still debated, and the Guidelines Development Group

paid close attention to evaluating the potential benefits and harms to the individual and community in developing these new recommendations.

**Initiating ART in individuals with symptomatic and asymptomatic HIV disease at a CD4 count  $\leq 350$  cells/mm $^3$  as a priority**

The benefits of initiating ART are greatest among individuals with symptomatic HIV disease or those with lower CD4 counts. The 2013 Guidelines Development Group did not change the strength and quality of evidence for this recommendation established in the 2010 ART guidelines. Moderate-quality evidence from two randomized controlled trials and several observational studies shows that initiating ART at CD4  $\leq 350$  cells/mm $^3$  significantly reduces mortality, disease progression and the incidence of opportunistic diseases, especially TB and non-AIDS-defining conditions.

**Initiating ART at a CD4 count between 350 and 500 cells/mm $^3$**

The risk-benefit analysis of the rationale for ART initiation between 350 and 500 CD4 cells/mm $^3$  in these guidelines was debated. The Guidelines Development Group agreed that impact on HIV transmission is strongly supported by the evidence. The quality of evidence for clinical benefit of earlier ART initiation was rated as moderate using the GRADE system, as it mostly relies on observational data mainly from high-income countries. The Guidelines Development Group strongly recommended earlier ART as a public health approach. In settings where feasibility of implementation is a concern, the Guidelines Development Group suggested conducting operational research during implementation to assess context-specific factors such as feasibility, linkage to and retention in care, adherence and resource allocation.

The recommendation for initiating ART at CD4 counts between 350 and 500 cells/mm $^3$  is based on a systematic review with GRADE evidence profiles (Web Annex [www.who.int/hiv/pub/guidelines/arv2013/annexes](http://www.who.int/hiv/pub/guidelines/arv2013/annexes)) that assessed the quality and strength of the evidence from 21 observational studies and three randomized controlled trials reporting morbidity, mortality and immunological and virological outcomes.

They showed that initiating ART at a CD4 count  $> 350$  cells/mm $^3$  compared with treatment at a CD4 count  $\leq 350$  cells/mm $^3$  reduced the risk of progression to AIDS and/or death,

TB, development of a non-AIDS-defining illness and increased the likelihood of immune recovery. Although no studies suggest that earlier ART causes individual harm, these studies were of limited duration. The pooled analysis of the observational studies found a consistent decreased risk of death with earlier initiation of ART in 13 studies and a decreased risk of progression to AIDS or death in 9 studies and 3 randomized controlled trials, with a low level of heterogeneity, supporting moderate-quality evidence for earlier treatment. A further subgroup analysis showed a reduced risk of mortality with a CD4 threshold for initiating

ART of 500 cell/mm<sup>3</sup>. The impact on immune recovery was inconsistent and rated as low- to very-low-quality evidence.

Two studies found no significant difference in the likelihood of virological suppression (<500 copies/ml), risk of virological failure and viral rebound when treatment is initiated at higher or lower CD4 cell counts.

In the pooled analysis of two randomized controlled trials there was low-quality evidence supporting ART initiation at higher CD4 thresholds for reducing mortality, disease progression or the combined outcome of death and/or progression and, in one trial, the risk of non-AIDS-defining illnesses. The risk of severe adverse events did not differ significantly, but the risk of Grade 3 or 4 laboratory abnormalities<sup>ii</sup> was increased in one randomized controlled trial. Since treatment in the delayed arm of the SMART trial was initiated when the CD4 count fell below 250 cells/mm<sup>3</sup> (rather than 350 cells/mm<sup>3</sup>), the quality of the evidence for clinical benefit was graded as low because of imprecision and indirectness.

A separate systematic review identified one randomized clinical trial (18) and two observational studies reporting a decreased risk of TB when individuals initiated ART with CD4 counts exceeding 350 cells/mm<sup>3</sup>. ART also reduces recurrent TB by about 50%. Dynamic models have suggested ART initiation above 350 cells/mm<sup>3</sup> could lead to a more substantial reduction in population tuberculosis incidence.

Finally, there is high-quality evidence from one randomized controlled trial indicating that earlier ART can markedly reduce the risk of sexual transmission to HIV negative sexual partners. This is supported by the secondary outcomes of a trial that also found a 92% reduction in HIV sexual transmission from partners with HIV taking ART.

#### **Cost and cost-effectiveness**

The Guidelines Development Group reviewed mathematical simulations of the costs and epidemiological benefits of initiating ART at a CD4 count  $\leq$ 350 cells/mm<sup>3</sup>, CD4 count  $\leq$ 500 cells/mm<sup>3</sup> and for all adults with HIV regardless of CD4 cell count. These models suggest that expanding the ART eligibility criteria to  $\leq$ 500 cells/mm<sup>3</sup> could lead to substantial health benefits and be cost-effective in both generalized and concentrated epidemic settings; the increased cost of earlier ART would be partly offset by subsequent reduced costs (such as decreased hospitalization and increased productivity) and preventing new HIV infections. However, these benefits depend on a high testing uptake, high treatment coverage, sustained adherence and high rates of retention in care. The models also show that, because the greatest costs are associated with full implementation of the 2010 ART guidelines (initiating ART at CD4 count  $\leq$ 350 cells/mm<sup>3</sup>), the incremental cost of moving the ART initiation criterion from a CD4 count  $\leq$ 350 cells/mm<sup>3</sup> to  $\leq$ 500 cells/mm<sup>3</sup> is relatively small, especially if countries already have a substantial number of people with HIV with a CD4 cell count less than 350 cells/mm<sup>3</sup> already receiving ART.

These modeling findings support the recommendation to initiate ART in adults and adolescents with HIV with a CD4 count  $\leq 350$  cells/mm<sup>3</sup> as a priority. However, the cost implications at the regional and country levels should be explored further, since countries have different levels of treatment coverage and local cost considerations depending on their context and resources.

### **Potential harms**

Not all observational studies have consistently demonstrated the beneficial impact of initiating ART earlier on mortality and the incidence of non-AIDS events associated with chronic inflammation and ongoing viral replication, and longer follow-up is needed to evaluate potential harms and benefits. The long-term safety profile of ART and the implications of earlier initiation on drug resistance and toxicity will also need to be closely monitored.

### **Feasibility**

According to cohort and national programme data, the number of people needing treatment could increase by up to 25% if eligibility is based on CD4 counts increasing from  $\leq 350$  cells/mm<sup>3</sup> to  $\leq 500$  cells/mm<sup>3</sup> (Web Annex [www.who.int/hiv/pub/guidelines/arv2013/annexes](http://www.who.int/hiv/pub/guidelines/arv2013/annexes)). However, country experience has also shown that moving to a higher CD4 threshold for ART initiation may not necessarily lead to a significant immediate increase in the numbers of people who actually access treatment in the absence of increased uptake of HIV testing and counseling, stronger linkages to care, adequate treatment monitoring and sustained adherence support. Implementing the recommendation to initiate ART in individuals with HIV with CD4 counts between 350 and 500 cells/mm<sup>3</sup> may involve additional human, infrastructure and financial resources.

### **Initiating ART regardless of CD4 cell count**

#### *HIV-positive partners in HIV-serodiscordant couples*

The results of the HPTN052 study (18) strongly support the use of ART to prevent HIV transmission among HIV-serodiscordant couples. The Guidelines Development Group therefore endorsed the recommendations established in the 2012 WHO guidance on HIV testing and counselling including ART for treatment and prevention in serodiscordant couples that the sexual partner with HIV in such a couple should be offered ART regardless of CD4 count.

#### *Treating active TB disease*

In 2010, WHO recommended starting ART in all people with HIV and active TB regardless of CD4 cell count, and that TB treatment should be started first, followed by ART, as soon as possible afterwards (and within the first eight weeks). The Guidelines Development Group reviewed evidence from three randomized clinical trials that showed for people with TB and severe immunodeficiency (CD4 count  $\leq 50$  cells/mm<sup>3</sup>), starting ART before eight weeks has a clinical benefit compared with deferring treatment to later than eight

weeks, and endorsed the 2010 recommendations. Implementation of the recommendations on HIV and TB management may be facilitated by integration of services.

#### **HIV and HBV coinfection with evidence of severe chronic liver disease**

HIV co-infection affects almost every aspect of the natural history of HBV infection. The consequences include higher rates of chronicity; less spontaneous HBV clearance; accelerated liver fibrosis progression with increased risk of cirrhosis and hepatocellular carcinoma; higher liver-related mortality and decreased ARV response. Liver disease has emerged as a leading cause of death in people co-infected with HIV and HBV.

The 2010 WHO ART guidelines *recommended* initiating ART among all individuals co-infected with HIV and HBV who require treatment for their HBV infection (defined as chronic active hepatitis), regardless of CD4 cell count or WHO clinical stage. However, in the absence of routine screening for HBV, most people are unaware of their HBV status. In addition, there is limited access to costly diagnostic tools for staging liver disease (liver biopsy, transient elastography, HBV-DNA and serum biomarkers) needed to establish the presence of chronic active liver disease and eligibility for HBV treatment.

A meta-analysis *and* a subgroup analysis of a randomized controlled trial (60) provide low-quality evidence of the overall impact of ART on liver-related morbidity and mortality among individuals co-infected with HIV and HBV, but these studies did not examine the benefit of initiating ART at higher CD4 counts.

Overall, the Guidelines Development Group considered that there was not sufficient evidence and/or a favourable risk–benefit profile to support initiating ART among all people coinfected with HIV and HBV with a CD4 count >500 cells/mm<sup>3</sup> or regardless of CD4 count or stage of liver disease. There are also risks associated with initiating ART earlier (hepatotoxicity, immune reconstitution inflammatory syndrome and hepatic flares).

However, the Guidelines Development Group does recommend providing ART to all people coinfected with HIV and HBV regardless of CD4 count in people with evidence of severe chronic liver disease, who are at greatest risk of liver disease progression and mortality. The term severe chronic liver disease was used instead of chronic active hepatitis (as in the 2010 guidelines), as this is a term that is more widely understood and applicable using clinical criteria alone. In settings where ART cannot be provided to all individuals with HIV with CD4 counts ≤500 cells/mm<sup>3</sup>, giving priority to diagnosing and treating individuals coinfected with HIV and HBV should be considered.

As reported in the 2010 WHO ART guidelines (2), data from one randomized controlled trial support the use of at least two agents with activity against HBV (TDF + 3TC or FTC) in terms of improved viral load response and reduced development of HBV drug resistance. Active TB disease refers to TB infection where the person has symptoms and clinical disease. Latent TB infection refers to TB infection where the

person does not have symptoms or clinical disease. Not all persons with latent TB infection will develop TB disease, but the risk of progressing to disease is very high in people with HIV.

Severe chronic liver disease includes cirrhosis and end-stage liver disease and is categorized into compensated and decompensated stages. Decompensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy) or liver insufficiency (jaundice).

#### **Populations for which no specific new recommendation is made**

The Guidelines Development Group did not find evidence and/or favourable risk–benefit profiles to support recommendations for initiating ART at CD4 cell count  $>500$  cells/mm<sup>3</sup> or regardless of CD4 cell count or WHO clinical stage in the following populations.

##### *Individuals with HIV who are 50 years of age and older*

A pooled analysis of data from 13 cohorts from Europe and North America showed increased risk of death and disease progression in people with HIV older than 50 years of age.

However, these data were not stratified by CD4 cell count and do not support initiating ART at CD4 counts  $> 500$  cells/mm<sup>3</sup> for this group.

##### *Individuals with HIV-2*

The lack of randomized treatment studies in individuals with HIV-2 makes it difficult to determine the optimal timing of ART initiation in this population. A systematic review (Web Annex [www.who.int/hiv/pub/guidelines/arv2013/annexes](http://www.who.int/hiv/pub/guidelines/arv2013/annexes)) evaluated observational data from 15 studies and showed no significant differences between initiating ART at a CD4 count  $\leq 350$  cells/mm<sup>3</sup> and  $> 350$  cells/mm<sup>3</sup>, considering the outcomes of mortality, disease progression, increase in CD4 cell count, virological response and risk of drug resistance. The quality of evidence was rated as low to very low, with serious risk of bias and imprecision (few events) for all these outcomes.

##### *Individuals co-infected with HIV and HCV*

Observational studies have shown that co-infection with HIV and HCV accelerates HCV related progression of liver fibrosis and leads to a higher rate of end-stage liver disease and mortality. There is consistent but low-quality observational data about the overall benefit of ART on mortality and progression of liver disease in individuals coinfected with HIV and HCV based on evidence from a meta-analysis, and a review of nine cohort studies that examined the relationship between ART and hepatic fibrosis showing that ART was associated with a decreased rate of liver fibrosis progression, although this was not evaluated by the level of CD4 count (Web Annex [www.who.int/hiv/pub/guidelines/arv2013/annexes](http://www.who.int/hiv/pub/guidelines/arv2013/annexes)). The Guidelines Development Group endorsed the special note in the 2010 guidelines (2) that initiating ART among people co-infected with HCV should follow the same principles as in HIV no infection.

Initiating ART regardless of CD4 cell count was not recommended because of lack of evidence. There are challenges in diagnosing and treating active HCV infection in settings with limited access to HCV antibody and RNA assays, diagnostic tools for staging of liver disease (such as biopsy) and HCV therapy and in certain populations such as people who inject drugs. However, limited access to HCV testing or treatment and/or high rates of HCV infection should not be barriers to initiating ART.

WHO hepatitis guidelines forthcoming in 2014 will provide detailed guidance on HCV screening, treatment and care. People co-infected with HIV and HCV receiving ART and HCV drugs require close monitoring because of potential drug interactions and increased risk for drug toxicity between HCV drugs (such as interferon, ribavirin and newer directly acting agents) and ARV drugs.

#### *Key populations*

The scale-up of ARV drugs for preventing HIV infection or reducing HIV incidence in key populations has been evaluated in community-wide and ecological studies and mathematical models (67–79). Some of these studies showed a reduction in the community viral load, with and without an associated decline in HIV incidence, invariably where ART coverage is high or access to ART is expanding rapidly. However, the Guidelines Development Group concluded that there is insufficient evidence to recommend earlier initiation of ART in key populations regardless of CD4 cell count. The initiation of ART in key populations should follow the same general principles and recommendations as in other adults and adolescents with HIV.

#### **Key research gaps**

Further research is required to determine more fully the clinical benefits and disadvantages of earlier ART initiation. Two large randomized trials are examining the optimal timing for initiating ART, with results expected in 2014 to 2015. The Strategic Timing of Antiretroviral Therapy (START) trial in ARV-naïve adults aged 18 years and older is comparing immediate ART in those with CD4 cell counts above 500 cells/mm<sup>3</sup> to ART deferred until the CD4 count falls below 350 cells/mm<sup>3</sup> or an AIDS event develops. The TEMPRANO trial (Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis against Tuberculosis in HIV-infected Adults – ANRS 12136) is comparing the benefits and risks of initiating ART according to the 2010 WHO guidelines ( $\leq 350$  cells/mm<sup>3</sup>) to the benefits and risks of initiating ART immediately among adults with CD4 counts  $>350$  cells/mm<sup>3</sup> in Côte d'Ivoire. These studies will inform future WHO recommendations. Other research priorities include assessing the incidence of severe adverse events as a result of increased exposure to ART and assessing ART acceptability, uptake, adherence and long-term retention in care for people who initiate ART at higher CD4 counts, and the magnitude of the prevention benefit of immediately initiating ART in key populations.

**Exercise:**

1. An HIV-positive patient with chronic fever and a CD4 of 50 cells/mm<sup>3</sup> comes to your clinic. What will you do?
  - a. Assess the fever and then start ART.
  - b. Start ART now, because ART will act to decrease the fever.
  - c. No ART. Recheck the CD4 count in 6 months.
2. An HIV-positive patient has had a headache and fever for 1 week. His CD4 is 20 cells/mm<sup>3</sup>. What will you do?
  - a. Further work-up of the headache and fever and then start ART.
  - b. Start ART now without further work-up, because the ART will decrease the headache and fever.
  - c. Recheck the CD4 count in 6 months.
3. A patient has oral thrush and chronic diarrhoea. You gave them empirical treatment for the diarrhoea which resolved and clotrimazole for the oral thrush and it disappeared. The CD4 count of the patient is 100 cells/mm<sup>3</sup>. He has no other symptoms. What will you do?
  - a. Start ART now.
  - b. Observe the patient regularly, but don't start ART yet. Recheck CD4 in 6 months.
  - c. Start ART in 6 months.
4. A patient had Herpes Zoster on the left side of the chest last week. His CD4 count is 268 cells/mm<sup>3</sup>. He has no other symptoms, and the herpes lesions start to heal. What will you do?
  - a. Start ART.
  - b. Observe the patient regularly and give cotrimoxazole prophylaxis. Check CD4 in 6 months.
  - c. Start ART in 6 months.
5. An HIV-positive patient has been diagnosed with pulmonary TB. His CD4 is 450 cells/mm<sup>3</sup>. What will you do?
  - a. Start TB treatment now and start ART once the TB treatment is finished.
  - b. Start TB treatment now and start ART within the first 8 weeks of an  $\infty$ -tuberculosis treatment (ATT) initiation.
  - c. Start ART now, and treat TB after 6 months.
  - d. Start TB treatment now, and monitor CD4. Do not start ART.
6. An HIV-positive patient has had an itchy papular skin eruption, mainly on the arms and legs for several months. He has no other symptoms. You have no CD4 available. What will you do?
  - a. Start ART now.

- b. Don't start ART yet, but start cotrimoxazole prophylaxis.
- 7. An HIV-positive patient who has been treated for a chronic genital herpes simplex lesion present for over a month. The CD4 is 385/cells/mm<sup>3</sup>. What will you do?
  - a. Start ART now. This is Stage 4 so you need to start ART despite the high CD4 count.
  - b. Don't start ART yet, because he does not meet criteria until his CD4 count is lower.
- 8. A new patient comes to the clinic reporting that he is HIV-infected. He says that he needs to start ART right away. He tells you that he had a "brain infection" last year.
  - a. Start ART now.
  - b. Ask for written documentation of his HIV test and previous records. If not available, start with VCT and work-up as appropriate.
- 9. An HIV-positive patient recently finished treatment for oesophageal thrush. You start preparing for ART, and she tells you that she took ART when she was pregnant so she knows all about it.

You should:

- a. Ask for records documenting which ARVs she took, but start first-line ART anyway.
- b. Start second-line ART.

10. An HIV-positive patient has a CD4 count of 351 cells/mm<sup>3</sup> and sores at the corner of his lips. He also says that he has lost weight. He tells you that he knows he needs ART, because it helped him put on weight before. What will you do?

- a. Ask him why he stopped taking it before and get more of a history about the previous ART regimen. Get documentation including drug regimens and CD4 counts, if possible. Then restart ART with first-line drugs.
- b. Start ART today without previous documentation.
- c. Give him cotrimoxazole and tell him that he does not need ART yet.

#### **4. Which ARVs to use for First-Line Therapy, Patient Follow-up and Monitoring**

##### **PURPOSE:**

In this session participants will learn about the approved antiretroviral agents and the current Guidelines first-line regimen. Participants will also learn about clinical and laboratory monitoring of patients on ART. This session addresses clinical, laboratory and efficacy monitoring; schedules for monitoring; and measures of toxicity and effectiveness.

## **OBJECTIVES:**

By the end of this session, participants will be able to:

1. Identify the drugs to be included in first-line ARV regimens.
2. Understand clinical monitoring, including clinical and laboratory parameters to follow, barriers, specimen transport and personnel capacity.
3. Describe how to monitor for tolerability, efficacy, toxicity and resistance to ARV therapy

### **1. What therapy to begin with:**

- a. The only regimens potent enough to reduce viral replication drastically and to prevent the emergence of resistance and treatment failure for a significant amount of time involve a combination of at least three ARVs.
- b. There are currently 6 classes of ARV drugs for the treatment of HIV-1 infection (in the U.S.).

These include nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitor (FI), CCR5 entry inhibitors and integrase inhibitors (INSTI).

### **New classes of drugs:**

Fusion inhibitors (FI): Enfuvirtide

CCR5 Antagonists: Maraviroc

Integrase Strand Transfer Inhibitors (INSTI): Raltegravir

### **2. Which ARVs to start:**

**The choice of regimen depends on:**

- Cost of therapy
- Availability
- Affordability of drugs
- Convenience and likelihood of adherence
- Regimen potency, tolerability and adverse effect profile
- Possible drug interactions and potential for alternative treatment options in the event that the initial drug regimen fails.

Antiretroviral therapy with single or dual drug regimen is not recommended except for the prevention of mother to child transmission and post-exposure prophylaxis of HIV.

The combination of a 2 NRTI with either an NNRTI or a protease inhibitor is potent and causes durable suppression of viral replication. Combination of ritonavir with another PI results in a boosting effect by increasing plasma concentration of these drugs, thereby reducing their doses frequency and pill burden.

Currently several regimens with acceptable antiviral potency are available. These regimes are composed of three or four drugs. Two NRTIs generally form the backbone of most combinations.

Using simplified, less toxic and more convenient regimens as fixed-dose combinations is recommended for first-line ART. Once-daily regimens comprising a non-thymidine NRTI backbone (TDF + FTC or TDF + 3TC) and one NNRTI (EFV) are maintained as the preferred choices in adults, adolescents and children older than three years. For children younger than three years, a PI-based regimen is the preferred approach (Table 16).

**Table 16: First-line ART regimens for adults, adolescents, pregnant and breastfeeding women and children**

First-line ART	Preferred first-line regimens	Alternative first-line Regimens <sup>a b</sup>
<b>Adults (including pregnant and breastfeeding women and adults with TB and HBV co-infection)</b>		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
<b>Adolescents (10 to 19 years) <math>\geq 35</math> kg</b>	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP ABC + 3TC + EFV (or NVP)
<b>Children 3 years to less than 10 years and adolescents <math>&lt; 35</math> kg</b>	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP
<b>Children <math>&lt; 3</math> years</b>	ABC or AZT + 3TC + LPV/r	ABC + 3TC + NVP AZT + 3TC + NVP

<sup>a</sup> For adolescents, using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used and to the shortest time possible, with close monitoring. For children, d4T use should be restricted to the situations in which there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible.

<sup>b</sup> ABC or boosted PIs (ATV/r, DRV/r, LPV/r) can be used in special circumstances.

### 3. First-line ART for adults

#### New recommendations

- First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI)

- TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (*strong recommendation, moderate-quality evidence*).
- If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following options is recommended:
  - AZT + 3TC + EFV
  - AZT + 3TC + NVP
  - TDF + 3TC (or FTC) + NVP

*(Strong recommendation, moderate-quality evidence).*

- Countries should discontinue d4T use in first-line regimens because of its well recognized metabolic toxicities (*strong recommendation, moderate-quality evidence*).

**Table 17: Summary of first-line ART regimens for adults**

First-line ART for adults (including pregnant and breastfeeding women and people with TB and HBV co-infection)	
Preferred regimens	TDF + 3TC (or FTC) + EFV
Alternative regimens	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Special circumstances <sup>b</sup>	Regimens containing ABC, d4T <sup>a</sup> and boosted PIs

<sup>a</sup> Using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used. The duration of therapy with this drug should be limited to the shortest time possible and include close monitoring.

<sup>b</sup> Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons.

#### Other issues:

- With HIV-2 infections and Group O HIV-1 sub-type, only triple NRTI and PI-based regimens should be used because of the inherent resistance of those viruses to NNRTI compounds. A PI-based regimen is the preferred option.
- When to start with Tenofovir (TDF) instead of Zidovudine (ZDV):
  - ZDV is preferred in most cases.
  - TDF should be used in the case of anemia or if ZDV is otherwise not tolerated.
  - TDF does not require hemoglobin monitoring.
  - ZDV may cause nausea, headache, anemia and neutropenia.

- WHO has recommended that Stavudine (d4T) be "phased out" due to unacceptable rates of toxicity.
- Patients started on or switched to Stavudine (d4T) for anemia can switch to Zidovudine after 6-12 months of stable Hb above the threshold, to avoid d4T toxicities.
- Abacavir can be used in the place of Tenofovir.
- Some other considerations for NRTIs:
  - Do not combine "d-drugs" (ddl (didanosine), d4T).
  - Do not give single d-drugs with pre-existing polyneuropathy.
  - Do not combine 3TC and FTC.
  - Do not combine ddl and TDF unless no other options exist. The dose of ddl must be reduced.
- The choice between Nevirapine (NVP) and Efavirenz (EFV):
  - NVP and EFV are both potent NNRTIs.
  - The major toxicities associated with EFV are central nervous system (CNS)-related, metabolic toxicity, teratogenicity and rash. The CNS symptoms typically abate within the first month of therapy.
  - NVP has higher incidence of rash, which may be severe and life threatening. NVP has also a higher risk of hepatotoxicity.
  - In women with CD4 counts over 250 cells/mm<sup>3</sup> and men with CD4 over 400 cells/mm<sup>3</sup>, NVP should be avoided if possible. If no other options exist, close liver function monitoring is essential.

For most patients ZDV/3TC/NVP will be preferred first-line ART. If Hb is less than 7gm%, the regimen of choice should be TDF/3TC/NVP. EFV should be avoided in female patients in the first trimester of pregnancy or who are likely to be pregnant. In patients at high risk for certain side effects, an alternative drug should be used.

**Triple NRTI first-line regimens** (ie. ZDV+3TC+ABC or ZDV+3TC+TDF) can be used in specific circumstances where both NNRTIs are contraindicated or not tolerated. Other triple NRTI combinations should not be used.

These regimens can be used in the following circumstances:

- Intolerance or resistance to NNRTIs;
- Psychiatric disorders;
- Women starting ART with CD4 >250, since great risk of NVP toxicity.
- Pre-existing liver disease: ALT increased by more than 3-5 fold or established cirrhosis;
- Co-infection with HBV or HCV;
- HIV-2 infection due to intrinsic resistance to NNRTI class; and

- Co-treatment of TB in women of child-bearing age, where adequate contraception cannot be guaranteed, and when NVP and boosted PIs cannot be used.

ZDV+3TC+ABC is not as strong virologically as EFV-based ART. Other triple NRTI-based regimens, such as ZDV+TDF+ABC or TDF+3TC+ddl have unacceptably high virological failure rates and resistance rates and should not be used.

#### **Boosted PIs are usually reserved for second-line ART.**

Rarely, they can be used as part of first-line ART together with two NRTIs when triple NRTI regimen is not available or deemed inappropriate and when there are contraindications to NNRTIs (i.e. neither EFV nor NVP can be prescribed) including:

- Psychiatric disorders;
- ALT increased by more than 3–5 folds;
- Cirrhosis;
- Pregnancy with CD4 count of >350 or 250-350 with no liver function testing available, first trimester (EFV is contraindicated);
- Starting ART within 12 months of sd NVP or ZDV+NVP for PMTCT without NRTI tail
- HIV-2 infection.

Note: If a patient fails a first-line ART regimen containing a PI, there are very limited second-line options in SAARC region. A failing PI regimen has more resistance than a failing NNRTI regimen. In general therefore it is recommended that PIs be reserved for second-line ART.

#### **Women with previous PMTCT exposure to NVP or EFV, who now need life-long ART**

- Women may have taken single-dose NVP or NVP in combination with other ARVs during previous pregnancies. They also may have been on triple ARVs, which were discontinued after breastfeeding.
- Many of these women are at risk for NVP resistance.

#### **4. Follow-up and monitoring of patients on ART**

##### **Case**

A 35 year old man is starting ART today with a regimen of ZDV, 3TC and NVP. Based on the guidelines, answer the following questions:

How often does he need to come in for follow-up visits with the doctor?

How often does he need to come in for refills of ART?

How will we know if the drugs are working?

What do we hope will happen to his HIV-specific laboratory examination results?

When will his blood be taken and for what?

## **1. Monitoring ARV therapy**

### **a. Gather the following information:**

- Clinical symptoms
- Detailed past and present history
  - Other medical problems
  - Other drugs, including herbs and ayurvedic treatments
- Thorough and regular physical examination

### **b. Laboratory**

- Absolute minimum tests: HIV test, hemoglobin or hematocrit level, pregnancy test
- Basic tests: CD4 count, WBC count, liver function tests (LFTs) and renal function tests (RFTs), blood glucose, RPR, Hepatitis B and C serologies, urinalysis
- Desirable tests: amylase, bilirubin, lipids, cervical cancer screening for women, viral load
- Radiologic tests: X-ray of chest PA view

### **c. Efficacy**

Look for:

- Decrease in or disappearance of symptoms
- Gains in body weight
- Decrease in frequency or severity of OIs
- Improvement of skin manifestations
- Increase in WBC count
- Increase in CD4 count
- Sustained suppression of VL

### **d. How to monitor patients on ART**

For clinical and efficacy monitoring, it is very important to examine the patient at every visit.

The monitoring schedule should be as follows:

- First month: two visits (every two weeks)
- Second and Third month: every month
- Fourth month onwards: one visit every three months

More frequent visits will be scheduled, if the patient develops symptoms or experiences difficulties in adhering to the medications.

At each visit, ask about symptoms, adherence, HIV- and non-HIV-related problems and quality of life.

Perform physical examination including body weight at each visit.

**e. Laboratory monitoring for tolerance and toxicities of ART:**

• Frequency of blood chemistries

- □ ALT, LFTs, Hb, CBC as in chart below.
- For all patients taking tenofovir (TDF), creatinine and urinalysis for proteinuria must be performed at baseline and then every 6 months while on tenofovir.
- Others such as glucose, amylases and lipids, when clinically indicated as at least annually for those on protease inhibitor-containing regimens.

• Desired CD4 count and viral load changes during ART

- Viral load decline of 1.5-2.0 logs in first month
- Viral load decline to <50 copies/ml in 80-90 percent of patients at 24 weeks
- Median CD4 increase 100-200 in the first year
- Median CD4 increase 100 per year after that.
- In patients with severe immune deficiency, it is likely that the rate of increase will be slower.

• CD4 count

• CD4 count: at baseline and then every six months

• Viral load

- For a patient who is not responding to treatment a viral load test will be requested whenever feasible.
- If viral load testing becomes readily available, the ideal testing schedule would be: if virologic failure is suspected and every six months after starting ART.
- Additionally, infected babies under 12 months of age who were exposed to NVP during PMTCT prophylaxis should have viral load monitoring.
- Pregnant women on ART near term (36 weeks) who are considering an elective caesarean section should be offered viral load testing.

• Resistance testing

- Is not currently available in Nepal and is very expensive.
- Should be reserved for those failing second-line therapy or with limited or no ARV options.

• Pregnancy test for women on EFV

- Baseline (Mandatory)
- Follow-up (as indicated)

**2. HIV drug resistance**

- Refers to the reduced ability of a drug, or a combination of drugs, to block HIV reproduction in the body. Resistance occurs because of the changes (or mutations) in the genetic structure of HIV resulting from the

rapid and often inaccurate reproduction of new viral copies. The best way to avoid the development of drug resistance is to keep HIV under control. The less virus there is in the body, the less likely it is that the virus will reproduce and mutate.

- Factors that can prevent HIV medications from controlling the virus are poor treatment adherence, poor drug absorption and varying pharmacokinetics (the individualized absorption, distribution, metabolizing and removal of drugs from the body).

- **Testing for resistance**

There are two ways to test for HIV drug resistance:

1. Genotypic testing: identifies mutations that are linked to the reverse transcriptase and protease genes of a person's HIV. Most commonly performed resistance testing is genotyping.
2. Phenotypic testing: measures the growth of HIV in the presence of HIV drugs (similar to bacterial culture sensitivities). It is very expensive and there are long delays for results.

- **Weaknesses and drawbacks:**

- The tests measure only the dominant HIV strains that exist at the time of testing, not *minority* strains or strains that may be hiding in resting cells.
- The tests should be performed when the patient is taking ARVs and no later than four weeks from stopping treatment. Otherwise, the virus will likely have reverted to *wild type* and mutations will not show on testing.
- The tests are difficult to interpret and often present conflicting results, particularly in patients who have had multiple regime failures.
- The tests are expensive.
- The patient must have a viral load of  $>1,000$  for accurate resistance testing.
- Because of the cost, resistance testing should only be considered in PLHIV with proven virological failure on second-line ART or those who have no treatment options left (due to hypersensitivities or contraindications).

### **3. Drug level monitoring**

a. At present, therapeutic drug monitoring is infrequently performed outside research settings.

Since this is a new and investigative area of HIV management, it seems unlikely to become widely available very quickly.

b. High peak levels or high drug exposures with the following drugs are associated with toxicities:

- Ritonavir with triglyceride elevations, circumoral paraesthesia, diarrhea.
- Indinavir with kidney stones, renal colic and other urinary tract or kidney problems associated with indinavir crystals.

- Efavirenz with central nervous system toxicities such as vivid dreams, anxiety, excessive fatigue or seizures. High drug levels have not been clearly linked to other adverse effects of therapy.

c. Summary: drug levels

- Poor treatment adherence is a major cause of low drug levels.
- Interactions between drugs can influence drug levels.
- Some people's bodies eliminate drugs faster than others.
- Low drug levels in the blood may cause treatment to fail.
- With treatment failure there is concern of developing resistance.
- Higher drug levels may cause more severe and more frequent side effects.

## 5. ART drug interactions

Providers should be aware of all drugs that people with HIV are taking when ART is initiated and new drugs that are added during treatment maintenance. There are several key drug interactions (Web Annex [www.who.int/hiv/pub/guidelines/arv2013/annexes](http://www.who.int/hiv/pub/guidelines/arv2013/annexes)).

WHO TB treatment guidelines review key considerations for managing co-infection with TB and HIV. A key contraindicated drug combination includes rifampicin and PIs. When people co-infected with TB and HIV is receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r and SQV/r can be used for the duration of TB treatment, if the boosting dose of RTV is increased or double the standard dose of LPV/r is used. For children, using a triple NRTI regimen (such as AZT + 3TC + ABC) should also be considered.

Ribavirin and peginterferon alpha-2a are often used for treating HCV. Administration of these agents with AZT has been associated with an increased risk of anaemia and hepatic decompensation. People coinfected with HCV and HIV and receiving AZT may need to be switched to TDF. Itraconazole and ketoconazole are often used to treat fungal infections. Studies have shown that NVP may decrease the concentrations of these antifungal agents to subtherapeutic levels.

Alternative antifungal agents (such as fluconazole) could be used to ensure adequate treatment of fungal infections among people with HIV. WHO recommends artemisinin-based combination therapies for treating uncomplicated *Plasmodium falciparum* malaria (217). One recommended artemisinin-based combination therapy is artesunate and amodiaquine. EFV increases the concentrations of amodiaquine and has been associated with significant elevations of liver transaminases. Alternative artemisinin-based combination therapies (such as artemether plus lumefantrine, artesunate plus mefloquine or artesunate plus sulfadoxine-pyrimethamine) could be used to prevent severe toxicity in people with HIV.

WHO recommends methadone and buprenorphine for treating opioid dependence. Co-administering EFV decreases methadone concentrations. This could subsequently cause withdrawal symptoms and increase

the risk of relapse to opioid use. People receiving methadone and EFV should be monitored closely, and those experiencing opioid withdrawal may need to adjust their methadone dose.

ARV drugs have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. Limited data suggest potential drug interactions between many ARV drugs (especially some NNRTIs and RTV-boosted PIs) and estrogen-based hormonal contraceptives. These interactions may alter the safety and effectiveness of both the hormonal contraceptive and the ARV drug. If women receiving ART decide to initiate or continue using hormonal contraceptives, consistently using condoms and other contraceptive methods is recommended both to prevent HIV transmission and to compensate for any possible reduction in the effectiveness of the hormonal contraception.

Concomitant use of boosted PIs and NNRTI with some antihistamine agents (such as astemizole and terfenadine) has been associated with severe and life-threatening reactions, such as cardiac arrhythmia. Alternative antihistamine agents include loratadine and cetirizine. WHO recommends using statins for people with a 10-year cardiovascular risk exceeding 30%. Boosted PIs may lead to increased concentrations of lovastatin and simvastatin. Increased concentrations may increase the risk of developing serious adverse events such as myopathy (including rhabdomyolysis). Alternative dyslipidaemia agents should be used to prevent severe toxicity among people with HIV.

#### **Mechanisms:**

- Changes in drug absorption (eg. ddI alters gastric pH)
- Chelation (binding of 2 drugs to form a complex). i.e. multivitamins decrease Ciprofloxacin absorption)
- Changes in distribution
  - i. Protein binding (i.e. Giving EFV with warfarin can lead to increased bleeding)
  - ii. Hypoalbuminemia (i.e. Phenytoin toxicity if low albumin level)
- Changes in metabolism (ARVs induce or inhibit the cytochrome P450 system leading to increased or decreased levels of other drugs, including other ARVs)
- Changes in elimination (i.e.. probenecid inhibits renal tubular secretion and can increase levels of ZDV).
- Overlapping toxicities- Zidovudine should be avoided when Gancyclovir is given to high risk of severe myelosuppression (anemia, neutropenia, thrombocytopenia)

#### **Metabolism in the liver cytochrome P450 system**

- The induction or inhibition of various P450 enzymes by one drug can significantly alter the serum concentration of another drug that is metabolized by the same P450 enzyme.
- The PIs and NNRTIs are primarily metabolized by the same P450 CYP3A4 isoenzyme and can inhibit or induce this isoenzyme, resulting in increases or decreases in concentration of concomitantly administered drugs.

- Other drugs that inhibit or induce this isoenzyme can change the level of PIs and/or NNRTIs.

Each PI and NNRTI has a different drug interaction profile, depending primarily on its potency as an inducer or inhibitor of CYP3A4 and/or other P450 enzymes.

- Ritonavir is the most potent CYP3A4 inhibitor and consequently has the largest amount of drug interactions and contraindications.
- NVP is a CYP3A4 inducer.
- EFV is both an inducer and inhibitor of CYP3A4.
- LPV/r, EFV and NVP can significantly decrease the estrogen levels in contraceptives.
- Women taking these drugs should not rely on oral contraceptives and should use another or an additional method of contraception.
- Rifampicin is a potent inducer of hepatic metabolism and significantly decreases the concentration of PIs to sub-therapeutic levels.

**Table 18: Key ARV drug interactions and suggested management <sup>a</sup>**

ARV drug	Key interactions	Suggested management
AZT	Ribavirin and peg-interferon alfa-2a	First-line: substitute AZT with TDF Second-line: substitute AZT with d4T
Boosted PI (ATV/r, LPV/r)	Rifampicin	Substitute rifampicin with rifabutin Adjust the PI dose or substitute with three NRTIs (for children)
	Lovastatin and simvastatin	Use an alternative dyslipidaemia agent (for example pravastatin)
	Estrogen-based hormonal contraception	Use alternative or additional contraceptive methods
	Methadone and buprenorphine	Adjust methadone and buprenorphine doses as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	TDF	Monitor renal function
EFV	Amodiaquine	Use an alternative antimalarial agent
	Methadone	Adjust the methadone dose as appropriate
	Estrogen-based hormonal contraception	Use alternative or additional contraceptive methods
	Astemizole and terfenadine	Use an alternative anti-histamine agent
NVP	Rifampicin	Substitute NVP with EFV
	Itraconazole and ketoconazole	Use an alternative antifungal agent (for example fluconazole)

<sup>a</sup> This table was developed using the University of Liverpool's drug interaction charts, a resource which can be found online at [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org). A more comprehensive table of ARV drug interactions is available on the Web Annex ([www.who.int/hiv/pub/guidelines/arv2013/annexes](http://www.who.int/hiv/pub/guidelines/arv2013/annexes)).

## 6. Pediatric HIV Infection and when to start ART

### PURPOSE:

In this session, participants will understand the clinical presentation of HIV in children. Manifestations specific to pediatrics will be discussed. They will learn about necessary follow-up of exposed and infected children as well as the immunization schedule. A discussion on infant feeding will take place. Participants will also learn about the natural course of HIV disease in children, how it differs from adults, how to make a diagnosis, the WHO clinical classification system for diagnosis and classification and ART therapy for children.

### OBJECTIVES:

By the end of this session, the participants will be able to:

1. Understand how children with HIV may present differently than adults with more rapidly progressive disease.
2. List various clinical manifestations of HIV/AIDS in infants and children that differ from adults.
3. Describe the follow-up and immunizations needed by HIV-exposed and HIV-infected children.
4. Understand the best way to feed babies of HIV-infected mothers.
5. Describe when and how to provide ART.
6. Understand new pediatric HIV guidelines and their significance,
7. Understand first and second line ART Regimen for children.
8. Understand issues of drug preparations and availability for the pediatric setting.
9. Explain how to monitor response to ART in children.
10. Describe specific adherence challenges in children.

### A. How are children with HIV different from adults with HIV?

- Diagnosis in children <18 months is complicated by maternal antibodies. (See diagnosis session)
- Non-HIV infected young children have higher CD4 counts than adults until about 5 or 6 years.
- Perinatally-infected children have very high HIV RNA levels by 2 months which persist until 1 year.
- Children's immune system is more immature.
- Pediatric HIV can be rapidly progressing, so early diagnosis is essential.

### 3 Broad Categories of Presentation

#### Category 1: Rapid progressors (25-30%)

- Manifestations of HIV-infection occur in the first few months of life.

- OI and neurological manifestations are usual clinical features.
- Undergo a rapid downhill progression; untreated die within 1 year.
- Are thought to have acquired the infection in-utero or in the early perinatal period.

**Category 2: Intermediate progressors (50-60%)**

- Develop manifestations early in life.
- Failure to thrive, recurrent bacterial infections and lymphoid interstitial pneumonitis usual presentations.
- Downhill course with death by age 3-5 years.

**Category 3: Slow progressors (5-25%)**

- Long term survivors.
- These children reveal minor manifestations later in their childhood.
- Live beyond age 8 years.
- May have had late postnatal acquisition (breastfeeding).

**Clinical Presentations in Children with HIV**

**1. Common in Both HIV-positive and HIV-negative Children**

- Dermatologic conditions (scabies, tinea, warts, molluscum contagiosum, HSV)
- Ear/nose/throat conditions (otitis media)
- Gastrointestinal conditions (diarrhea)
- Pulmonary conditions (pneumonia)
- Tuberculosis (all children w/ TB should get HTC)
- Malnutrition

**2. Much more common in HIV-infected children:**

- Persistent or recurrent oral thrush
- Herpes zoster (shingles)
- Parotid enlargement
- Neurological dysfunction
- Persistent generalized dermatitis
- Recurrent severe bacterial infection
- Pneumonia, sepsis, meningitis
- Generalized lymphadenopathy
- Hepatosplenomegaly
- Lymphoma
- Persistent or recurrent fever

### **3. Specific for HIV Infection:**

- Esophageal candidiasis
- Pneumocystis jirovecii pneumonia (PCP)
- Lymphoid Interstitial Pneumonitis (LIP)
- Extrapulmonary cryptococcosis
- Toxoplasmosis
- Kaposi sarcoma

**High index of suspicion by clinician is important!**

**Alarming signs and symptoms: "Red flags"**

- Failure to thrive
- Persistent cough
- Prolonged fever
- Recurrent infections
- Lymphadenopathy
- Hepatosplenomegaly
- Oral thrush
- Persistent diarrhea
- Unusual infections

### **WHO Clinical Staging for Infants and Children with Established HIV Infection**

#### **Clinical Stage 1**

- Asymptomatic
- Persistent generalized lymphadenopathy

#### **Clinical Stage 2(i)**

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Recurrent oral ulceration
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
- Fungal nail infections

### **Clinical Stage 3(i)**

- Unexplained moderate malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhea (14 days or more)
- Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than 1 month)
- Persistent oral candidiasis (after first 6 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis/periodontitis
- Lymph node TB
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including bronchiectasis
- Unexplained anemia (<8.0 g/dl), neutropaenia (<0.5 × 10<sup>9</sup>/L3)  
or chronic thrombocytopenia (<50 × 10<sup>9</sup>/L3)

### **Clinical Stage 4(i) (ii)**

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration, or visceral at any site)
- Extrapulmonary TB
- Kaposi sarcoma
- Oesophageal candidiasis (or candida of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after the neonatal period)
- HIV encephalopathy
- Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month)
- Extrapulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacterial infection

- Cerebral or B-cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- HIV-associated cardiomyopathy or neuropathy

i) Unexplained refers to where the condition is not explained by other causes.

ii) Some additional specific conditions can also be included in regional classifications (e.g. Penicilliosis in Asia).

### How clinical presentation differs in children from adults

HIV often presents differently in children than in adults. Manifestations of HIV infection can be caused by immunosuppression or direct HIV viremia. Most children have a rapidly progressive or intermediately progressive disease course, with 75% mortality by 5 years old if untreated. Some clinical presentations are unique to children, many of which will be discussed below.

#### 1. General manifestation

##### a. Failure to Thrive

- Can be seen at any age
- Does not always mean losing weight
- Crosses two percentiles

Causes:

- Less food intake, anorexia, mouth ulcers, oral thrush
- Increased nutrient loss from malabsorption, diarrhea, HIV enteropathy
- Increased metabolic rate because of OIs and HIV infection itself.

##### b. Parotid enlargement

##### c. Generalized lymphadenitis

#### 2. Respiratory manifestation

##### a. Bacterial pneumonia

##### b. PCP

##### c. LIP

##### d. TB

##### e. Fungal pneumonia

##### f. Viral pneumonia

#### 3. GI manifestation

##### a. Diarrhea

##### b. Oral/ esophageal candidiasis

c. Hepatosplenomegaly

**4. Neurological**

a. HIV encephalopathy

b. Toxoplasma gondii

c. Cerebral TB

d. Cerebral malaria

**5. Others**

a. Lymphoma

b. Dermatological problems

c. Other manifestations

**Table 19: Differentiating LIP from miliary TB & PCP**

	LIP	Miliary TB	PCP
Age	Older	Any	Younger
Immunosuppression	Mild to advanced	Mild to severe	Severe
Clinical features	Chronic cough, no fever	Fever, cough, weight loss	Acute cough + tachypnea
X-ray findings	Persistent reticulonodular opacities +/- hilar LNE	Miliary mottling	Perihilar diffuse infiltrates
Response to Rx	No response to antibiotics or ATT	Responds to ATT	Responds to Cotrimox + Prednisolone

**B. Monitoring and follow up of HIV exposed and infected children**

**Table 20: Monitoring and Follow-up of HIV-exposed and infected children**

**Recommended schedule of follow-up visits for HIV-exposed and HIV infected children**

Birth	Infant feeding counseling
6 – 14 weeks of age	At 6, 10 and 14 weeks at the time of immunization (reinforce infant feeding counseling)
14 weeks to 1 year of age	Monthly
1 year of age and older	Every 3 months
18 months of age	Confirmatory HIV Antibody test
Child is sick	Any time

## **What to do at Each Pediatric HIV Visit**

- Establish Diagnosis (if not yet done)
- History and Physical Examination
- Growth Monitoring (Ht, Wt, HC)
- Developmental assessment
- WHO Staging
- Cotrimoxazole prophylaxis (needed?)
- Feeding counseling
- Immunizations
- Counseling on issues such as disclosure and adherence

### **1. Growth Monitoring**

- Growth failure is one of the first indicators of rapid progression of HIV.
- Growth monitoring can be the best tool for assessing risk of disease progression in HIV exposed or infected children.
- Weight for age is an indicator of short term growth and recent events.
- Height for age reflects long term growth.
- "Stunting" may indicate long term undernourishment.
- Height, weight, and head-circumference should be measured, recorded and plotted on a growth chart each visit.

### **2. Head Circumference**

- It is an early predictor of HIV-associated progressive encephalopathy in infants.
- Plot in standard head circumference-for-age charts.
- Is the rate of head growth normal?
- Is there micro or macrocephaly?
- If head size is abnormal or not growing at appropriate rate conduct full neurologic exam and consider causes.

### **3. Developmental Assessment**

- Failure to achieve or loss of previously achieved developmental milestones indicates progressive HIV disease with neurological involvement.
- Record the milestones of development at every visit. Observe the child and ask simple questions about the child's activities to assess the development.

### **4. Immunization Schedule for HIV-exposed or infected child**

**Table 21: Monitoring and Follow-up of HIV-exposed and infected children**

Age of infant	Vaccine
Birth	BCG
6 weeks	DPT1, HBV1, Hib 1, OPV1
10 weeks	DPT2, HBV2, Hib 2, OPV2
14 weeks	DPT3, HBV3, Hib 3, OPV3
6 months	Extra dose of Measles*
9 months	Measles

\* Because of the increased risk of early and severe measles infection, HIV-exposed infants who are not severely immunocompromised should receive an extra-dose of standard measles vaccine at 6 months of age with a second dose as soon after the age of 9 months as possible.

### Infant Feeding in the context of HIV infection

- ARV prophylaxis administered to the mother and infant reduces MTCT.
- 5 to 20% of infant's breastfed by HIV-infected mothers are at risk of acquiring HIV.
- Exclusive BF along with ARV can reduce transmission significantly.
- Infants of mothers on triple ARV prophylaxis should receive daily NVP from birth until 6 weeks of age.

#### 1. Exclusive breastfeeding is much safer than mixed feeding.

Exclusive Breastfeeding= Giving only breast milk (no water, food, other liquids)

Mixed Feeding= Giving breast milk plus anything else

#### Mixed Feeding vs Exclusive Breast-Feeding

- 4495 HIV +ve mothers
- 2060 live borns evaluated
  - PCR negative at 6 weeks
  - All initiated breastfeeding
- Early mixed breastfeeding (solids and breast milk substitutes)
  - 4.03, 3.79 and 2.60 times greater risk of converting to positive at 6, 12 and 18 months respectively
- Predominant breastfeeding (Non milk liquids)
  - 2.63, 2.69 and 1.61 times risk

#### 2. Formula feeding under 6 months is risky.

##### Risks of Formula Feeding

- Kenya (7 mo mortality) 11% FF vs 9% BF
- Botswana (7 mo mortality) 7.6% FF vs 3.7% EBF
- South Africa (3 month mortality) 15.1% FF vs 6.1% EBF
- Ivory Coast (urban): Equivalent 2 year health status in FF and EBF children. Increased diarrhea and respiratory infections in FF, but no increased hospitalization or death.

- In addition to other risk, mothers may "cheat" and breastfeed under economic or social pressure or when dealing with a crying hungry infant— hence mixed feeding.

### **3. Infant Feeding in the context of HIV infection**

- With exclusive breastfeeding, the risk of HIV transmission is low even in the absence of ARV prophylaxis.
- The risk is much higher for babies who receive other food or liquids in addition to breast milk before 6 months of age.
- Mixed feeding is when the baby receives other food or liquids in addition to breast milk before 6 months of age.
- Mixed feeding before or after 14 weeks nearly doubled transmission risk and the addition of solids increased the risk 11-fold in the absence of ARVs.
- The mortality by 3 months of age for replacement-fed babies is more than double that of those who were exclusively breastfed (15% vs 6%).
- This result adds to the accumulation of new evidence on the hazards of formula feeding.

#### **Infant Feeding Counseling**

Provide information and assistance on:

- What to do if problems occur (i.e. mastitis, infant oral thrush)
- Counseling on how to exclusively breastfeed and what to do if problems arise (i.e. not enough milk, diarrhea).
- When to wean to animal milk at 12 months
- How to wean
- How to prepare animal milk (clean hands, cup, boil milk)
- Complementary food after 6 months
- Where to access food support, if needed
- Need for maternal ARV prophylaxis during breastfeeding

#### **When to start ART in Children:**

##### **Indications for starting ART in HIV-infected infants/children**

###### **1. Indications for starting ART in HIV-Infected Children under 24 months of age**

- Treat all children who are DNA PCR positive, irrespective of clinical or immunological stage.
- Repeat virologic testing to confirm HIV status ASAP in babies under 18 months of age. This can be done with a repeat DNA-PCR or viral load (RNA-PCR) testing.
- ART initiation should not wait for the results of a confirmatory test, but rather be started as soon as possible, due to the aggressive nature of HIV in babies.

- Where DNA PCR is not available, ART needs should be based on presumptive clinical diagnosis of severe HIV disease.

#### **Presumptive Clinical Severe HIV Disease in Infants/Children <18 months**

**Criteria for presumptive clinical diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not available.**

A presumptive diagnosis of severe HIV disease in these situations should be made if:

- The infant is confirmed HIV antibody positive; and
- Diagnosis of any Clinical Stage 4 or AIDS-indicator condition(s) can be made; or
- The infant is symptomatic with two or more of the following:

- Oral thrush;
- Severe pneumonia;
- Severe sepsis.

Other factors that support the diagnosis of severe HIV disease in an HIV-seropositive infant include:

- Recent HIV-related maternal death; or Advanced HIV disease in the mother;
- CD4 <20%

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

Notes: It is unclear how often CD4 is lowered in the above conditions of HIV-uninfected children

#### **2. Indications for starting ART in HIV-Infected Children above 24 months of age**

Decision for ART initiation should be based on the following:

**Clinical status:** All children from 2 years of age and above in WHO Clinical Stage 3 or 4, irrespective of CD4 cell count.

#### **Immunological status (CD4 Absolute Counts / CD4 %)**

- Children between 2 and 5 yrs: CD4 count  $\leq$ 750 or %CD4  $\leq$ 25%, irrespective of WHO stage.
- Children  $>$  5 years with a CD4 count of  $\leq$ 350 irrespective of WHO stage.

#### **New recommendations**

- ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count
  - Infants diagnosed in the first year of life

*(Strong recommendation, moderate-quality evidence)*

- Children infected with HIV one year to less than five years of age

*(Conditional recommendation<sup>a</sup>, very low-quality evidence).*

- ART should be initiated in all HIV-infected children five years of age and older with CD4 cell count  $\leq 500$  cells/mm<sup>3</sup>, regardless of WHO clinical stage
  - CD4 count  $\leq 350$  cells/mm<sup>3</sup> (*strong recommendation, moderate-quality evidence*)
  - CD4 count between 350 and 500 cells/mm<sup>3</sup> (*conditional recommendation<sup>b</sup>, very-low-quality evidence*).
- ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count (*strong recommendation, moderate-quality evidence*).
- ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis<sup>c</sup> of HIV infection (*strong recommendation, low-quality evidence*).

<sup>a</sup> This recommendation is conditional because of the lack of evidence supporting earlier initiation in this age group, but this approach is expected to provide significant programmatic advantages in settings with limited access to immunological testing, high burden of paediatric HIV disease and low ART coverage among children, since simplifying eligibility criteria for initiating ART is likely to increase ART coverage in children infected with HIV and improve their health outcomes. Priority for ART initiation should be given to children younger than two years of age, regardless of WHO clinical stage or CD4 cell count, because of higher mortality risk, and to children between two and five years of age with advanced disease (WHO HIV clinical stages 3 and 4) or with CD4 count  $\leq 750$  cells/mm<sup>3</sup> or <25%, whichever is lower), regardless of WHO clinical stage (*strong recommendation, very low-quality evidence*).

<sup>b</sup> This recommendation is conditional because of the lack of evidence in this population for individual benefit as a result of initiating ART earlier; however, this approach is expected to provide significant programmatic advantages in settings with high coverage of paediatric ART and a programmatic need to align with ARV drug recommendations for adults. If this recommendation is not adopted, ART should be initiated at WHO HIV clinical stages 3 and 4 or with CD4 count  $\leq 350$  cells/mm<sup>3</sup> regardless of WHO clinical stage (*strong recommendation, very-low-quality evidence*).

<sup>c</sup> See Web Annex [www.who.int/hiv/pub/guidelines/arv2013/annexes](http://www.who.int/hiv/pub/guidelines/arv2013/annexes)

**Table 22: Summary: when to start ART in children**

Age	When you start
<b>Infants (&lt;1 year)</b>	Treat all individuals
<b>1 year to less than 5 years</b>	Treat all individuals (children $\leq$ 2 years or with WHO stage 3 or 4 or CD4 count $\leq$ 750 cells/mm $^3$ or $<25\%$ as a priority)
<b>5 years and above</b>	WHO stage 3 or 4 or CD4 $\leq$ 500 cells/mm $^3$ (CD4 $\leq$ 350 cells/mm $^3$ as a priority)

**Children with previous PMTCT exposure to NVP:** If a mother took ARVs during pregnancy, it is possible that the baby may become infected with a drug-resistant virus or acquire resistance due to drug exposure.

- Children starting ART before 2 years of age with previous NVP exposure from maternal or infant doses should start LPV/r as the third drug, if available.

**Breastfeeding exposure to maternal ART:** If a breastfeeding infant requires ART, the administration of ARVs at standard pediatric doses should be initiated regardless of whether the mother is receiving ART, with closer monitoring of the infant for potential toxicity to be considered. Extended breastfeeding should be encouraged because of its benefits in all infants known to be already HIV-infected.

#### **ARV drug preparations for children**

Ideal dosing is with suspensions or pediatric chewable/dissolvable tablets. If no suspensions are available, some adult tablets can be broken for children over 11 kg. Try to avoid breaking adult tablets more than by half.

#### **Practical issues with pediatric ARV formulations**

##### **• Zidovudine (ZDV or AZT)**

Take with or without food. Oral solution, tablets or capsules. Store at room temperature in a glass container. Large volume required.

##### **• Stavudine (d4T)**

Take with or without food. Oral solution or capsules. Oral solution must be refrigerated and stored in a glass bottle. Capsules can be opened and sprinkled over soft food.

##### **• Lamivudine (3TC)**

Taken with or without food. Oral solution or tablets. Tablets can be crushed and given with a small amount of water or food. Store at room temperature.

##### **• Abacavir (ABC)**

Taken with or without food. Oral solution or tablets. Tablets can be crushed. Store at room temperature.

- **Didanosine (ddI)**

Adults must take on an empty stomach 30 minutes before or 2 hours after a meal. Recent advice is that children can take ddI with or without food. Oral solution, tablets or enteric coated capsule. Oral solution: refrigerate and shake well. Tablets: must give two tablets to ensure buffering. Dissolve in water or chew. Enteric capsule: can be given once daily.

- **Lopinavir/Ritonavir**

Tablet or oral solution. Refrigerate suspension and give with food. Tablet formulation is twice daily. No food restrictions or refrigeration with tablet. Can use tablets in children 12 kg or more.

- **Nevirapine (NVP)**

Taken with or without food. Tablet or oral solution. Store at room temperature. Dose escalate by giving the dose once a day for first 14 days. If no rash or other side effects occur, increase to bid at 14 days.

- **Efavirenz (EFV)**

Taken with or without food (but avoid high fat meals). Store at room temperature. Capsules can be opened and sprinkled on food. Give once daily at bed time to reduce side effects.

- **Triomune Junior and Triomune Baby (d4T/3TC/NVP)**

Fixed dose combinations especially for small children. These can be started at 5 kg weight. Avoid splitting of adult pills. Avoid dispensing 3 different bottles of medicine. This is much easier for the family.

**Splitting Adult Fixed Dose Combinations for children:**

zidovudine+ lamivudine

zidovudine+ lamivudine+ nevirapine

stavudine+ lamivudine

stavudine + lamivudine+ nevirapine

Tablets can be stored at room temperature. May be taken with or without food. Advantage of lower pill burden. Cutting pills: Not ideal. Never cut to smaller than 1/2 pill. Use a pill cutter. Children may need extra Nevirapine, for correct dosing

**Reminders:**

- Pediatric ARV dosing and dispensing is NOT easy!
- Always consult the guidelines for the correct dosing.
- Adjust according to the dose combination and formulation.
- Have someone double check (doctor/paramedics).
- Change dose as child grows.
- Make sure that caretaker understands the regimen and doses (can get quite complicated sometimes combinations of pills and syrups)

- Always check for drug interactions before prescribing concomitant medications.

### **Children on ART: Monitoring and Follow-up**

#### **1. Monitoring response to ARV therapy**

In children, it is generally advisable to monitor clinical response as well as the CD4 count and percentage if available.

Clinical monitoring in children should include:

- Monitoring of weight and height gain, assessing using growth charts;
- Developmental milestones;
- Types and frequency of OIs.

Important clinical signs of ARV drug failure include:

- Lack of growth response to treatment;
- Falling off the growth curve in children who show an initial growth response to therapy;
- Loss of neuro-developmental milestones (regression);
- Recurrent oral thrush and other OI.

*With children who manifest with signs of drug failure it should be considered whether this is drug failure or another problem with a decision made regarding the need to switch to second-line regimens.*

#### **2. Manage side effects and new symptoms**

- Presentations of drug side effects could be different in children depending on their age.
- Young children may not complain of headache but they may become irritable because of pain, have poor feeding and reduce their activity.
- Children may not be able to locate abdominal pain or neuritis.
- Nightmares may be difficult to recognize in the young child.

Other than these differences, the side effects of ARV are similar to those of adults.

#### **3. Immune reconstitution syndrome (IRS)**

When children are put on ARV, similar to adults, they may respond with immune reconstitution syndrome in the first few (up to 12) weeks after ART initiation. Immune reconstitution syndrome in children may manifest with reactivation of extensive molluscum contagiosum, multiple abscesses, pyomyositis, tuberculosis, leprosy, etc.

#### **4. Adherence**

- Adherence is the cornerstone of successful ART in children.
- It is important that the child is involved depending on his/her age and maturity.
- Adherence can be especially challenging in children and adolescents.

- Disclosure of HIV status to child and others can be a difficult issue that must be dealt with as the child grows.

## ARV Treatment Failure in Children

## 1. Clinical Failure:

The appearance or reappearance of WHO Clinical Stage 3 or 4 events after at least 24 weeks on ART in a treatment-adherent child

## 2. Immunologic Failure

### **CD4 criteria suggesting immunological failure**

Immunological failure is recognized as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment adherent child:

- >2 years to <5 years of age CD4 count of <200 or %CD4 of <10%
- > 5 years of age CD4 count of <100

a. Preferably at least two CD4 measurements should be available

b. Use of CD4 % in children <5 years of age and absolute CD4 in those >5 years of age is preferred.

If serial CD4 values are available, the rate of decline should be taken into consideration.

### 3. Virologic Failure

- Virological failure is diagnosed with the use of viral load testing (HIV RNA levels).
- Where CD4 and clinical criteria for recognizing treatment failure are conflicting then viral load may be a useful adjuvant to guide decisions on the need to switch therapy.
- Use threshold of VL >5,000 copies/mL to define virologic failure in children.

**Table 23: Second-line Pediatric ART**

First Line NRTI	Second Line NRTI	Second Line Protease Inhibitor (PI)
ZDV or d4T + 3TC	Preferred ABC + 3TC Alternate ddI + ABC	LPV/r
ABC + 3TC	Preferred AZT + 3TC Alternative ddI + AZT	

- For difficult second-line regimen decisions consult an expert HIV clinician.
- Tenofovir in children: TDF has limited pediatric data and is not recommended due to concerns about bone toxicity and a lack of pediatric formulation. In 2010, TDF was approved for use in children 12 years of age and older. Consider using TDF in place of d4T for adolescents over 12 years of age.

## **7. HIV and Pregnancy: Prevention of Mother-to-Child Transmission, ART during Pregnancy and ART in Pregnant Women with Previous Exposure to NVP**

### **PURPOSE:**

This session discusses mother-to-child transmission (MTCT), including all four prongs. A discussion on family planning options will take place, as well as the factors that may increase transmission, measures that reduce MTCT and the use and ARV prophylaxis and ART as preventive measures.

### **OBJECTIVES:**

By the end of this session, the participants will be able to:

1. Describe the 4 Prongs of PMTCT.
2. Briefly discuss Prongs 1, 2 and 4.
3. Understand the effects of HIV on pregnancy.
4. Understand MTCT, factors that may increase transmission and measures that reduce transmission.
5. Describe how ART is used for the prevention of MTCT
6. Describe the drug regimens for life-long ART and those for triple ARV prophylaxis.
7. Also discuss about ART in Pregnant Women with Previous Exposure to NVP

#### **A. Introduction:**

HIV can influence reproductive health and be transmitted from mother to child. While asymptomatic, many women are unaware of their HIV infection. The woman may be blamed for bringing HIV into the family, especially if they are the first member to test positive. Women with AIDS may be less fertile, but starting ART often increases fertility. Providers need to be aware of possible unmet family planning needs for women initiating ART.

#### **Four-Pronged Strategy for PMTCT**

Prong 1	Prevent HIV infection in women of reproductive age;
Prong 2	Prevent unintended pregnancy in HIV-positive women;
Prong 3	Prevent mother-to-child transmission of HIV through: - ARV prophylaxis for mother and baby - Safer delivery practices - Safer infant feeding choices;
Prong 4	Provide care, treatment and support to HIV-infected parents, infants and families.

#### **Prong 1:**

Preventing HIV infection in the woman in the first place will ensure that none of her children are HIV infected through MTCT. Education, knowing the woman's HIV status, risk reduction with harm reduction referrals and condom promotion are all important components. Antenatal clinic (ANC) and labor room

counseling and testing are great opportunities to promote primary prevention for those found to be HIV-negative. Partner testing is a very important component, even if the woman tests negative. Finding a positive man and providing counseling on protecting his partner could save multiple lives.

**Prong 2:** Preventing unintended pregnancy in women with HIV has the potential to have a far greater impact than expensive prong 3 programs. However proper counseling on the safest ways to conceive are needed for PLHIV who wish to have more children.

**Prong 4:** Treatment, care and support for woman, child and family. Strong linkages to full comprehensive care are needed. All positive women should immediately be assessed for ART and cotrimoxazole needs. Baseline laboratory counts are needed. Exposed infants should be followed by the ART clinic until they are 18 months and test HIV-negative. Other children and partners should be offered HIV testing and HIV-specific care if found to be infected. Without Prong 4, we only prevent infections while creating orphans. In addition, most of the benefits of ANC and labor and delivery testing are lost if ongoing care and support services are not accessed.

Following points are related to Prong 4:

- Conduct clinical evaluation, staging and/or CD4 testing during pregnancy for ART eligibility, and family planning counseling during the postnatal period.
- Support for OI prophylaxis and treatment for the HIV-positive mother and baby.
- Support early infant diagnosis services to HIV-exposed babies using DBS technology.
- Follow up on infant feeding and nutrition.
- Follow up on immunization and birth registration.
- Identify all children affected by AIDS (CABA) in the household and link with CABA support services.

#### **Prong 2 HIV, ART and Family Planning Options**

Which of the following options are recommended for PLHIV (give details)?

- Condoms (Male or female)
- Oral contraceptives
- Injectable contraceptives (Progesterone only)
- Emergency contraception
- Intra-Uterine contraceptive devices (IUD)
- Male and Female Sterilization
- Lactational Amenorrhea Method

## B. HIV Infection and Pregnancy

### 1. Effects of HIV on pregnancy

- Some studies suggest that HIV may have an adverse affect on fertility in both symptomatic and asymptomatic women. Pregnancy rates are lower and fetal loss more common in those who are HIV infected. Others show that fertility is affected only in late HIV disease.
- Women with advanced AIDS may regain fertility once immune status improves through ART.
- When comparing changes in CD4 count/percentage over time, there is no difference between HIV-positive pregnant and non-pregnant women.
- HIV does not seem to be a significant cause of congenital abnormalities.
- Pregnancy does not accelerate disease progression in HIV infection.
- HIV disease may affect the outcome of pregnancy including poor fetal growth, pre-term delivery, low birth weight and prenatal and neonatal death.
- Common HIV-related problems are no different in pregnant and non-pregnant women, and both groups should receive the same management (except for drugs that are contraindicated or used with caution, like streptomycin and efavirenz).

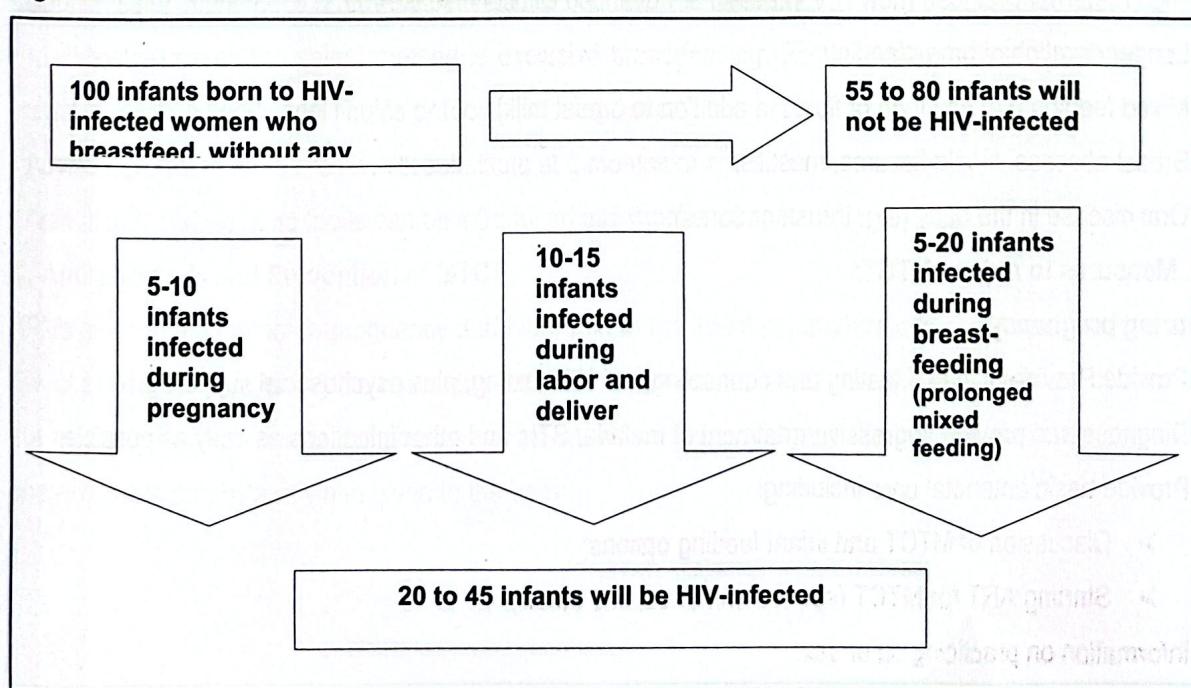
### 2. Mother-to-Child Transmission of HIV

#### a. Transmission

HIV may be transmitted to the infant during pregnancy, at the time of delivery, and through breastfeeding although most often transmission is thought to take place during delivery. Other routes of transmission have included the baby being given pre-chewed food by a PLHIV (few cases reported).

- Many studies indicate that the risk of breast milk transmission is higher in the first few months of life, with a subsequent tapering off of risk.
- HIV transmission is also higher if the mother has mastitis, cracked nipples or pediatric oral thrush is present.
- For mothers who acquire HIV postnatally, the risk of transmission is much higher.

Figure 20: HIV Outcomes of infants born to women infected with HIV



**b. Factors that increase the risk of transmission:**

**During pregnancy:**

- High maternal viral load: >5-10,000 copies/ml: VL is highest at the time of seroconversion and during late HIV disease;
- Low maternal CD4 cell counts: <100 cells/mm<sup>3</sup>;
- Recurrent STIs;
- Viral, bacterial or parasitic placental infection (e.g. malaria);
- Maternal malnutrition (indirect cause);

**During Labor and Delivery:**

- High maternal viral load (new HIV infection or advanced clinical disease);
- Rupture of membranes more than 4 hours before labour begins;
- Invasive delivery procedures that increase contact with mother's infected blood or body fluids (e.g. episiotomy, fetal scalp monitoring);
- First infant in a multiple birth;
- Chorioamnionitis (e.g. from untreated STI or other infection);
- Preterm delivery;
- Vaginal delivery;
- Placental disruption;
- Mechanical nasal suction after delivery;

**During Infant Feeding**

- High maternal viral load (new HIV infection or advanced clinical disease);
- Longer duration of breastfeeding;
- Mixed feeding (i.e. any food or fluids in addition to breast milk);
- Breast abscess, nipple fissures, mastitis;
- Oral disease in the baby (e.g. thrush or sores);

**c. Measures to reduce MTCT:**

**During pregnancy:**

- Provide Provider initiated testing and counseling and HIV testing, plus psychosocial support.
- Diagnose and provide aggressive treatment of malaria, STIs and other infections as early as possible.
- Provide basic antenatal care including:
  - Discussion of MTCT and infant feeding options;
  - Starting ART for MTCT (see recommendations below);
- Information on practicing safer sex.

### **During labor and delivery:**

- Delay the rupturing of membranes.
- Do only minimal digital examinations after rupture of membranes.
- Limit use of assisted delivery with forceps.
- Limit unnecessary episiotomies.
- Elective cesarean section is more protective against MTCT than vaginal delivery. It can reduce transmission by 50% if performed prior to labor onset or the rupture of membranes. Cesarean section should be considered if the client is not on ART or if viral load is unknown or greater than 1,000.
- Consider the benefits and risks of vaginal versus elective caesarean delivery.
- Take into account the surgical and anesthetic facilities, availability of safe blood for transfusion, standards of post-operative and neonatal care and attitude of the woman and her family.
- If not on ART, give ARV prophylaxis standard regimen as described below.
- If no ARV standard regimen is available and the client is not on ART, give single dose NVP according to the protocol as described below.
- If women who have not been tested during ANC present to the health system at the time of labor with unknown HIV status, it is recommended that the opt-out approach to testing be used during labor and that post-test counseling be provided after delivery.

### **After Delivery:**

- Avoid mechanical nasal suction.
- Clean the newborn immediately to remove all maternal secretions and blood.
- Support safer infant feeding (covered in detail in Pediatric HIV session).
- In almost all cases the safest method is exclusive breastfeeding. (Exclusive breastfeeding means only breast milk with no additional liquids or foods including water.)
- Advise rapid weaning to breast milk substitute at 6 months of age.
- Animal milk and weaning foods can be introduced at 6 months of age.

### **C. Antiretrovirals and Prevention of MTCT**

ARVs given to the mother in pregnancy and labor and to the infant postpartum can significantly reduce the risk of transmission including the risk of breastfeeding transmission. ARVs decrease the amount of virus in the mother's blood, lowering the chance her infant will be exposed to the virus. They also may serve as post-exposure prophylaxis when given to the baby.

#### New recommendations

- All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART  
(*strong recommendation, moderate-quality evidence*).
- For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment  
(*conditional recommendation, low-quality evidence*).
- In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased  
(*conditional recommendation, low-quality evidence*).

Table 25: Use of ARV medications in pregnancy:

AZT (ZDV) (Zidovudine)	<ul style="list-style-type: none"> <li>• Can cause anemia</li> <li>• Can cause nausea and vomiting</li> <li>• Longest safety record</li> <li>• Very effective at reducing MTCT</li> </ul>
NVP (Nevirapine)	<ul style="list-style-type: none"> <li>• Long half life protects the infant</li> <li>• Can cause hepatotoxicity in women with higher CD4</li> <li>• No hepatotoxicity, if she takes only one dose</li> <li>• Can cause viral resistance even after one dose</li> <li>• Very safe for baby</li> </ul>
3TC (Lamivudine)	<ul style="list-style-type: none"> <li>• Absorbed quickly</li> <li>• Very safe for baby</li> </ul>

Table 26: Programme options for ART for PMTCT

National PMTCT programme option	Pregnant and breastfeeding women with HIV	HIV-exposed infant	
Use lifelong ART for all pregnant and breastfeeding women ("Option B+")	Regardless of WHO clinical stage or CD4 cell count	Breastfeeding	Replacement feeding
	Initiate ART and maintain after delivery and cessation of breastfeeding	6 weeks of infant prophylaxis with once-daily NVP	4–6 weeks of infant prophylaxis with once-daily NVP (or twice-daily AZT)
Use lifelong ART only for pregnant and breastfeeding women eligible	Eligible for Treatment <sup>a</sup>		
	Initiate ART and maintain	Not eligible for Treatment <sup>a</sup>	Initiate ART and stop after delivery

for treatment ("Option B")	after delivery and cessation of breastfeeding <sup>b</sup>	and cessation of breastfeeding <sup>b c</sup>		
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<sup>a</sup> CD4 count  $\leq 500$  cells/mm<sup>3</sup> or clinical stage 3 or 4 disease at the time of ART initiation or in accordance with national guidelines.

<sup>b</sup> Patients who develop clinical or laboratory criteria indicating failure during pregnancy or the breastfeeding period should be assessed for second-line therapy.

<sup>c</sup> In the case of breastfeeding stop ART one week after breastfeeding ends. In the case of replacement feeding stop ART after delivery.

#### AVOID:

EFV during the first trimester: associated with severe fetal CNS birth defects

ddl and d4T: associated with lactic acidosis in pregnancy

#### All Women testing HIV-positive during pregnancy

- Need immediate full evaluation at ART clinic including history, WHO staging, cotrimoxazole assessment, CD4 count and baseline labs.
- Pregnant women eligible for ART:
  - Should start ART as soon as possible and stay on it for life.
- Pregnant Women not eligible for ART
  - Should start triple ARV prophylaxis at 14 weeks or when first seen (if after 14 weeks)

#### Special situation where mother is not able to access triple ARVs/ART

- For HIV-infected women delivering before initiating ART or triple ARVs and in settings where access to full PMTCT medications is not possible, single dose NVP can be given to the mother in labour. This is 200mg nevirapine one time only.
- Baby should then take NVP daily for 6 weeks.
- Mother should be referred for starting ARVs immediately for breastfeeding prophylaxis.
- Drug resistance of the HIV virus can develop when a single dose of NVP is given during labor so this is no longer the best option but rather an emergency response to try and decrease infant HIV infection.

#### D. HIV-infected women already on ART who become pregnant

- Continue ART. Stopping ART can lead to viral rebound and CD4 decline, risking the woman's health and increasing MTCT risk.
- ZDV can cause nausea, which may aggravate pregnancy-related nausea. If intolerable consider change to TDF.
- Efavirenz is teratogenic. It should only be used in the first trimester when the benefits outweigh risks. Efavirenz is safe and very effective in the second and third trimester of pregnancy. If pregnancy is discovered after 28

days of gestation (about 6 weeks after her last menstrual period (LMP)) the woman can continue with EFV as neural tube is closed at this point. If woman is less than 6 weeks since LMP, should change to an alternative third drug and stop EFV.

#### **Guidelines on Infant Feeding**

- Mothers should exclusively breastfeed until 6 months of age and continue breastfeeding until 12 months of age, with additional complimentary feeds at 6 months.
- ARV prophylaxis should be given while breastfeeding.
  - Triple ARVs should be given to mother from the antenatal period (starting from 14 weeks of gestation) until one week after cessation of breastfeeding.
  - The option of daily NVP dose for the baby must be available for mothers who are unable to take triple ARVs yet continue breastfeeding (i.e. poor maternal adherence to ARVs) If replacement feeding, give daily NVP to the infant from birth until 6 weeks of age.

**E. NVP in women with CD4 count of 200–350 cells/mm<sup>3</sup>:** There are data to show that women with a CD4 count of >250 cells/mm<sup>3</sup> face a higher risk of severe hepatotoxicity when they are started on an NVP-based regimen. This happens most often in the first 6–12 weeks of therapy. It is recommended that such women should undergo the following:

- Close observation over the first 12 weeks of therapy (every 2 weeks).
- Baseline and regular monitoring of liver enzymes (at baseline and at 2, 4, 8 and 12 weeks, followed by symptom-directed evaluation).
- Patient education to encourage them to return if there are problems such as rash, abdominal pain, jaundice and fever.

If the liver enzymes increase to grade 3 or higher (ALT and/or AST >5.1 times the upper normal limit) without an alternative explanation, NVP should be permanently discontinued. If symptoms suggesting hepatic toxicity, including rash, develop in pregnant women, NVP should be discontinued immediately.

For those with anaemia during pregnancy, the problem should be managed by conservative methods, such as giving ferrous folate, other oral preparations and blood transfusion (if required).

The preferred NRTIs for use in pregnant women are AZT and 3TC. The combination of ddI and d4T should not be used because of associated increased toxicities in pregnant women. Studies have shown that TDF is associated with decreased foetal growth and bone demineralization.

The preferred NNRTI is NVP, with which there has been extensive clinical experience globally. Its efficacy in reducing mother-to-child transmission has been proven. SQV/r and Nelfinavir (NLF) are the preferred PIs if the woman needs to take PIs. EFV may be considered after the first trimester.

**Small Group Exercise:**

1. A 22-year-old woman presents to ANC. She is HIV-positive but is very surprised as she feels very healthy and has not suffered any illness. The physical examination is normal and she is 4 months pregnant. You assess her and conclude that she is in WHO clinical stage 1 with a CD4 count of 380.

What type of intervention(s) does this woman need?

2. A 25-year-old HIV positive woman is 5 months pregnant. She is thin and she has just started TB treatment for smear-positive pulmonary TB. She also had oral thrush 2 weeks ago.

What will you do?

3. A 26-year old HIV-positive woman is 3 months pregnant. She feels fine and has no problems. On one side of the trunk, you see scars from herpes zoster.

What will you do?

4. 34-year-old woman has been taking ART for 2 years. She tolerates the therapy and is adherent. Her weight has increased and she has not had any serious OIs lately. She was in stage 4 when she started ART. Her regimen is d4T/3TC/NVP. She is now pregnant in her first trimester.

What will you do?

5. A woman is taking AZT-3TC-EFV. When she previously took AZT-3TC-NVP she had to interrupt it due to a severe rash on NVP. Now she comes to the health centre and tells you she is pregnant in her first trimester. When she started ART she was in stage 4, but now she feels fine.

What will you do?

6. A young woman is 10 weeks pregnant and has lymph node TB and HIV. Her CD4 is 400 cells/mm<sup>3</sup>. You know that she needs ART as she has TB, regardless of CD4 count. You realize that the baby will benefit from ART as soon as possible. What ART regimen should you give her, especially with such a high CD4 count.

**Section – B: Management of Opportunistic Infections before starting ART**

1. TB/HIV Co-infection (TB Infection Prevention, Active Case Finding, and Isoniazid Preventive Therapy)

**PURPOSE:**

In this session, participants will learn about the management of TB in an HIV patient. Recommendations for ART in co-infected client will be discussed. In addition, TB prevention by prevention of transmission and Isoniazid Preventive Therapy (IPT) will be discussed.

**OBJECTIVES:**

By the end of this session, participants will be able to:

1. Describe the relationship and interaction between TB and HIV co-infection.
2. Understand the management and treatment of people with TB and HIV co-infection in relation to ART.
3. Understand activities for prevention of TB transmission including intensive case finding.
4. Describe infection prevention.
5. Describe Isoniazid Preventive Therapy.

## Background

Among people living with HIV, TB is the most frequent life-threatening opportunistic infection and a leading cause of death. ART should be provided to all people with HIV with active TB disease. HIV care settings should implement the WHO *Three I's* strategy: intensified TB case-finding, isoniazid preventive therapy (IPT) and infection control at all clinical encounters.

### A: Tuberculosis: HIV-TB interaction and co-infection

#### Overview:

- TB is the most common cause of death in people with HIV worldwide.
- HIV infection increases the likelihood that new infection with *M. tuberculosis* (due to immune suppression) will progress rapidly to TB disease.
- HIV is the most potent factor known to increase the risk of progression from *M. tuberculosis* infection to disease.
- Among HIV-infected individuals, life time risk of developing active TB is 50 percent, compared to 5-10 percent in persons who are not HIV-infected.
- In a person infected with HIV, the presence of other infections, including TB, allows HIV to multiply more quickly. This may result in a more rapid progression of HIV infection.
- HIV-related TB can present typical or atypical clinical and/or radiological features. Atypical features are usually found in HIV-infected individuals with severe immunosuppression.
- Initial signs of TB disease may become apparent at any time during the evolution of HIV infection.
- May be pulmonary or extra-pulmonary.

### B. Antiretroviral therapy for individuals with tuberculosis co-infection

#### 1. Strategy for initiation of treatment for both TB and HIV infection

1. Start ART in all PLHIV with active TB, irrespective of CD4 count.
2. Start TB treatment first, followed by ART as soon as possible thereafter, but between 2 and 8 weeks.
3. Use Efavirenz as preferred NNRTI in TB-HIV co-infection

## **2. ART drug choice in TB co-infection:**

- The first-line treatment options are ZDV/3TC or TDF/3TC plus Efavirenz (600mg once daily).
- Dose increases of Efavirenz are no longer recommended during ATT.
- The first alternative is ZDV/3TC plus Abacavir.
- The second alternative is ZDV/3TC or TDF/3TC plus nevirapine for those unable to take EFV or ABC.
- Rifampicin decreases nevirapine levels by hepatic induction, which potentially could lead to lower ART efficacy. There are also concerns of additive liver toxicities. However, with close monitoring, NVP-containing regimens may be considered. One exception is that women with baseline CD4 >250 should not be given NVP along with Rifampicin. Nevirapine should be started at 200 mg bid. No dose escalation is needed for patients also taking rifampicin.
- ART patients who subsequently develop TB should have their ART adjusted to be compatible with TB treatment.
- Once ATT is completed, the ART regimen can be continued or changed depending upon the clinical and immunologic status of the patient.

## **3. Second-line ART and TB co-infection: Drug choices: Use of Rifabutin in TB-HIV co-therapy**

- If a patient needs both second-line ART and ATT, drug interactions are a problem due to the rifampicin lowering protease inhibitor levels through cytochrome P450 interactions.
- Rifampicin should not be taken with any boosted PI-based regimens.
- For patients who need ATT in Nepal and who need a boosted PI, the only option is to substitute rifabutin for rifampicin in the anti -TB regimen and maintain the standard PI- based ART regimen. Rifabutin dose is 150 mg 3 times a week when taken with LPV/r containing ART.

## **C. Intensified TB case findings in ART centers**

### **What is intensive TB Case finding?**

Intensified case finding refers to the approach of finding TB cases actively by routinely screening clients visiting specific clinics for purposes not related to TB. Since TB is one of the most common OIs among PLHIV, all those visiting ART sites should be screened for TB using a standard screening process.

### **Why intensive case finding is necessary?**

HIV-infected persons attending ART centers for the first time have a high prevalence of TB. The incidence of TB among ART clients is also very high. While ART reduces the risk of TB disease, this risk still remains many times higher than the general population. Hence intensified TB case finding at ART centers is very important for early suspicion and diagnosis of TB. It also helps to decrease healthcare related transmission of TB.

### Early identification of TB and treatment in PLHIV:

- Increases the chances of survival;
- Improves quality of life;
- Reduces transmission of TB in the community.

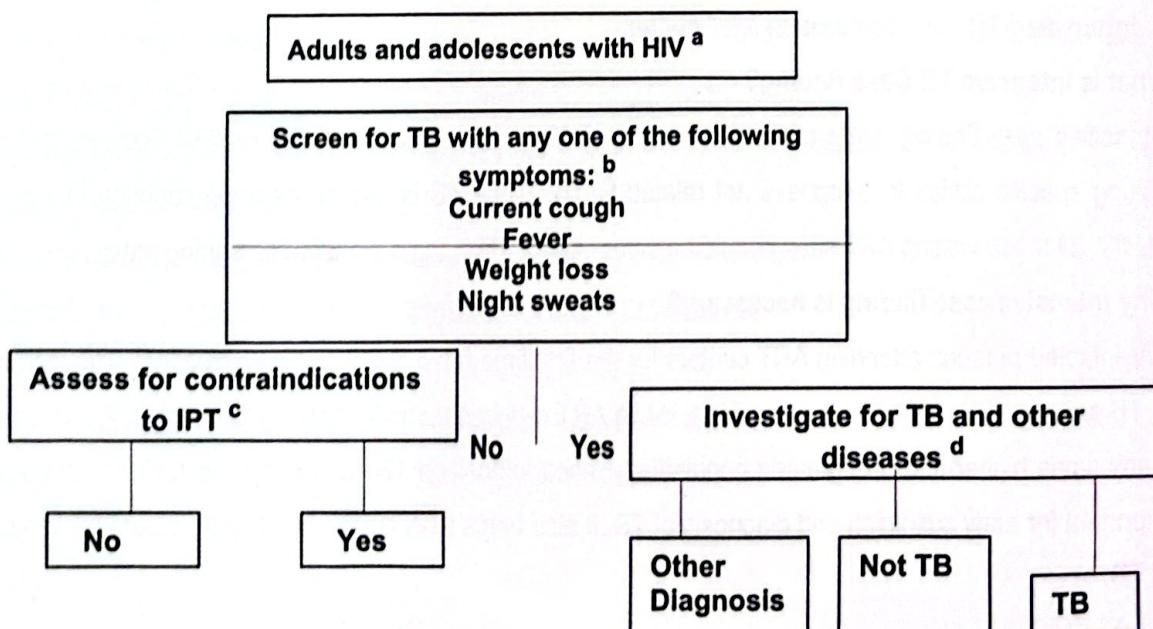
### How is Intensive case finding implemented?

All clients seen at ART, pre-ART, OI clinics and Community Care Centres, should undergo screening for tuberculosis using the 4 questionnaires at initial and follow-up visits every 3 months by health care provider.

#### TB case-finding and anti-tuberculosis treatment

- Adults and adolescents living with HIV should be screened for TB with a clinical algorithm; those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases (Fig. 21)
- Children living with HIV who have any of the following symptoms of poor weight gain, fever or current cough or contact history with a TB case may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, children should be offered isoniazid preventive therapy regardless of their age (Fig. 22)
- TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least six months of rifampicin treatment regimen.  
The optimal dosing frequency is daily during the intensive and continuation phases.
- Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having HIV-associated TB or multidrug-resistant TB.

Fig. 21: Algorithm for TB screening among adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings



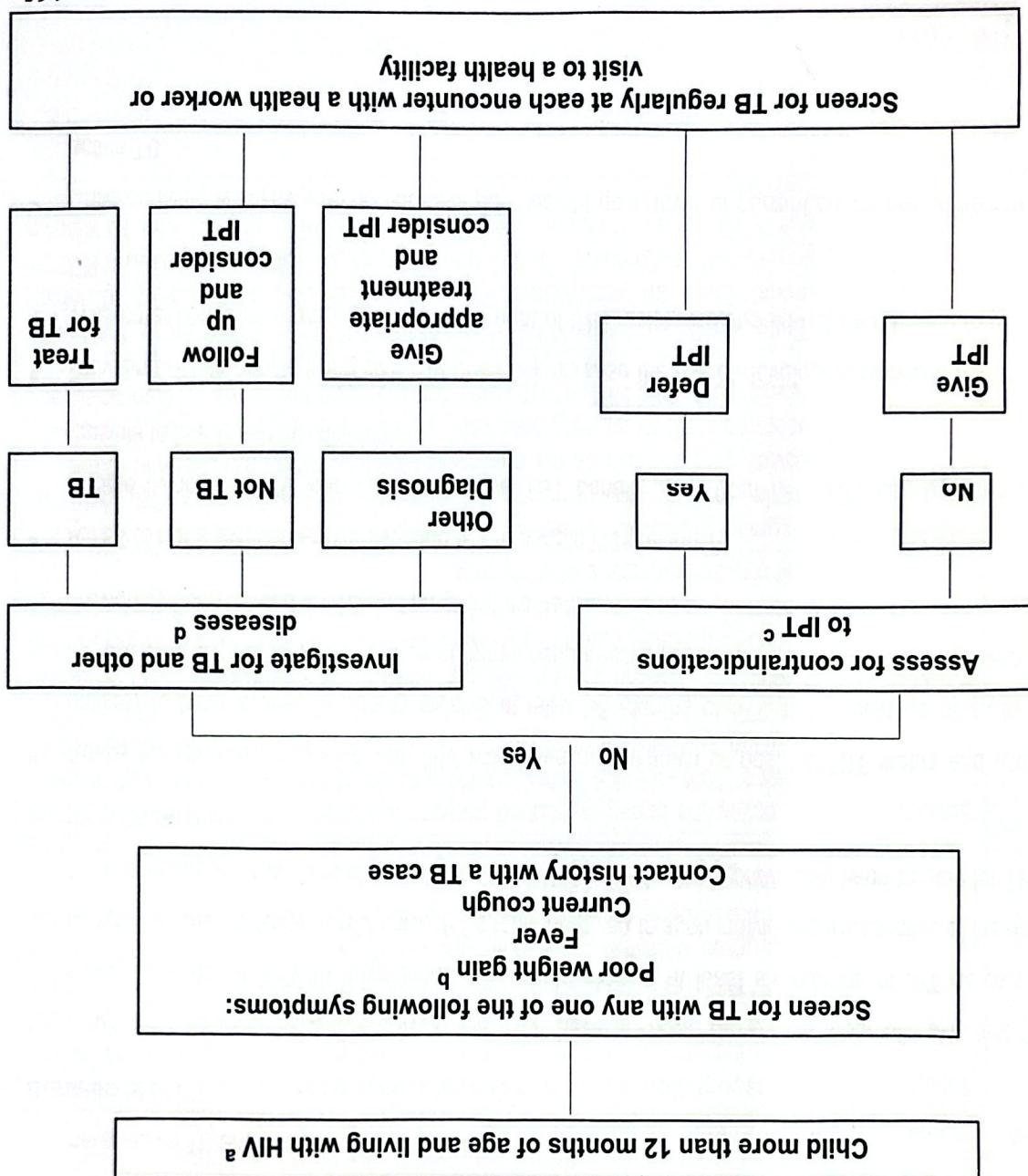


Fig. 22: Algorithm for TB screening among children older than one year of age and living with HIV

- d Investigations for TB should be performed in accordance with existing national guidelines.
- e Eligibility screening in some settings.
- f Although not a requirement for initiating IPT, tuberculin skin testing may be performed as a part of starting IPT. A history of TB and current pregnancy should not be contraindications for symptoms of peripheral neuropathy. Past history of TB and current pregnancy should not be contraindications for contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and strong consideration must be given to adding other sensitive investigations.
- g Chest radiography can be done if available but is not required to classify people into TB and non-TB groups. In settings with high HIV prevalence and a high TB prevalence among people living with HIV (such as exceeding 10%), chest radiography can be given priority to reduce *Mycobacterium tuberculosis* transmission in all settings that provide care.
- h Measures should be given priority to reduce *Mycobacterium tuberculosis* transmission in all settings that provide care.
- i Every adult and adolescent should be evaluated for eligibility to receive antiretroviral therapy. Infection control

- All infants younger than one year should be provided with IPT if they have a history of household contact with a person with TB.
- Poor weight gain is defined as (1) reported weight loss or very low weight (weight for age less than -3 z-score), (2) underweight (weight for age less than -2 z-score), (3) confirmed weight loss (>5%) since the last visit or (4) growth curve flattening.
- Contraindications include: active hepatitis (acute or chronic) and symptoms of peripheral neuropathy. A past history of TB should not be a contraindication to starting IPT. Although not a requirement for initiating IPT, tuberculin skin testing may be performed as part of eligibility screening in some settings.
- Investigations for TB must be performed in accordance with existing national guidelines.

#### **D. Isoniazid preventive therapy (IPT)**

- Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT

#### **Duration of IPT**

- Adults and adolescents who are living with HIV, have unknown or positive tuberculin skin test (TST) status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.
- Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also those on ART, those who have previously been treated for TB and pregnant women.
- A TST is not a requirement for initiating IPT in people living with HIV.  
People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals.
- Providing IPT to people living with HIV does not increase the risk of developing isoniazid-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.
- Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB.

- Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care services.
- In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease.
- All children living with HIV, after successful completion of treatment for TB disease, should receive isoniazid for an additional six months.

**Table 27: TB Prevention in HIV care settings**

Five steps for patient management to prevent transmission of TB in HIV care settings		
Step	Action	Description
1.	Screen	Early <b>recognition</b> of patients with suspected or confirmed TB disease is the first step in the protocol. It can be achieved by assigning a staff member to screen patients for prolonged duration of cough immediately after they arrive at the facility. Patients with a cough of more than two weeks duration, or who report being under investigation or treatment for TB*, should not be allowed to wait in the line with other patients to enter, register, or get a card. Instead, they should be managed as outlined below.
2.	Educate	Instructing the above mentioned persons identified through screening in cough hygiene. This includes instructing them to cover their noses and mouths when coughing or sneezing, and when possible providing face masks or tissues to assist them in covering their mouths.
3.	Separate	Patients who are identified as TB suspects or cases by the screening questions must be separated from other patients and requested to wait in a separate well ventilated waiting area, and provided with a surgical mask or tissues to cover their mouths and noses while waiting.
4.	Provide HIV Services	Triaging symptomatic patients to the front of the line for the services they are seeking (e.g. voluntary HIV counseling and testing, medication refills), to quickly provide care and reduce the amount of time that others are exposed to them is recommended. In an integrated service delivery setting, if possible, the patient should receive the HIV services they are accessing before the TB investigation.
5.	Investigate for TB or Refer	TB diagnostic tests should be done onsite or, if not available onsite, the facility should have an established link with a TB diagnostic center to which symptomatic patients can be referred. Also, each facility should have a linkage with a TB treatment center to which those who are diagnosed with TB can be referred.

- Although TB patients on adequate treatment are no longer infectious, it may be difficult for the facility to determine if anyone reporting being on treatment for TB has indeed received adequate treatment. The most cautious procedure is to manage those who are on treatment in the manner described.

### Source for recommendations

- *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva, World Health Organization, 2012* ([www.who.int/tb/publications/2012/tb\\_hiv\\_policy\\_9789241503006/en](http://www.who.int/tb/publications/2012/tb_hiv_policy_9789241503006/en)).
- *Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational "how-to". Practical considerations. Geneva, World Health Organization, 2011* ([whqlibdoc.who.int/publications/2011/9789241501569\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501569_eng.pdf)).

## 2. HIV and Hepatitis, Co-infections

### PURPOSE:

In this session, participants will learn about Hepatitis B and Hepatitis C co-infection with HIV and the appropriate management of both infections.

### OBJECTIVES:

By the end of this session, the participants will be able to:

- Describe the overview and natural history of viral hepatitis/HIV co-infection.
- Explain the influence of viral hepatitis on progression of HIV.
- Explain the influence of HIV on progression of viral hepatitis,
- Understand the approach to HCV and HBV treatment in the context of HIV infection.
- Understand the approach to HIV treatment in the context of viral hepatitis, including how to choose an appropriate ART regimen.
- Describe the importance of preventing blood-borne virus transmission in co-infection.

### Background

Chronic hepatitis B virus infection affects 5–20% of the 33 million people living with HIV worldwide, and hepatitis C affects 5–15%, although this may be up to 90% among people who inject drugs. The burden of coinfection is greatest in low- and middle-income countries, particularly in South-East Asia and sub-Saharan Africa for hepatitis B. Viral hepatitis is an increasing cause of morbidity and mortality among people living with HIV, including those on ART. A comprehensive approach includes prevention, hepatitis B and hepatitis C screening, hepatitis B vaccination and treatment and care for people with HIV co-infected with hepatitis B and/or hepatitis C.

#### A. The Virus Hepatitis C

It is a member of the Flaviviridae family. Other viruses of this family include Japanese encephalitis, dengue and West Nile virus. It is unrelated to the other hepatitis viruses, except that they all cause inflammation of

the liver. It is an RNA virus, and is therefore highly variable in its expression (many mutations during replication similar to HIV). This is one reason why it is able to evade the immune system. During infection, HCV exists as many similar, but not identical, species (quasispecies) generally within the same genotype. There are nine genotypes (numbers 1–9), within which there are subtypes (letters a, b, c), so a viral infection is known as, for example, 1a or 3a or 2b, etc.). Genotypes 1, 2, and 3 are widely distributed throughout the West and in East Asia (Japan, China, Taiwan, Thailand). Types 5 and 6 are mainly confined to South Africa and South-East Asia, respectively, in contrast to type 4, which is predominant in the Middle East and Central Africa.

HCV is transmitted primarily through blood-to-blood contact. Sharing injecting equipment and blood transfusion are the most efficient mechanisms of transmission. The rate of vertical transmission (mother to child) is low (<5%). The most important factor in vertical transmission is the level of virus in the mother (high level relates to a high chance of transmission). Sexual transmission is remote in mono-infection due to HCV. In HCV/HIV co-infection, sexual transmission is more common, though still very low. Hepatitis C viral load can be substantially higher in the presence of co-morbid HIV infection. Factors increasing the sexual transmission of hepatitis C in co-infection are high hepatitis C viral load, trauma during sex and possibly the presence of a sexually transmitted infection (STI).

### **1. Natural History**

The natural history of HCV infection is relatively benign, at least in the first few years of infection. Once transmitted, a viremia develops. This is followed by seroconversion (development of antibodies to hepatitis C), which takes between six weeks and six months to occur. Acute infection is asymptomatic in 60% of individuals. Common symptoms include fatigue, lethargy, nausea and other constitutional symptoms. Jaundice is uncommon and occurs in <25% of individuals.

Acute infection spontaneously clears in about 15% of individuals. This generally occurs within the first three to six months of infection. There is no relationship between the genotype of HCV infection and the likelihood of clearance. The presence of HIV or other immunosuppression markedly reduces the likelihood of viral clearance. The rate of clearance among HIV-positive individuals is between 5% and 8%. If the virus is not cleared within the first few months, it is very unlikely that viral clearance will occur. Individuals with HIV co-infection generally have substantially higher viral loads than HCV mono-infected individuals.

Chronic HCV infection has an indolent course. Around one third of individuals with chronic hepatitis C infection have mild hepatitis with normal liver function tests (LFT). The other two third have abnormal LFT with moderate to severe inflammation. The rate of cirrhosis (significant liver scarring resulting in impaired liver function) is around 20% in those with chronic hepatitis after 20 years of infection.

## **2. Effect of HCV on HIV Progression**

The effect of HCV on HIV progression is somewhat controversial. A number of studies have demonstrated that HCV may accelerate the course of HIV infection. The mechanism is not well known, although HCV is known to have immunomodulatory effects. A number of studies have also demonstrated that when controlled for influencing variables such as CD4 count, age and whether or not on ART, there is no difference in the progression of HIV between HCV/HIV co-infected and HIV mono-infected individuals. The latter variable (ART) is probably the most important factor. Co-infection is much more common in IDU, who often have reduced access to effective HIV treatment, thus differences in disease outcome may be attributable to differences in HIV treatment access.

## **3. Effect of HIV on HCV Progression**

HIV does influence the progression of HCV in co-infection. Infection with HIV has been shown to result in a higher hepatitis C viral load, liver fibrosis, progression to cirrhosis, liver failure and hepatocellular carcinoma (HCC). Factors associated with an increased risk of liver disease progression in people with HIV/HCV co-infection include heavy alcohol (ethanol) intake (>50 g/day), older age at HCV acquisition, low CD4 count, increased quasispecies variability and occult hepatitis B virus (HBV) infection.

Despite this, adequate immune reconstitution with ART has been shown to modify the course of HCV in HIV infection including slowing the rate of progression of liver fibrosis and reducing complications from HCV. Better survival rates among individuals with HIV treated with effective ART have also increased the proportion of liver-related mortality and morbidity in developed countries.

### **Hepatitis C information: Do's and Don'ts DO's**

- Vaccinate against hepatitis B and A if required
- Go for regular health check-ups
- Stop or reduce alcohol intake: alcohol use *significantly* increases the risk of developing cirrhosis and liver cancer
- Protect from *re-infection*: the presence of hepatitis C antibodies will *not protect* one from getting infected again
- Eat a balanced diet of fresh vegetables, fruits, beans, whole grains and lean meats; a healthy balance of protein in the diet
- Drink lots of fluids
- Exercise regularly
- Follow a stress reduction plan

### **Don'ts**

- Drinking alcohol; even one drink a day can accelerate the progression of liver disease

- Taking large amounts of paracetamol as it is toxic to the liver
- Taking paracetamol and alcohol together they can cause severe liver damage
- Breathing in pollutants, chemicals, cleaning products, fumes from paint, paint thinners, chemical solvents, spray adhesives, insect sprays and cleaners as these can be harmful to the liver
- Foods with high salt, sugar or fat content
- Too much fried foods
- High doses of vitamins A, D, E or K
- Taking iron supplements unless advised by the doctor

#### 4. Treatment of HCV in HIV Co-infection

Interferon and ribavirin decrease viral load drastically reducing morbidity and mortality. However it is very expensive treatment. Standard treatment is a subcutaneous injection of pegylated interferon (PEG-IFN) weekly in combination with ribavirin (RBV) tablets or capsules (dose depending on weight and genotype) twice daily. The duration of treatment for HIV/HCV co-infection is 48 weeks for all genotypes. In HCV mono-infection, the treatment length can vary, depending on the genotype.

#### 5. Treatment of HIV in HCV co-infection

It has become clear that effective HIV treatment (ART) reduces the progression of liver disease in HIV/HCV co-infected individuals. Co-infection with Hepatitis C increases the risk of hepatotoxicity with ART. However, the majority of patients with HCV are able to tolerate ART. Where there is a previous history of injecting drug use, HCV and HBV screening should be included in the baseline testing. The progression of liver disease is greater in the setting of HIV–HCV co-infection. However, as with HBV, the effect of HCV on HIV disease progression is uncertain.

**Table 27: Principles of ART in HCV co-infection**

<b>HCV therapy</b>	No ARV drugs are directly active against HCV. However, ART has been shown to delay the progression of HCV liver disease in HCV–HIV co-infection. The only effective treatment consists of pegylated IFN and RBV, which are generally not available widely
<b>HCV therapy outcomes</b>	Clinical trial outcomes <ul style="list-style-type: none"> <li>• HCV genotype 1: 15–28% sustained virological response rates</li> <li>• HCV genotypes 2 and 3: 60–70% virological response rates</li> </ul>
<b>Side-effects of IFN</b>	Up to 60% of individuals treated with IFN experience psychiatric problems, mostly commonly depression. Monitor mental health closely
<b>Timing of HCV therapy in relation to ART</b>	<ul style="list-style-type: none"> <li>• Commence anti-HCV therapy before the CD4 count drops to levels where ART is required, i.e. &lt;200 cells/ mm<sup>3</sup></li> <li>• If ART is required, the patient should be stable on ART with a CD4 count &gt;200 cells/mm<sup>3</sup> before anti-HCV therapy is considered, in order to get better anti-HCV response rates after immune recovery</li> </ul>

Preferred first-line ART regimen	<ul style="list-style-type: none"> <li>The choice of NRTI is the same as that for patients without HCV</li> <li>EFV is the preferred NNRTI where liver dysfunction is noted</li> <li>NVP should be used with care and regular monitoring in patients who have known HIV–HBV/HCV co-infection and grade 1, 2 or 3 increase in ALT/AST</li> <li>NVP is not recommended for patients with a grade 4 or higher increase in ALT/AST</li> </ul>
Drug interactions	<ul style="list-style-type: none"> <li>RBV and d4T/ddI: do not co-administer as there is a risk of pancreatitis/lactic acidosis/liver decompensation</li> <li>RBV and AZT: monitor closely for anaemia</li> <li>IFN and EFV: monitor closely for depression</li> </ul>
Hepatic flares	Soon after initiation of ART, as part of IRIS
<p><i>Notes:</i> It is recommended that HBV and HCV disease be co-managed with specialized departments (gastroenterology/hepatology). As prevention is the mainstay of HCV management, treatment should be made available to IDUs as a part of a package of services, including harm reduction and substitution programmes.</p>	

## 6. Monitoring during initiation and treatment

IDUs with HIV should be tested for HCV antibody prior to HIV treatment initiation. A positive test in the presence of abnormal liver function tests (particularly ALT) should indicate HCV infection. Individuals should be vaccinated against HBV if necessary and if the CD4 count is  $>200$  cells/mm $^3$ , and asked to avoid alcohol. The LFT should be monitored.

## 7. Conclusion

- HIV/HCV co-infection is very common in HIV-positive IDUs.
- Test for HCV-Ab + LFT prior to initiating ART.
- Treat HIV first if CD4 count  $<350$  cells/mm $^3$ , then HCV if drugs are available.
- Avoid alcohol, treat substance use.
- Advise use of sterile injecting equipment.
- Use EFV instead of NVP for those with HIV/HCV co-infection.
- It is possible to use NVP in individuals with <grade 3 elevation of ALT if LFT can be monitored regularly.
- Do not use NVP if there is grade 4 elevation of ALT.

## B. Hepatitis B Co-infection

As Hepatitis B is endemic, with varying geographical prevalence, HIV-infected persons especially those with a history of blood transfusion and injecting drug use and a history suggestive of hepatitis will be screened for baseline HBV/HCV status under the national programme. Vaccination may be considered for those attending STI clinics and HIV-infected persons who are found to be HbsAg-negative. HIV modifies

the natural history of HBV infection: higher rates of progression to advanced liver disease occur among persons with HIV/HBV co-infection. The presence of HIV infection is associated with greater rates of progression to cirrhosis. The impact of HBV on the natural history of HIV is less known.

### **Hepatitis B is transmitted:**

- Vertically (mother to child) in about 5% of pregnancies among hepatitis B carriers;
- Horizontally through unprotected sex, sharing of injecting equipment and through close contact particularly between infants and neonates (perinatal transmission);
- Through unsterile medical injections and unscreened blood products.

### **Hepatitis B NOT transmitted:**

- Through food or water, casual contact, such as hugging or shaking hands, or through kissing, sneezing or coughing.
- Through breastfeeding.
- Vaccination does not help individuals who are already infected with HBV.

### **The Hepatitis B Virus and Testing**

Hepatitis B is a DNA virus of the Hepadnavirus family. It infects and replicates within the hepatocytes (liver cells) though it causes little or no damage to the cells. Liver damage is caused by the immune response to the virus and hence chronic infection results in greater hepatic dysfunction from a chronic immune response.

**Table 28: Markers of hepatitis B disease (Source: WHO, 2002.)**

Marker	Full form	Indicates
HBsAg	Hepatitis B surface antigen	Current infection with hepatitis B (a carrier)
HBsAb	Hepatitis B surface anti-i body	Immuno-protection against hepatitis from either vaccination or previous exposure
HBcAb	Hepatitis B core antibody	Previous exposure to hepatitis B
HBeAg	Hepatitis B e antigen	Marker of active replication/active disease
HBeAb	Hepatitis B e antibody	Marker of inactive disease, so called "e seroconversion"
HBV DNA	Hepatitis B DNA	Presence indicates active replication and disease. Amount of DNA is "HBV viral load"
HIV and HBV co-infection		
AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)		

<sup>2</sup> ABC and ddc can be used as NRTI backup options but add complexity and cost without clinical advantages. DRV/r can be used as an alternative PI and SQV/r in special situations, but neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is in development.

**Table 29 Interpretation of hepatitis B tests**

Test combination	Results	Interpretation
HBsAg	-	
HBcAb	-	Susceptible to hepatitis B
HBsAb	-	
HBsAg	-	
HBcAb	+	Past history of HBV with current immunoprotection
HBsAb	+	
HBsAg	-	
HBcAb	-	Immune due to hepatitis B vaccination
HBsAb	+	
HBsAg	-	
HBcAb	+	Past history of HBV infection
HBsAb	-	

All IDUs should be tested for hepatitis B. Testing in HIV-positive individuals is more difficult, as markers of the disease may not always be present. Initial tests should include HBsAg and if possible HBsAb and HBcAb. In HIV-positive individuals, HBsAg may be negative although the virus is present and therefore if available HBV DNA should be done for confirmation of the disease (occult HBV infection).

### **Natural History**

In infancy and early childhood (<2 years old) acute infection is usually asymptomatic but much more likely to result in chronic infection (>90% of individuals <6 months). In adulthood, acute infection is usually symptomatic with jaundice, nausea, fatigue and lethargy in 75% of people but <5 per cent go on to have chronic infection. The presence of HIV is more likely to result in chronic infection. In the presence of HIV, HBV viral replication and therefore its viral load are higher. Liver injury is usually reduced with immunosuppression such as in HIV infection. In some people with very high viral loads, HBV can directly cause injury to the liver cells (known as fibrosing cholestatic hepatitis).

### **Effect of HBV on HIV Progression**

Evidence from the ART era has suggested that HBV does not appear to alter the course of HIV.

### **Effect of HIV on HBV Progression**

HIV co-infection influences the course and natural history of HBV infection by impairing the quantity and quality of the innate and adaptive immune response. The rates of spontaneous resolution after acute infection and spontaneous anti -HBe and anti -HBs seroconversion are decreased, and levels of HBV replication are increased in HIV-infected patients. A more rapid progression of liver fibrosis and a higher rate of cirrhosis leading to decompensation (but not HCC) have been demonstrated in co-infected patients.

The risk of HBV-associated end-stage liver disease (ESLD) and liver-related mortality may be increased by HIV co-infection.

ART can have a major impact on HBV co-infection because of the restoration of immune responses and improved regulation of the immune system. In addition, at least three ARVs (3TC, TDF and FTC) are potent inhibitors of HBV replication. There is also some evidence that 3TC may prevent acute hepatitis B infection in HIV-positive individuals exposed to hepatitis on an ART regimen that contains 3TC.

#### **Treatment of Hepatitis B in HIV Co-infection**

Start ART in all HIV/HBV co-infected individuals who require treatment for their HBV infection (chronic active hepatitis), irrespective of CD4 count or WHO stage.

Start TDF and 3TC containing ARVs in all HIV/HBV co-infected individuals needing treatment.

#### **Treatment of HIV in HBV Co-infection**

This is discussed above, but the important aspects are:

All cases of chronic active hepatitis B should start ART using appropriate drugs.

Additionally exposing the individual to the development of resistance to ARVs is unwise.

When HIV treatment is indicated, use a regimen with 3TC and TDF which also have activity against HBV.

EFV is the preferred NNRTI option in individuals with HBV/HIV co-infection.

NVP may be used with care and regular monitoring in patients who have known HBV/HIV co-infection and  $\leq$ grade 3 elevation of ALT.

NVP is not recommended for those with  $\geq$ grade 4 ALT elevation.

#### **Prevention**

There is an effective vaccine available for the prevention of hepatitis B. All at-risk individuals who are not immunoprotected (no HBsAb nor HBcAb) should be vaccinated. Those who are HIV positive are less likely to respond to HBV vaccine (especially if the CD4 count is  $<200$  cells/mm $^3$ ), have lower mean antibody titres (by a factor of about 30), and lose protective antibody levels more quickly. The vaccination regimen in co-infection should be 0, 1, 6 months or 0, 1, 2, 12 months. Non-responders should have a further three shots at double the dose.

#### **Conclusion**

- Hepatitis B is very common in HIV-positive IDUs.
- All HIV-positive IDUs should be screened for HBV.
- All HIV-positive IDUs should be vaccinated against HBV if not already immunoprotected.
- HIV treatment regimens in the context of HBV should incorporate agents that have activity against HBV.
- ALT should be monitored during HBV treatment.
- TDF and 3TC should be used together to avoid resistance.

- EFV is the preferred NNRTI option in individuals with HBV/HIV co-infection.
- NVP may be used with care and regular monitoring in patients who have known HBV/HIV co-infection and  $\leq$  grade 3 elevation of ALT.
- NVP is not recommended for those with  $\geq$  grade 4 ALT elevation

Source: Guidance on prevention of viral hepatitis B and C among people who inject drugs. Geneva, World Health Organization, 2012 ([www.who.int/hiv/pub/guidelines/hepatitis/en/index.html](http://www.who.int/hiv/pub/guidelines/hepatitis/en/index.html)).

### 3. ART for IDUs and PLHA on Substitution therapy including opioid Substitution therapy (OST)

#### PURPOSE:

In this session, participants will learn about Epidemiology, Services for people who inject drugs and ART for IDUs.

#### OBJECTIVES:

By the end of this session, the participants will be able to:

- Describe the Epidemiology of HIV and injecting drug use.
- Explain the Medical care services for IDUs.
- Understand the approach to Harm Reduction program.
- Understand the Drug dependence treatment and opioid substitution therapy (OST) including how to choose an appropriate ART regimen.
- Describe the importance of psychosocial support.

#### 1. Epidemiology of HIV and injecting drug use

Estimates suggest that by the end of 2003, there were approximately 13.2 million people worldwide who injected drugs, the majority (10.3 million [78%]) in developing and transitional countries. The number of people who inject drugs in South and South-East Asia was estimated at 3.3 million. HIV epidemics in many parts of the world are driven by injection drug use (IDU) and sexual contact with those who inject drugs. It is estimated that at least 10% of all new infections in the world – a figure that rises to 30% when Africa is excluded – can be attributed to IDU and that approximately 3 million past and current people who inject drugs are living with HIV/AIDS. In most parts of the South-East Asia and Western Pacific Regions, HIV epidemics have been largely driven by IDU, although HIV transmission is also high among commercial sex workers and their clients. Bangladesh, Lao PDR and the Philippines currently have low prevalence rates of HIV, although the risk environment is in place for a scenario of rapid HIV transmission among people who inject drugs. The countries most affected are primarily those where access to prevention, care and treatment are limited, needle and syringe programmes, and drug substitution therapy are not widely available (if not illegal), and law enforcement is the dominant response to drug use.

A study from eastern India, which borders Nepal, Bangladesh and Bhutan, found that over 50% of men who inject drugs visited a commercial sex worker in the previous year and this has significant implications for cross-border transmission of HIV. The increasing rates of HIV infection among non-injecting sex partners of people who inject drugs should also receive intensive prevention efforts. In Chennai, India, not only were HIV rates among female sex partners of people who inject drugs very high, but there was also an alarmingly low perception of HIV risk. The lack of access to prevention and treatment interventions (notably harm reduction), and high efficiency of blood borne transmission of HIV through needle-sharing and sharing of other drug paraphernalia explain these explosive epidemics. An additional factor is the elevated level of viraemia characteristic of the first weeks and months after seroconversion, which may contribute to the high HIV transmission rates typical of these epidemics.

In addition to the general principles governing the care and treatment of people living with HIV/AIDS (PLWHA), the following specific principles should be applied to people who inject drugs:

- ART is as effective for people who inject drugs as for other people with HIV/AIDS.
- Given appropriate support, former and current users of injection drugs can adhere to and have equal success on ART.
- Current or past drug use should not be a criterion for deciding on who should receive ART.
- Special attention should be paid to the particular needs of former and current users of injection drugs, including those related to substance dependence, co-morbidities and co-infections.
- A public health policy that acknowledges and addresses the need to treat both substance dependence and HIV/AIDS improves patient wellbeing, reduces stigma and promotes delivery of comprehensive, ethical medical care.
- The most effective response consists of a combination of prevention, care, treatment and support within a harm reduction framework.
- Provision of quality OST for opioid-dependent people who inject drugs is an important component of HIV/AIDS care and treatment, and is highly effective.
- A supportive environment, upholding the human rights and dignity of people who inject drugs and helping to expand and improve access to drug dependence treatment, should be ensured.
- Countries with HIV epidemics fuelled by IDU should respond immediately to the needs of people who inject drugs with preventive and treatment services.

## **2. Services for people who inject drugs**

Four types of interrelated and linked services are crucial for the treatment of substance dependence and HIV/AIDS. These are:

- a. General medical care;**
- b. Harm reduction;**
- c. Drug dependence treatment and opioid substitution therapy (OST)**
- d. Psychosocial support.**

**a. Medical care should be comprehensive in order to address HIV infection. In addition, people who inject drugs require:**

- Treatment adherence support;
- Drug (opioid) substitution therapy (OST);
- Other substance dependence treatment;
- Reduction of risk behaviours, including both drug use and sexual behaviours;
- Support for sexual partners;
- Support for social matters (through social services); and
- Health education.

**b. Harm reduction:**

As HIV-infected IDUs have special needs with regard to drug use, ART should be given as part of a comprehensive package of prevention (including harm reduction), care and support, and treatment. Harm reduction programmes have trained staff (social workers, counsellors and outreach workers), who are experienced in reaching out to and communicating with IDUs, and have established credibility and trust.

The key components of an effective harm reduction package targeting drug users include:

- Community outreach, with a focus on peer approaches;
- Behavior change communication, including risk reduction information;
- Access to clean needles and syringes as well as their safe disposal;
- Drug dependence treatment, particularly OST;
- HIV testing and counselling (voluntary and confidential, and provider initiated);
- Prevention of sexual transmission through interventions such as providing condoms, and STI prevention and treatment;
- HIV/AIDS care and treatment, including ART;
- Primary health care, including hepatitis B vaccination, vein and abscess/ulcer care, overdose management; and

- Supportive policy and legislative environment.
- Support for ART adherence.
- Follow-up of patients who drop out of care or default on scheduled visits.
- Patient education and peer support.

#### **c. Drug dependence treatment and opioid substitution therapy (OST)**

HIV and drug dependence are not isolated problems, but influence the progression of each other. There are a variety of treatment modalities for drug dependence, including drug-free residential therapy, outpatient counselling-based treatment, and medication-assisted substitution and detoxification for opioid dependence. Effective treatment options using evidence-based counselling approaches for dependence on cocaine and amphetamine-type stimulants (ATS) should also be offered. Medication-assisted therapy for cocaine and ATS dependence may be of benefit, although substitution therapy for non-opioid dependence is much less developed and generally unavailable outside of research protocols. Given the chronic and relapsing nature of substance dependence, detoxification alone is seldom effective in producing long-term and sustained change.

Treatment of drug dependence, in particular through OST, provides many benefits in the prevention and treatment of HIV/AIDS by:

- improving access to HIV care and treatment and general health care;
- retaining active drug users in treatment;
- reducing the transmission of HIV, viral hepatitis and bacterial infections;
- decreasing the need for hospitalization;
- improving and facilitating adherence and follow up of patients on ART;
- reducing illicit opioid use;
- reducing criminal activity;
- decreasing deaths due to overdose;
- cutting down on behaviours with a high risk of HIV transmission; and
- improving social integration.

The benefits of substitution therapy programmes can be maximized by:

- prescribing methadone or buprenorphine in doses that effectively prevent craving and reduce drug use;
- orientating programmes towards maintenance rather than abstinence;
- offering counselling, assessment and treatment for psychiatric comorbidity and social problems;
- using evidence-based strategies such as motivational interviewing or contingency management to assist patients in reducing the use of additional drugs; and

- ensuring ready access to services, including convenient geographical location and opening hours, and affordable cost.

Where substitution therapy is available, consideration should be given to offering HIV/AIDS medical care and dispensing ART at the same site from which drug substitution therapy is dispensed. This approach can:

- achieve maximal levels of treatment supervision and improve adherence;
- reduce the risk of developing ARV drug resistance;
- facilitate the management of interactions between methadone and HIV/AIDS medications;
- provide the opportunity to administer DAART to patients attending daily to receive methadone (a second "take-home" ARV dose is usually needed).

The two main medications used for OST – methadone and buprenorphine – have been included in the WHO list of essential medicines since 2005, although their availability may be limited in parts of Asia. OST dispensed on a daily basis can promote frequent contact with staff and may improve access and adherence to ART.

**Table 29: Comparison between Buprenorphine and Methadone**

Buprenorphine	Methadone
Partial agonist and produces only mild euphoria.	Full agonist and can produce significant intoxication.
Has low dependence potential compared to full opioid agonists.	Potential to produce significant dependence. As tolerance increases, dose increases over time are required.
Abstinence leads to mild withdrawal symptoms.	Abstinence leads to marked withdrawal symptoms.
At high doses, there is a ceiling effect. The risk of fatal respiratory depression by overdose of buprenorphine by itself is minimal. But when combined with benzodiazepines (diazepam), alcohol and other CNS depressants, respiratory depression has been reported.	Risk of fatal overdose by respiratory depression.
Sublingual tablets are effectively absorbed. It is not orally active. Sublingual tablets can be crushed, easily dissolved and injected.	Orally active.
Relatively expensive	Cheaper

can make needed referrals

**Table 30: Frequency and doses of Opioid Substitution Therapy**

Medication	Initial dose	Maximum dose	Reduction rate	Duration of detoxification
Buprenorphine	4–6 mg daily	12 mg per day	2 mg per day	5–8 days
Methadone	20–30 mg daily	40 mg per day	5 mg on alternate days	2–3 weeks
Clonidine	75–300 mcg daily in divided doses	900 mcg per day in divided doses	150 mcg per day	5–8 days

**d. Psychosocial support**

Concurrent services that address both the biomedical needs and the psychosocial issues of people who inject drugs are essential. A wide range of psychosocial support services should be available and accessed according to the needs of the patient, including:

- support services for adherence to ART;
- psychological support/counselling, group therapy for people who inject drugs and family members;
- peer support groups;
- educational programmes;
- psychiatric/psychological services for assessment and management of mental health disorders; and
- social/welfare services to deal with problems related to housing, employment, finances, legal issues, discrimination and other issues.

People who injected drugs in the past often have unique success in educating and motivating people who currently inject drugs, including:

- accessing the hard-to-reach sectors of the population and referring them to effective prevention, care and treatment services;
- preparing people who inject drugs for treatment, such as advising them on the potential side-effects associated with ART; and
- supporting people who inject drugs to adhere to ART and other treatment.

The inclusion of former injecting drug users in education and outreach programmes requires adequate training and supervision, as well as close monitoring, as there is a high risk of relapse to illicit drug use for these peer workers.

### 3. ART for HIV-infected IDUs

Substance-using PLHA (current or previous) who are medically eligible for ART should be given care and treatment as per the national guidelines. Refer to the harm reduction programme if required.

**Table 31: Initiating ART in substance-using patients**

<b>Initiating ART</b>	<p>The criteria for initiating ART in substance-using patients are the same as in the case of other patients with HIV</p> <ul style="list-style-type: none"> <li>Before starting ART, specific factors that may affect the timing of initiation and the choice of ART should be considered: social instability, active use of illicit drugs and the presence of co-morbidities, such as mental problems and co-infection with hepatitis viruses</li> <li>Unavailability of OST or active use of illicit drugs should not hinder access to ART for those in need of treatment</li> <li>Effective links between ART and harm-reduction programmes are essential.</li> <li>Initiate ART once the patient has been adequately prepared and counseled for treatment adherence</li> <li>Spending adequate time on preparing patients for ART, and helping them understand the treatment goals, need for adherence and lifelong nature of ART will maximize treatment outcomes</li> </ul>
<b>Choice of ART</b>	<p>National regimens can be chosen for the majority of IDUs.</p> <p>The choice of specific ARV drugs depends on:</p> <ul style="list-style-type: none"> <li>Co-morbidities (especially hepatitis B/C and psychiatric disorders).</li> <li>Drug interactions (methadone)</li> <li>Adherence.</li> </ul>
<b>Preferred first line regimen</b>	<p><b>AZT + 3TC + EFV</b> if liver dysfunction is noted</p> <p><b>AZT + 3TC + NVP</b> if patient is stable; monitor closely for hepatitis</p> <p>With this combination, 3TC is the only drug with anti-HBV activity (thus, there is a higher risk of HBV resistance to 3TC)</p>
<b>Choice of NNRTI</b>	<p>Hepatitis C and B infections are extremely common in IDUs. Monitoring hepatotoxicity is strongly recommended in IDUs receiving NNRTI-based ART, especially NVP</p> <p><b>Efavirenz</b></p> <p>EFV is preferred in patients with clinical and/or laboratory evidence of significant (grade 3 or 4) hepatic dysfunction. It should be used with caution in patients with depression or other significant psychiatric conditions</p> <p><b>Nevirapine</b></p> <p>NVP is recommended in patients with no other significant co-morbidities, specifically, those with no clinical signs of hepatic dysfunction or increase in hepatic transaminases (grade 3 or 4). Use NVP under close clinical and laboratory (liver enzymes) monitoring</p>
<b>Alternative first-line regimen</b>	<p><b>d4T + 3TC + (EFV or NVP)</b></p> <p>AZT may be replaced by d4T in any regimen in case of toxicity or other contraindications eg. anaemia</p> <p><b>TDF + 3TC + (EFV or NVP)</b> in special circumstances, for example, if the patient is intolerant to d4T or AZT</p>
<b>Second-line regimen</b>	The recommendations are the same as those for other patients with HIV

<b>Adherence</b>	Given a good patient-clinical team relationship and adequate support, IDUs can adhere to ART and have clinical outcomes comparable with those of HIV patients who do not use drugs
<b>Buprenorphine</b>	There is no significant drug interaction between the first-line ARV drugs and buprenorphine
<b>Methadone</b>	There is no significant drug interaction between the first-line ARV drugs and methadone

Source: Antiretroviral Therapy Guidelines for HIV-infected Adults and Adolescents including Post-exposure Prophylaxis NACO, India May 2007.

HIV/AIDS care and treatment for people who inject drugs in Asia and the Pacific: an essential practice guide. ISBN 978 92 9061 320 6; World Health Organization 2008.

Lawyers Collective HIV/AIDS Unit; legal and policy concerns related to IDU harm reduction in SAARC countries, 2007.

Dr. M. Suresh Kumar, opioid substitution treatment; United Nations Office on Drugs and Crime, Regional Office for South Asia, 2012.

HIV/AIDS treatment and care clinical protocols for the WHO European Region published by World Health Organization 2007

### **Section – C: Management of side effects and Treatment failure**

#### **PURPOSE:**

In this session the participants will learn about Antiretroviral Drug Toxicity and management, ARV Treatment Failure and When to switch and Choice of ARV Regimens in the Event of Failure of First-line Regiment.

#### **OBJECTIVES:**

By the end of this session, participants will be able to:

1. List various toxicities and common side effects.
2. Explain monitoring and management of toxicities and side effects.
3. Describe class adverse drug reactions, including class-specific and ARV-specific adverse effects of ART.
4. Explain immune reconstitution inflammatory syndrome.
5. Explain about ART regimen to switch to second-line ART when failure
6. Describe choice of Third-line ART regimen

#### **3. Antiretroviral Drug Toxicity and management**

##### **A. Common side effects and toxicities and how to monitor:**

All ARV medications can be associated with side effects. Most are mild, but some infrequently are severe and even life-threatening. Major side effects need to be distinguished from minor side effects.

- Minor side effects such as nausea, fatigue, minor rash and insomnia can be very difficult for the client, but they usually resolve in 2 to 4 weeks of ART initiation. They can be managed clinically and through careful counseling. It is important to warn about these in advance and manage these minor side effects well, because they can negatively affect adherence.
- Major side effects are those where the ARVs are having a major negative impact on the body. These need careful clinical management and may result in stopping the ARV drug that caused the side effect and replacing it with a new one. Major side effects are diagnosed by a combination of clinical evaluation (history and examination), routine laboratory monitoring and extra laboratory testing when needed. They include severe rash, hepatotoxicity, peripheral neuropathy, bone marrow suppression and lactic acidosis.

#### **B. Guiding principles in the management of ARV drug toxicity**

1. Determine the seriousness of the toxicity.
2. Evaluate concurrent medications and establish whether the toxicity is attributable to an ARV drug or drugs or to a non-ARV medication.
3. Consider other disease processes and IRIS (e.g. hepatitis in an individual on ARV drugs in the first 2 months of treatment) because not all problems that arise during treatment are caused by ARVs.
4. Manage the adverse event according to severity. In general:
  - Severe life-threatening reactions: Immediately discontinue all ARV drugs, manage the medical event (i.e. symptomatic and supportive therapy) and reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitution for the off ending drug) when the patient is stabilized.
  - Severe reactions: Substitute the off ending drug without stopping ART.
  - Moderate reactions: Consider continuation of ART as long as feasible. If the patient does not improve on symptomatic therapy, consider single-drug substitutions.
  - Mild reactions are bothersome but do not require changes in therapy.
5. Stress the maintenance of adherence despite toxicity for mild and moderate reactions.
6. If there is a need to discontinue ART because of life-threatening toxicity, all ARV drugs should be stopped until the patient is stabilized.

#### **C. Major types of ARV toxicities**

The 2010 WHO ART guidelines recommended a symptom-directed approach to laboratory monitoring of the safety and toxicity of ART regimens. At the same time, several laboratory tests for monitoring ARV toxicity were advised (but not required) for specific high-risk people using certain drugs. Below table lists key types of toxicity and associated risk factors for the major ARV drugs.

Monitoring drug toxicity using a symptom-directed approach needs to be investigated further to optimize treatment. More data are needed on whether routine or periodic laboratory monitoring for specific types of

toxicity (such as renal function monitoring among TDF users) is required for all individuals or only people at higher risk.

**Table 32: Types of toxicities associated with first-, second- and third-line ARV drugs**

ARV drug	Major types of toxicity	Risk factors	Suggested management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 gene	If ABC is being used in first-line ART, substitute with TDF or AZT or d4T If ABC is being used in second-line ART, substitute with TDF
ATV/r	Electrocardiographic abnormalities (PR interval prolongation)	Pre-existing conduction disease Concomitant use of other drugs that may prolong the PR interval	LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider integrase inhibitors
	Indirect hyperbilirubinaemia (clinical jaundice)	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs	
	Nephrolithiasis and risk of prematurity	Risk factors unknown	
AZT	Anaemia, neutropaenia, myopathy, lipoatrophy or lipodystrophy	Baseline anaemia or neutropaenia CD4 count $\leq$ 200 cells/mm <sup>3</sup>	If AZT is being used in first-line ART, substitute with TDF or ABC If AZT is being used in second-line ART, substitute with d4T
	Lactic acidosis or severe hepatomegaly with steatosis	BMI $>$ 25 (or body weight $>$ 75 kg) Prolonged exposure to nucleoside analogues	
d4T	Peripheral neuropathy, lipoatrophy or lipodystrophy	Older age CD4 count $\leq$ 200 cells/mm <sup>3</sup> Concomitant use of isoniazid or ddI	If d4T is being used in first-line ART, substitute with TDF or AZT or ABC If d4T is being used in second-line ART (after TDF or ABC are used in first-line ART), substitute with AZT
	Lactic acidosis or severe hepatomegaly with steatosis, acute pancreatitis	BMI $>$ 25 (or body weight $>$ 75 kg) Prolonged exposure to nucleoside analogues	
DRV/r	Hepatotoxicity	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs	If DRV/r is being used in secondline ART, substituting with ATV/r or LPV/r can be considered. When it is used in third-line ART, limited options are available
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	
	Persistent central nervous system toxicity (such as abnormal dreams, depression or mental confusion)	Depression or other mental disorder (previous or at baseline) Daytime dosing	

EFV	Hepatotoxicity	Underlying hepatic disease -HBV and HCV co-infection Concomitant use of hepatotoxic drug	NVP. If the person cannot tolerate either NNRTI, use boosted PIs
	Convulsions	History of seizure	
	Hypersensitivity reaction, Stevens-Johnson syndrome Potential risk of neural tube birth defects (very low risk in humans) Male gynaecomastia	Risk factors unknown	
ETV	Severe skin and hypersensitivity reactions	Unknown	Limited options are available
LPV/r	Electrocardiographic abnormalities (PR and QT interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR interval	If LPV/r is used in first-line ART for children, use an age-appropriate NNRTI (NVP for children younger than 3 years and EFV for children 3 years and older). ATV can be used for children older than 6 years If LPV/r is used in second-line ART for adults, use ATV/r or DRV/r. If boosted PIs are contraindicated and the person has failed on treatment with NNRTI in first-line ART, consider integrase inhibitors
	QT interval prolongation	Congenital long QT syndrome Hypokalaemia Concomitant use of drugs that may prolong the QT interval	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs	
	Pancreatitis	Advanced HIV disease	
	Risk of prematurity, lipoatrophy or metabolic syndrome, dyslipidaemia or severe diarrhoea	Risk factors unknown	
NVP	Hepatotoxicity	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs CD4 >250 cells/mm <sup>3</sup> in Women CD4 >400 cells/mm <sup>3</sup> for men First month of therapy (if lead-in dose is not used)	EFV. If the person cannot tolerate either NNRTI, use boosted PIs
	Severe skin rash and hypersensitivity reaction (Stevens-Johnson syndrome)	Risk factors unknown	

RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis	Limited options are available
TDF	Tubular renal dysfunction, Fanconi syndrome	Underlying renal disease Older age BMI <18.5 (or body weight <50 kg) Untreated diabetes mellitus Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	If TDF is being used in first-line ART, substitute with AZT or d4T or ABC If TDF is being used in second-line ART (after d4T + AZT use in first-line ART), substitute with ABC or ddI
	Decreases in bone mineral density	History of osteomalacia and pathological fracture Risk factors for osteoporosis or bone loss	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity	
	Exacerbation of hepatitis B (hepatic flares)	Discontinuation of TDF due to toxicity	Use alternative drug for hepatitis B treatment (such as entecavir)

#### D. Immune Reconstitution Inflammatory Syndrome (IRIS)

- Immune Reconstitution Inflammatory Syndrome is a spectrum of clinical signs and symptoms resulting from the restored ability to mount an inflammatory response associated with immune recovery.
- 3 types of IRIS presentations
  - Signs and symptoms of a previously subclinical and unrecognized OI;
  - Paradoxical worsening of an OI already being treated several weeks into therapy; or
  - An autoimmune disease.
- Typically occurs within two to twelve weeks of the initiation of ART, although it may present up to 24 weeks after ART initiation.
- The incidence is about 10%-32% of adults initiating ART. There is a higher risk in those starting ART with lower CD4 counts.
- The syndrome can be characterized by fever, lymphadenopathy, worsening pulmonary lesions (on x-ray examination), expanding central nervous system (CNS) lesions, elevation of hepatic enzymes (Hep B co-infection), skin lesions or signs of autoimmune diseases.
- Treatment: Continue routine OI treatment
- For moderate or severe IRIS, Prednisolone (or prednisone) at 0.5 mg/kg/day for five to ten days. This may reduce inflammation and improve severe respiratory or CNS symptoms.

#### 2. What ART regimen to switch to (second-line ART)

Using a boosted PI + two NRTI combinations is recommended as the preferred strategy for second-line ART for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART. In children using a PI-based regimen for first-line ART, switching to NNRTI or maintaining the PI regimen is recommended according with age.

**Table 33: Summary of preferred second-line ART regimens for adults, adolescents, pregnant women and children**

Second-line ART		Preferred regimens	Alternative regimens					
<b>Adults and adolescents (≥10 years), including pregnant and breastfeeding women</b>		AZT + 3TC + LPV/r <sup>a</sup> AZT + 3TC + ATV/r <sup>a</sup>	TDF + 3TC (or FTC) + ATV/r TDF + 3TC (or FTC) + LPV/r					
<b>Children</b>	<b>If a NNRTI-based first-line regimen was used</b>	ABC + 3TC + LPV/r <sup>b</sup>	ABC + 3TC + LPV/r <sup>b</sup> TDF + 3TC (or FTC) + LPV/r <sup>b</sup>					
	<b>If a PI-based first-line regimen was used</b>	<table border="1"> <tr> <td><b>&lt;3 years</b></td> <td>No change from first-line regimen in use<sup>c</sup></td> <td>AZT (or ABC) + 3TC + NVP</td> </tr> <tr> <td><b>3 years to less than 10 years</b></td> <td>AZT (or ABC) + 3TC + EFV</td> <td>ABC (or TDF) + 3TC + NVP</td> </tr> </table>	<b>&lt;3 years</b>	No change from first-line regimen in use <sup>c</sup>	AZT (or ABC) + 3TC + NVP	<b>3 years to less than 10 years</b>	AZT (or ABC) + 3TC + EFV	ABC (or TDF) + 3TC + NVP
<b>&lt;3 years</b>	No change from first-line regimen in use <sup>c</sup>	AZT (or ABC) + 3TC + NVP						
<b>3 years to less than 10 years</b>	AZT (or ABC) + 3TC + EFV	ABC (or TDF) + 3TC + NVP						

<sup>a</sup> DRV/r can be used as an alternative PI and SQV/r in special situations; neither is currently available as a heatstable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is currently in development.

<sup>b</sup> ATV/r can be used as an alternative to LPV/r for children older than six years.

<sup>c</sup> Unless failure is caused by lack of adherence resulting from poor palatability of LPV/r.

## Second-line ART for adults and adolescents

### New recommendations

- Second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI).
  - The following sequence of second-line NRTI options is recommended:
    - After failure on a TDF + 3TC (or FTC)-based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens.
    - After failure on an AZT or d4T + 3TC-based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens.
    - Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach.
- Heat-stable fixed-dose combinations of ATV/r and LPV/r are the preferred boosted PI options for second-line ART.

Table 34: Summary of preferred second-line ART regimens for adults and adolescents

Target population	Preferred second-line regimen <sup>a</sup>	
Adults and adolescents (≥10 years)	If d4T or AZT was used in first-line ART	TDF + 3TC (or FTC) + ATV/r or LPV/r
	If TDF was used in first-line ART	AZT + 3TC + ATV/r or LPV/r
Pregnant women	Same regimens recommended for adults and adolescents	
HIV and TB co-infection	If rifabutin is available	Standard PI-containing regimens as recommended for adults and adolescents
	If rifabutin is not available	Same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800 mg/200 mg twice daily) or standard LPV dose with an adjusted dose of RTV (that is, LPV/r 400 mg/400 mg twice daily)
HIV and HBV co-infection	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)	

<sup>a</sup> ABC and ddI can be used as NRTI backup options but add complexity and cost without clinical advantages. DRV/r can be used as an alternative PI and SQV/r in special situations, but neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is in development.

## Third-line ART

### Background

In 2010, WHO made recommendations on third-line ART in the context of limited evidence to guide third-line strategies. Although there were few studies of newer agents, cohort data showed high mortality among people for whom second-line ART had failed.

### New recommendations

- National programmes should develop policies for third-line ART
- Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second-generation NNRTIs and PIs.
- Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen.

## Section – D: RAPID ADVICE

### PURPOSE:

In this session, participants will learn about nutrition, the interaction between HIV and nutrition. They will learn about the Community and Home-Based Care and Palliative Care.

### OBJECTIVES:

By the end of this session, participants will be able to:

- Define the interaction between HIV and nutrition.
- Explain the barrier to good nutrition.
- Explain the relationship between HIV and malnutrition.
- Describe the effect of nutrition on HIV/AIDS.
- Explain about symptom-based nutritional care.

### 1. Nutrition and HIV

#### a. HIV and Nutrition—the Interaction

Malnutrition is a serious danger for people living with HIV. Even at the early stages of HIV infection, when no symptoms are apparent, HIV makes demands on the body's nutritional status. The risk of malnutrition increases significantly during the course of the infection. Good nutrition cannot cure AIDS or prevent HIV infection, but it can help to maintain and improve the nutritional status of a person with HIV infection and delay progression of HIV disease, thereby improving the quality of life of PLHIV. Nutritional care and support are important from the early stages of the infection to prevent the development of nutritional deficiencies. A healthy and balanced diet will help to maintain body weight and fitness. Eating well helps to

maintain and improve the performance of the immune system—the body's protection against infection—and thereby helps a person to stay healthy.

Many of the conditions associated with HIV affect food intake, digestion and absorption, while others influence the functions of the body. Many of the symptoms of these conditions (for example, diarrhea, weight loss, sore mouth and throat, nausea or vomiting) are manageable with appropriate nutrition. Good nutrition will complement and reinforce the effect of any medication taken.

**b. Barriers to good nutrition include the following:**

- Barriers related to information: provider barriers, client barriers, system barriers
- Barriers related to food choices: economic, geographical, physical, time constraints
- Barriers related to cooking and supplying: who will cook/supply
- Cultural, social and religious barriers: vegetarians
- Personal barriers: depression, loss of appetite, concurrent substance abuse, alcohol use

**c. Depending upon the stage of the disease, HIV/AIDS produces**

- Reduction in food intake
- Difficulties related to digestion
- Difficulties related to absorption
- Altered metabolism of nutrients (e.g. metabolism of carbohydrates/lipids may be different in HIV)
- Altered body functions: inability to produce saliva, other juices
- Improper utilization of fats

**d. Increased Resting Energy Expenditure (REE) is Observed in HIV-infected Adults**

- Energy requirements are likely to increase by 10% to maintain body weight and physical activity in asymptomatic HIV-infected adults, and maintain growth in asymptomatic children.
- During symptomatic HIV, and subsequently during AIDS, energy requirements increase by approximately 20–30% to maintain adult body weight.

Table 35: Relationship between HIV and malnutrition

Effect of malnutrition on HIV	Effect of good nutrition on HIV
Increased mouth ulcers, sores, etc., which facilitate transmission of infections	Reduced complications of HIV (diarrhoea, fever, muscle wasting, weight loss)
Reduced immunity to OIs, TB, pneumonia, etc.	Stronger immune system (proteins, antioxidants, zinc, selenium)
Rapid progression from HIV infection to AIDS	Maintenance of required body weight, improving energy level, productivity, sense of wellbeing
	Supports the effective action of OI treatment and ART
<i>Nutrition is an investment that has both physical and psychological benefits.</i>	

Figure 23: Effect of nutrition on HIV/AIDS

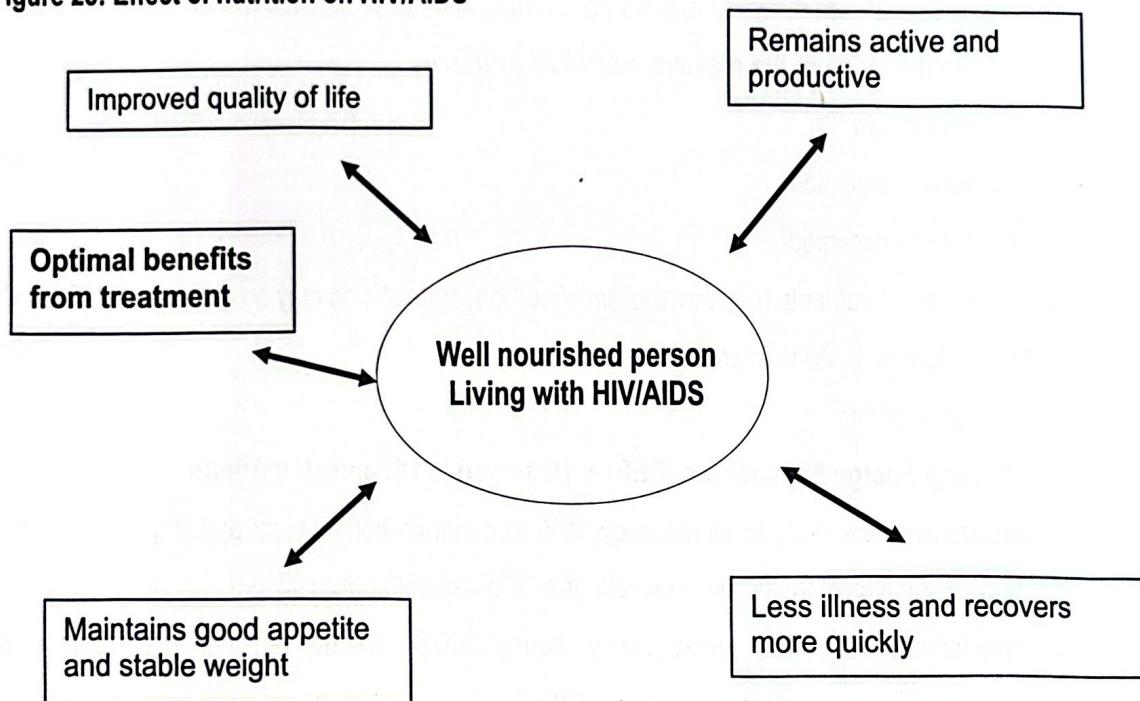


Table 36: Symptom-based nutritional care

Symptoms	Management
Loss of appetite	<ul style="list-style-type: none"> <li>• Eat small, frequent meals (5—6 meals/day)</li> <li>• Eat nutritious snacks</li> <li>• Drink plenty of liquids</li> <li>• Take walks before meals—the fresh air helps to stimulate appetite</li> <li>• Have family or friends assist with food preparation</li> <li>• Take light exercise and do light activity</li> <li>• Add flavour to drink and food</li> </ul>
Mouth ulcer	<ul style="list-style-type: none"> <li>• Avoid citrus fruits and acidic and spicy foods</li> <li>• Eat food at room temperature</li> <li>• Eat soft and moist food</li> <li>• Avoid caffeine and alcohol</li> </ul>
Candidiasis	<ul style="list-style-type: none"> <li>• Eat soft, cool and bland foods (like rice porridge, oat meal, mashed vegetables, apple juice, milk)</li> <li>• Add garlic (optional)</li> <li>• Avoid sugar (glucose, cane sugar), yeast, caffeine, spicy food, carbonated drinks and alcohol</li> </ul>
Nausea and vomiting	<ul style="list-style-type: none"> <li>• Eat small, frequent meals</li> <li>• Avoid an empty stomach as this makes the nausea worse.</li> <li>• Eat bland food</li> <li>• Avoid food with strong or unpleasant odours</li> <li>• Drink plenty of liquids</li> <li>• Rest and relax after meals</li> <li>• Avoid lying down immediately after eating</li> <li>• Avoid coffee and alcohol</li> </ul>
Constipation	<ul style="list-style-type: none"> <li>• Eat fibre-rich food and sprouted food</li> <li>• Take light exercise and do light activity</li> <li>• Drink plenty of water</li> <li>• Take warm drinks</li> </ul>
Anaemia	<ul style="list-style-type: none"> <li>• Eat meat and fish</li> <li>• Eat cereals like ragi and bajra</li> <li>• Eat a variety of green leafy vegetables (radish greens, mint, paruppu keerai/ kulfa kan, cauliflower leaves and sundaikai). The best way for the body to utilize iron from plant sources is to combine food rich in iron with a food rich in vitamin C, like oranges, lemons, tomatoes and papaya.</li> <li>• Take jaggery and dates between meals</li> </ul>

**Additional guidance**

- *Guidance on Nutrition assessment, education, counselling and support for adolescents and adults living with HIV.* Geneva, World Food Programme and World Health Organization, 2013.
- *Guidelines on HIV and infant feeding.* Geneva, World Health Organization, 2010 ([http://whqlibdoc.who.int/publications/2010/9789241599535\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241599535_eng.pdf)).

- *Guidelines for an integrated approach to the nutritional care of HIV-infected children (6 months – 14 years): handbook. Preliminary version for country introduction.* Geneva, World Health Organization, 2009 ([http://whqlibdoc.who.int/publications/2009/9789241597524\\_eng\\_Handbook.pdf](http://whqlibdoc.who.int/publications/2009/9789241597524_eng_Handbook.pdf)).
- *WHO and FAO. Nutritional care and support for people living with HIV/AIDS: a training course.* Geneva, World Health Organization, 2009 ([www.who.int/nutrition/publications/hivaids/9789241591898/en/index.html](http://www.who.int/nutrition/publications/hivaids/9789241591898/en/index.html)).

## 2. Community and Home-Based Care and Palliative Care

### PURPOSE:

In this session, participants will learn about community home-based care, including the essential elements of home-based care, patient assessment in the home, making the care plan, setting realistic goals, adherence monitoring and follow-up. They will also learn about the goal and management of palliative care, including management of symptoms such as pain, nausea and vomiting, anxiety and persistent diarrhea.

### OBJECTIVES:

By the end of this session, participants will be able to:

1. Define community and home-based care (CHBC)
2. List the service delivery approaches of community home-based care (CHBC).
3. List the essential elements and principles that should be in CHBC programs.
4. Define the major factors to address when assessing potential CHBC clients and families.
5. Define palliative care and its goal.
6. Assess various pain and the barriers to its management.
7. Manage palliative care through an interdisciplinary team approach

### 1. Definition of community home-based care (CHBC)

CHBC provides comprehensive services in the home, including health and social services, by formal and informal caregivers. Services are aimed at promoting, restoring and maintaining a person's maximal level of comfort, function and health, and at helping with a dignified death. CHBC includes physical, psychosocial, palliative and spiritual activities. It is a very important component of the continuum of care, which extends from the hospital, through different levels of the health and social welfare facilities, to the home.

### 2. Goal of CHBC

The goal of CHBC is to provide hope through good care, helping patients and families maintain their independence and have the best quality of life.

### 3. CHBC service delivery approach

There are approaches of home-based care, depending on national policy or local community situations. In determining which model is best for a given situation, you need to take into account such factors as cost, stigma, community resources, sustainability and adequacy of systems available to support CHBC.

**a. NGO /CBO**

- An outreach program that sends health care workers or teams out periodically to visit the homes and families of PLHIV.
- Active networking & referral with essential service providers is vital for the effectiveness of this approach.

**b. Government Approach**

The set up could be village health workers (VHW), PLHIV, maternal-child health worker (MCHW), community level health staff and other health facility staff who link for referrals to government health facilities.

- Community-driven and owned; typically relies on volunteers who reside in the communities covered by the program.
- Volunteers are trained to provide basic nursing care as well as emotional and spiritual support to the patient and family members.
- Volunteers instruct family members in caring for the patient and provide back-up support through regular visits.
- Transportation costs are minimal since volunteers live close to families.
- The challenge is to maintain and support the volunteers.

**c. Comprehensive Approach**

Utilizing resources from the private and government sectors, the comprehensive approach has the capacity to provide all essential services related to HIV care and support and features essential service providers (e.g. peer PLHIV, health workers, social workers, faith-based organizations, counselors, nutritionists, and community volunteers). This is an ideal service delivery approach as it can have strong linkages between the home, community and health facilities (up to tertiary level hospitals). Every CHBC setup should strive to create a comprehensive CHBC approach in their areas.

**d. Community care approach**

- Patients come to a site for a few hours during the day and get services such as symptom monitoring, drugs, recreation and counseling. This also gives caregivers a respite.

**4. Essential elements of home-based care**

- Clinical care;
- Basic nursing care;
- Psychological and spiritual care;
- Palliative care and pain relief;
- End of life care;
- Social support;

### **Care of affected and infected children**

- In addition to the more immediate issues addressed below, this also involves advance or succession planning for surviving children and dependents.
- HIV/AIDS and other terminal illnesses have a profound effect on children's lives. Economic hardships can lead to malnutrition, prostitution, life as a street child and early marriage. Their education is often interrupted and they feel the pressure of caring for sick family members or orphaned siblings. Emotional suffering can lead to other problems, such as depression, aggression, drug abuse, insomnia and failure to thrive. Children suffering multiple losses can experience profound grief, stigma and poverty. Psychosocial support is critical and involves a continuing process of meeting their physical, emotional, social and spiritual needs.
- CHBC programs can become involved in orphan care. They can promote an environment that enables psychosocial support for vulnerable children and can help create an expanded response by families, communities, governments and faith-based and other organizations.

Programs should include:

- Information and education for patients and families
- Training for family caregivers
- Immediate practical support for children and families in distress (material, nutritional, financial, funeral arrangements)
- Linkages and referral mechanisms for services such as schooling, nutrition and legal support.

### **5. Selected basic principles to guide home-based care programs**

- It is good practice to include all sectors of society, that is, communities, public and private institutions, and traditional groups.
- CHBC does not aim to shift the burden solely onto the community, but there should be active efforts to empower families and communities to take responsibility for their health, with the community sharing responsibility for care within that community.
- People living with HIV should be integral to the planning, design, monitoring and evaluation of programs.
- Provide services along a continuum of care that responds to needs of the infected and affected across different stages of illness and in a variety of settings. CHBC should reduce unnecessary visits and admissions to health facilities.
- Ideally, home-based care workers are part of a multidisciplinary team that provides access to the diverse service needs of patients and families. Where this is a luxury, as is often the case, training must help CHBC workers meet and assess their own needs, so they understand their own limitations and know where they can make needed referrals.

- There must be care for the caregivers: family members, community volunteers and health care workers.
- Raise awareness and build skills to support confidentiality about disclosing patients' HIV status to families and caregivers. Patients have a right to privacy.
- CHBC should be an entry point to other services such as legal aid, household aid and facility based care for patients and families. A home-based care program should ensure that children and families have access to social services.
- Programs must address the special needs of orphans and vulnerable children.

## 6. Assessing the patient in the home and developing a supportive action plan

Using a holistic approach, begin with a thorough assessment that addresses, among other elements:

a. Patient and family needs and current capacity for:

- Maintaining basic hygiene (personal, food, water, environment);
- Maintaining good nutrition and exercise;
- Taking comfort measures;
- Preventing HIV transmission;
- Managing symptoms;
- Taking drugs and medical measures that require physician input;
- Maintaining food and income security;
- Reaching sources of psychosocial and spiritual support;
- Getting legal support;
- Joining support group;
- Referral for appropriate for income generation activities.

b. Set realistic goals

- With the patient, family members and interdisciplinary team, establish a supportive plan based on the assessment above.
- Set realistic goals based on the patient's condition, disease stage, supportive plan and available resources.

c. Establish linkages between CHBC and other care and prevention programs.

- CHBC volunteers can help support HIV-infected patients with TB.
- Volunteers can also participate as supports for ART- DOTS patients.
- CHBC programs can provide mechanisms for support in PMTCT programs, including documentation of any inadvertent negative outcomes.
- CHBC plays a role in ART adherence for PMTCT programs or chronic ART management.

## **7. Definition and Goals of Palliative Care**

### **a) Introduction**

In spite of recent advances in the treatment of HIV/AIDS, there is no known cure. Unlike other terminal diseases, it is not easy to predict when death is imminent. A patient may die as a consequence of his or her first HIV manifestation or may develop a life-threatening OI and recover if appropriate timely treatment is given. Most patients, however, will experience an increasing frequency of health problems and finally reach a stage of severe immunosuppression over a period of several years. As the disease progresses, the need for symptomatic relief will become more important than curative treatment.

### **b) Definition**

Palliative care is the active total care of patients, their families and friends when a patient's disease is no longer responsive to curative treatment and life expectancy is relatively short.

### **c) Goals of palliative care**

To provide support and care that makes life comfortable for patients throughout all phases of the disease so they can live as comfortably as possible.

### **d) The underlying principles include:**

- Management of symptoms
- Psychosocial and spiritual support
- Teamwork and partnership with support groups
- Appropriate ethical considerations

### **e. Initiating and managing palliative care**

The decision to stop causal treatment should be based on two criteria:

- The patient has had a long course of progressively worsening illness (is in an advanced stage of immunodeficiency).
- Everything possible has been done to investigate and manage the specific conditions from which the patient is suffering and, despite adequate management, the patient continues to deteriorate.

### **• Managing palliative care**

- It is essential to establish interdisciplinary teams to deal with all the problems, for no single health or social worker can adequately address HIV-related problems in all their complexity, and it is emotionally draining on staff to support persons and families affected by HIV.
- The core of this team are the medical, nursing, counseling, social and other services working in collaboration with NGOs, the private sector, volunteers and community-based support groups.
- Transition from active care to palliative care does not happen at a single point in time.

- Palliative care is most successful when initiated early in the disease process since it takes time to develop the necessary supportive relationships between the patient and the interdisciplinary team.

**Table 37: Continuum of Care in the Management of HIV Disease and AIDS**

	Medical	Management	Palliative Care	
Stages of HIV disease	Early HIV disease (stage 2)	Intermediate HIV disease (stage 3)	Advanced HIV disease AIDS (stage 4)	D
Clinical problems	Frequent infections with common pathogens	Infections with common and opportunistic pathogens	Combination of health problems (e.g., chronic diarrhea, weight loss, fever, anemia)	E
General condition	Mobile and active. Rapid response to treatment.	Mostly mobile with increasing periods of illness	Patients often at home or in bed	A
Medical treatment	Curative anti-infectious treatment	Curative or causal treatment. Consider prophylaxis or maintenance treatment. Supportive treatment (skin lesions, anemia nutrition, vitamins).	Supportive treatment (skin lesions, anemia, diarrhea, etc.). Maintain nutrition. Discontinue causative treatment and prophylaxis?	T
Palliative care	Analgesics, Antipyretics. Pre-and post-test counseling. Involve family member(s) or other persons of confidence.	Analgesics, antipyretics. Follow-up counseling with family members. Address social issues. Nursing care during periods of illness.	Narcotic analgesics when needed. Continuous (home) nursing care. Terminal counseling and support.	H

## 8. Pain

- Definition:

Persistent or recurrent pain lasting more than 48 hours and not alleviated by simple comfort measures. It can be burning; tingling; flashes of pain or unremitting pain that is sharp, aching or dull.

- Types and common causes of pain:

**Table 38: Types and common causes of pain**

Headache	Cryptococcal meningitis, TB meningitis, Viral meningitis (HIV, CMV) Malaria, Muscle tension headache, Neurosyphilis, Side-effect of some medications, Toxoplasmosis Dehydration, Lymphoma of the brain, Herpes zoster
Peripheral neuropathy	HIV Cytomegalovirus, From medication, Diabetes Avitaminosis, Post-herpetic neuralgia
Abdominal pain	Peptic ulcer, Gastroenteritis Retroperitoneal adenopathy Abdominal tumors (lymphomas and Kaposi's sarcoma) Pelvic inflammatory disease Abdominal abscesses, Worm infestations, Acute abdomen
Oropharyngeal and esophageal pain	Reflux esophagitis Candidiasis Herpes simplex Kaposi's sarcoma Tonsillitis/Pharyngitis Aphous ulcers
Skin pain Herpes	Herpes zoster (either acute initial or post-herpetic pain) Skin sepsis
Chest pain	Lung infections Mediastinal lesions (retrosternal adenopathy, Kaposi's sarcoma, etc.) Esophageal candidiasis
Generalized pain	Fever Bedridden status Rheumatism Non-specific etiology

#### Barriers to pain management:

- Problems related to health care providers
- Problems related to patients
- Problems related to health care system

#### 9. Palliative care

##### Introduction

- The most common symptoms are:

- Pain
- Fatigue/weakness
- Shortness of breath/dyspnea
- Persistent diarrhea

- Difficulty sleeping/insomnia
- Nausea and vomiting
- Providers may overlook these symptoms because they do not know how to manage them or feel inadequate to address them.
- Patients may avoid acknowledging them to providers because they believe they must "put up with them" or "it is God's punishment."
- Effective symptom management is based on a thorough understanding of the symptom and education of patient and family.
  - It requires a multidisciplinary approach.
  - The goal is to help the patient move from a feeling of helplessness to a feeling of supremacy over the symptom and develop or retain as much control as possible over his or her life and illness.
  - Medication and/or non-pharmacologic interventions can manage symptoms.
- You can identify all symptoms by reviewing each of them: ask about its character (what it feels like), the location, what makes it worse, what makes it better, are other symptoms associated with it and how does it limit or affect the patient's daily life.
  - Asking these questions conveys your interest in the patient.
  - Just the act of asking and being aware how important a symptom is to the patient provides some relief from it; a symptom often worsens when a patient has to deal with it alone and has growing fear about what is causing it.
  - A review of the symptoms will also alert the provider to the appearance of new symptoms that might herald progression of disease.

#### **Pain management: Assess the patient for pain**

- Determine the cause of the pain by history and examination (for new pain and any change in pain):  
Where is the pain? What makes it better/worse? Describe it. What type of pain is it? What are you taking now for the pain?
- Determine the type of pain: is it common pain or special pains (such as shooting nerve pain, zoster, colic or muscle spasms)?
- Is there a psychological or spiritual component?
- Grade the pain by number of fingers or pointing on a ruler or other methods.

#### **Pain management: Treat pain**

- With analgesics, according to the analgesic ladder.
- Reassess need for pain medication and other interventions frequently.

- Repeat grading of the pain.
- Investigate any new problems.
- Give analgesics:

*By mouth*

- If possible, give by mouth (rectal is an alternative; avoid intramuscular).

*By the clock*

- Give painkillers at fixed time intervals (by clock or radio or sun).
- Start with a small dose, and then titrate dose against the patient's pain levels, until the patient is comfortable.
- Next dose should be given before the effect of previous dose wears off.
- For breakthrough pain, give an extra rescue dose (same dosing of the four-hourly dose) in addition to the regular schedule.

*By the individual*

- Link first and last doses with waking and sleeping times.
- Write out drug regimen in full or present in a drawing.
- Teach about drug use.
- Check to be sure patient and family or caregiver understands.
- Ensure that pain does not return and patient is as alert as possible.

*By the analgesic ladder (see the following figure):*

- Give only one drug from the opioid and non-opioid group at a time.

Exception: If no codeine is given, aspirin every four hours can be combined with paracetamol every four hours. Overlap so one is given every two hours

**Use of opioid and non-opioid analgesics**

Table 39: Use of opioids and non-opioid analgesics

Analgesics	Starting dose in adults	Range	Side effects/cautions
<b>Non-opioid</b>			
Paracetamol (also lowers fever).	500 mg 2 tablets every 4 to 6 hour (skip dose at night or give another analgesic to keep total to 8 tablets).	Only 1 tablet may be required in elderly or very ill or when combined with opioid. Mild pain might be controlled with every 6 hour dosing	Do not exceed eight 500 mg tablets in 24 hours (more can cause serious liver toxicity).
Aspirin (acetylsalicylic	600 mg (2 tablets)		Avoid use if gastric

acid) (also anti-inflammatory and lowers fever).	of 300 mg) every 4 hours.		problems. Stop if epigastric pain, indigestion, black stools petechiae or bleeding. Do not give to children under 12 years. Avoid if presence of any bleeding.
Ibuprofen (also anti-inflammatory, lowers fever, for bone pain).	400 mg every 6 hours.		Max. 8 tablets per day. Gastric irritation. Need to take with food/milk
<b>Opioid for mild to moderate pain (give in addition to aspirin or paracetamol)</b>			
Codeine (if not available, consider alternating aspirin and paracetamol*).	30 mg every 4 hours.	30-60 mg every 4 to 8 hrs. Maximum daily dose for pain 180-240 mg due to constipation switch to morphine.	Give laxative to avoid constipation unless diarrhea. May causes drowsiness. Use caution when driving or operating machinery.
<b>Opioid for moderate to severe pain</b>			
Oral morphine 5 mg/5 ml or 50 mg/5 ml. Drop into mouth. Can also be given rectally (by syringe).	2.5-5 mg every 4 hours (dose can be increased by 1.5 or doubled after 24 hours if pain persists).	According to need of patient and breathing. There is NO ceiling dose.	Give laxative to avoid constipation unless diarrhea. Side effects include nausea, vomiting, drowsiness and itchiness

\* *Exception: If no codeine, aspirin every 4 hours can be combined with paracetamol every 4 hours—overlap so one is given every 2 hours.*

*Note:* Give only one drug from the opioid and non-opioid group at a time

**Table 40: Respond to side effects of morphine or other opioids**

If patient has a side effect:	Then manage as follows:
Constipation	<ul style="list-style-type: none"> <li>• Increase fluids and bulk.</li> <li>• Give stool softener (docusate) at time of prescribing plus stimulant (senna).</li> <li>• Liquid Parafin is available locally</li> <li>• Prevent by prophylaxis (unless diarrhea).</li> </ul>

<b>Nausea and/or vomiting</b>	Give an antiemetic (metoclopramide, haloperidol or chlorpromazine). Usually resolves in several days. May need round-the-clock dosing.
<b>Respiratory depression (rare when oral morphine is increased step by step for pain)</b>	If severe, consider withholding next opioid dose, then halve dose.
<b>Confusion or drowsiness (if due to opioid)</b> <b>Decreased alertness</b> <b>Trouble with decision making</b>	Usually occurs at start of treatment or when dose is increased. Usually resolves within a few days. Can occur at end of life with renal failure. Halve dose or increase <del>me</del> between doses. Or provide time with less analgesia when the <del>patient wants to be more fully alert to make</del>
<b>Twitching (myoclonus—if severe or bothers patient during waking hours)</b>	If on high dose, consider reducing dose or changing opioids (consult or refer). Re-assess the pain and its treatment.
<b>Somnolence (excessively sleepy)</b>	Extended sleep can be from exhaustion due to pain. If persists more than 2 days after starting, reduce the dose by half.

#### Give medications to control special pain problems

There are nerve injury pains and pains from special conditions which can be relieved by specific medication. Provide specific treatment in combination with drugs from the analgesic ladder.

#### The use of steroids:

- You can use steroids, provided you treat any concurrent infection at the same time and give nystatin or ketoconazole to prevent/treat thrush.
- Side effects are seen with prolonged use; use lowest effective dose.
- If you see no benefit, withdraw steroids after 1-2 weeks.

#### Additional guidance

*IMAI district clinician manual: hospital care for adolescents and adults. Guidelines for the management of common illnesses with limited resources. Geneva, World Health Organization, 2011 ([www.who.int/hiv/pub/imai/imai2011/en](http://www.who.int/hiv/pub/imai/imai2011/en)).*

## **Module-III: HIV Testing and Counseling (HTC) and Provider Initiated Testing and Counseling (PITC) and Post Exposure Prophylaxis (PEP)**

### **Section – A: HIV Testing and Counseling (HTC) and Provider Initiated Testing and Counseling (PITC)**

#### **PURPOSE:**

In this session, participants will learn about the importance of adherence, issues involved in promoting ARV drug adherence. They will have the opportunity to learn regarding HIV Testing and Counseling (HTC) and Provider Initiated Testing and Counseling (PITC).

#### **OBJECTIVES:**

By the end of this session, the participants will be able to:

- Explain the importance of adherence to ensure the maximum and most prolonged benefit from ART.
- Conduct an assessment of the potential individual barriers to adherence
- Calculate the individual client's adherence
- Offer clients simple strategies for overcoming adherence problems
- Explain Pretest information and informed consent
- Describe Post Test Counseling
- Also describe Counseling- all Epidemics Settings

#### **1. Adherence Counseling**

##### **A. Adherence**

###### **What Is Adherence?**

- Adherence is patient participation in a plan of care
  - Attending clinic visits
  - Taking medications as prescribed
  - Following medical advice (disclosure, substance use, condom use)
  - Implies a collaboration between patient and provider
- This is different from "Compliance" which means that a patient just does what the health care worker tells him/her.

###### **Why Is Adherence Important?**

- Adherence is Important because
  - Regular follow up with medical staff is critical
  - Near perfect pill taking is needed for viral suppression
  - Near perfect pill taking is needed to avoid viral resistance

- If HIV becomes resistant to certain ARVs, those drugs will not work for the rest of their lives.
- In fact, the efficacy of other drugs that they have never taken may be reduced due to "cross resistance"

### **Assessing Adherence**

- **When to assess:**

- Beginning of treatment: assess potential barriers.
- Ideally, clients should have three adherence counseling sessions before starting ART.
- During treatment: assess success and barriers
- No progress
- Relapse
- Non compliance with attendance
- Inconsistent laboratory results

- **What to assess:**

- Logistic barriers
- Medication barriers
- Psychosocial barriers
- Understanding
- Health Beliefs
- Stigma
- Mental Health
- Communication
- Developmental Issues
- Forgetting
- Neglect by care giver

### **Adherence Assessment**

#### **Methods of assessing adherence?**

- Direct methods (therapeutic drug monitoring, other drug marker)
- Indirect methods:
  - Self report
  - Caregiver report
  - Clinician assessment
  - Medical chart review
  - Clinic attendance
  - Pill count
  - Pharmacy refill record
  - Electronic drug monitoring
  - DOT
  - Resistance test
  - Therapeutic impact (CD4, VL)
  - Disease progression

- Mortality

### Steps in Assessing Adherence

- Establish a relationship with the patient/family

- Spend time talking with them, even about topics other than medical care
- This makes it more likely that they will tell you about adherence problems

- Confirm understanding of the regimen

- Names of drugs
- Doses
- Timing of dosing figure

- Use open-ended (NOT "yes/no") questions and acknowledges barriers

- "These are a lot of medicines to have to take, some people have trouble remembering to take their medications regularly"
- "When was the last time you missed a dose?"

- Assume some non-adherence

- This removes judgment from missed doses
- Increases likelihood of revealing difficulties with adherence

- Ask about recent past

- Difficult to recall long periods; families will be most accurate about past few days

- Anticipate/Normalize

- "Sometimes people forget to take their ARVs. How often has that been a problem for you?"

### B. Continued Adherence information

#### Factors Affecting Adherence

##### • Patient-related factors

- Patient readiness/commitment
- Forgetfulness
- Travel away from home
- Lifestyle
- Active Mental Illness (e.g. Depression)
- Cultural
- Socioeconomic
- Burn out
- Perceived lack of need ("I'm feeling fine, now")
- Lack of trust of health care provider

- **Provider-related factors**

- Provider readiness - knowledge, skills
- Provider Time constraints
- Counseling
- Patient education
- Medication alerts, e.g., charts, diaries, etc.
- Adherence team
- Provider support

- **Regimen/Drug-related factors**

- Pill burden
- Frequency
- Side effects (fear of potential side effects)
- Food restrictions
- Drug interactions
- Storage
- Patient unable to identify their medications

- **Other factors**

- Cost
- Sustainable supply
- Multisectoral Adherence Support
- Clinic staff , PLHIV Groups, CHBC Workers
- Domestic Violence
- Discrimination
- Lack of reliable access to primary medical care

### **Key Advice to prepare patient for ART**

- HIV and progression of its related illnesses
- ART- life saving, but life-long commitment required, does not cure.
- Need for complete adherence: If forget more than 3 times in a month, it may fail.
- Side effects and drug interactions
- Importance of disclosure of status
- Importance of testing partners and children

### **Adherence Intervention Strategies**

- Educate and motivate: basic drug info, importance of adherence, timing of medications, drug interactions,

- Simplify regimen
- Tailor treatment to patient's lifestyle
- Prepare for and manage side effects
- All HCW's working with patient to discuss adherence: Doctor, nurse, counselor
- Employ an adherence team
- Discuss adherence at EACH visit (even after long period on treatment)
- Provide emotional and practical life support
- Address patient related issues
- Recruit an adherence monitor
- Provide adherence promoting devices
- Use home-based care staff to promote adherence
- Use adaptation of directly observed therapy for time to be determined

#### **Advice for "forgotten doses".**

If a patient forgets a dose of ART, what should you advise?

- When you notice that you missed a dose, take your pill right away.

#### **For the NEXT DOSE**

- If the next planned pill-taking time is four hours away or less, DO NOT take your next dose.

Instead wait four hours and then take your next dose. After this follow your regular dosing schedule.

- Do not take two doses at one time.

- If it is already time for the next dose, just take that dose and carry on with the treatment schedule.

#### **HIV Testing and Counseling (HTC) and Provider Initiated Testing and Counseling (PITC)**

(source:<http://www.aids.gov/hiv-aids-basics/prevention/hiv-testing/pre-post-test-counseling>)

#### **Background**

Prior to establish the counseling services, efforts must be made to ensure that a supportive social, policy and legal framework is in place to maximize positive outcomes and minimize potential harms to patients.

When recommending HIV testing and counseling, service providers should always aim to do what is in the best interests of the individual patient. This requires giving sufficient information to the clients in order to make an informed and voluntary decision to uptake the HIV test, maintaining patient confidentiality, performing post-test counseling and making referrals to appropriate services.

In many low and middle income countries, the primary model for HIV testing has been the provision of client-initiated HIV testing and counseling (HTC) services. The HTC service facilitates early referral for care and support of HIV infected individuals and is an effective method of preventing onward transmission of

HIV infection. HTC services may result in positive behavioural change e.g. avoiding/minimizing unprotected sexual intercourse.

Increasingly, provider-initiated approaches in clinical settings are being promoted, i.e. health care providers routinely offer HIV testing in a context in which the provision of, or referral to, effective prevention and treatment services is assured.

**Client-initiated HIV testing and counseling (also called HIV Testing and Counseling HTC)** involves individuals actively seeking HIV testing and counseling at a facility that offers these services. Client-initiated HIV testing and counseling usually emphasizes individual risk assessment and management by counselors, addressing issues such as the desirability and implications of taking an HIV test and the development of individual risk reduction strategies.

Client-initiated HIV testing and counseling is conducted in a wide variety of settings including health facilities, stand-alone facilities outside health institutions, through mobile services & in community-based settings.

**Provider-initiated HIV testing and counseling** refers to HIV testing and counseling which is recommended by health care providers to persons attending health care facilities as a standard component of medical care. The major purpose of such testing and counseling is to enable specific clinical decisions to be made and/or specific medical services to be offered that would not be possible without knowledge of the person's HIV status.

An "opt-out" approach is recommended to adopt in HTC and provider-initiated HIV testing and counseling in health facilities. With this approach, an HIV test is recommended;

- 1) For all patients, irrespective of epidemic setting, whose clinical presentation might result from underlying HIV infection.
- 2) As a standard part of medical care for all patients attending health facilities in generalized HIV epidemics; and
- 3) More selectively in concentrated and low-level epidemics.

Individuals must specifically decline the HIV test if they do not want it to be performed. Additional discussion of the right to decline HIV testing, of the risks and benefits of HIV testing and disclosure, and about social support available may be required for groups especially vulnerable to adverse consequences upon disclosure of an HIV test result. An "opt-in" approach with informed consent may merit consideration for highly vulnerable populations.

## **2. Pre-test information and Informed consent**

Depending on local conditions, pre-test information can be provided in the form of individual information sessions or in group health information talks. Informed consent should always be given individually, in private, in the presence of a health care provider. When recommending HIV testing and counseling to a patient, the health care provider should at a minimum provide the following information to the client:

- The reasons why HIV testing and counseling is being recommended.
- The clinical and prevention benefits of HIV testing and the potential risks, such as discrimination, abandonment or violence.
- The services that are available either for a HIV-negative or for a HIV-positive client including availability of antiretroviral treatment.
- The fact that the test result will be treated confidentially and will not be shared with anyone other than health care providers directly involved in providing services to the client.
- The fact that the client has the right to decline the test and that testing will be performed unless the patient exercises that right.
- The fact that declining an HIV test will not affect the client's access to services that do not depend upon knowledge of HIV status.
- In the event of an HIV-positive test result, encouragement of disclosure to other persons who may be at risk of exposure to HIV.
- An opportunity to ask the questions from health care provider.

Patients should also be made aware of relevant laws in jurisdictions that mandate the disclosure of HIV status to sexual and/or drug injecting partners.

Verbal communication is normally adequate for the purpose of obtaining informed consent. Jurisdictions that require consent to be given in writing are encouraged to review this policy.

Pre-test information for women who are or may become pregnant should also include:

- The risks of transmitting HIV to the infant
- Measures that can be taken to reduce mother-to-child transmission, including antiretroviral prophylaxis and infant feeding counseling
- The benefits to infants of early diagnosis of HIV.

Special considerations apply in the case of children and adolescents who are below the legal age of maturity (usually 18 years of age). As minors, children cannot legally provide informed consent. However, they have the right to be involved in all decisions affecting their lives and to make their views known according to their level of development. Every attempt should be made to inform and involve the child and to obtain her/his consent. Informed consent from the child's parent or guardian is required.

Declining an HIV test should not result in reduced quality or denial of services that do not depend on knowledge of HIV status.

### **3. Post-test counselling**

Post-test counseling is an integral component of the HIV testing process. All individuals undergoing HIV testing must be counseled when their test results are given, regardless of the test result. Results should be

given to patients in person by health care providers or by trained lay personnel. Ideally, post-test counseling should be provided by the same health care provider who initiated HIV testing and counseling. Results should not be given in group settings.

Counseling for those whose test result is *HIV-negative* should include the following minimum information:

- An explanation of the test result, including information about the window period for the appearance of HIV-antibodies and a recommendation to re-test in case of a recent exposure.
- Basic advice on methods to prevent HIV transmission.
- Provision of male and female condoms and guidance on their use.

The focus of **Post-test counseling for people with HIV-positive test results** is psychosocial support to cope with the emotional impact of the test result, facilitate access to treatment, care and prevention services, prevention of transmission and disclosure to sexual and injecting partners. Health care providers should:

- Inform the patient of the result simply and clearly, and give the patient time to consider it
- Ensure that the patient understands the result
- Allow the patient to ask questions
- Help the patient cope with emotions arising from the test result
- Discuss any immediate concerns and assist the patient to determine a person available in her/his social network and who may accept to offer immediate support
- Describe follow-up services that are available in the health facility and in the community, with special attention to the available treatment, PMTCT, and care and support services
- Provide information on how to prevent transmission of HIV, including provision of male and female condoms and guidance on their use
- Provide information on other relevant preventive health measures such as good nutrition, use of co-trimoxazole and, in malarious areas, insecticide-treated bed nets
- Discuss possible disclosure of the result, when and how this may happen and to whom
- Encourage and offer referral for testing and counseling of partners and children.
- Assess the risk of violence or suicide and discuss possible steps to ensure the physical safety of clients, particularly women, who are diagnosed HIV-positive
- Arrange a specific date and time for follow-up visits or referrals for treatment, care, counseling, support and other services as appropriate (e.g. tuberculosis screening and treatment, prophylaxis for opportunistic infections, STI treatment, family planning, antenatal care, opioid substitution therapy, and access to sterile needles and syringes).

**Post-test counseling for pregnant women whose test result is HIV-positive** should also address the following:

- Childbirth plans
- Use of antiretroviral drugs for the client's own health, and to prevent mother-to-child transmission including the information on availability of ARV & when to commence.
- Adequate maternal nutrition, including iron and folic acid
- Infant feeding options and support to carry out the mother's infant feeding choice
- HIV testing for the infant and the follow-up.
- Partner testing

It is emphasized that, as in the case of client-initiated HIV testing and counseling, provider initiated HIV testing and counseling is to be voluntary and the "three C's" – (informed consent, Counseling and confidentiality –) must be observed.

• **Basic prevention services for persons diagnosed HIV-negative:**

- Post-test HIV prevention counseling for individuals or couples that includes information about prevention services
- Promotion and provision of male and female condoms
- Needle and syringe access and other harm reduction interventions for injecting drug users
- Post-exposure prophylaxis, where indicated

• **Basic prevention services for persons diagnosed HIV-positive:**

- Individual post-test counseling by a trained provider that includes information about and referral to prevention, care and treatment services, as required
- Support for disclosure to partner and couples counseling
- HIV testing and counseling for partners and children
- Safer sex and risk reduction counseling with promotion and provision of male and female condoms
- Needle and syringe access and other harm reduction interventions for injecting drug users
- Interventions to prevent mother-to-child transmission for pregnant women, including antiretroviral prophylaxis
- Reproductive health services, family planning counseling and access to contraceptives

• **Basic care and support services for persons diagnosed HIV-positive:**

- Education, psychosocial and peer support for management of HIV
- Periodic clinical assessment and clinical staging
- Management and treatment of common opportunistic infections

- Co-trimoxazole prophylaxis
- Tuberculosis screening and treatment when indicated; preventive therapy when appropriate
- Malaria prevention and treatment, where appropriate
- STI case management and treatment
- Palliative care and symptom management
- Advice and support on other prevention interventions, such as safe drinking water
- Nutrition advice
- Infant feeding counseling
- Antiretroviral treatment

#### **4. Counseling - all epidemic settings**

HIV testing and counseling should be recommended in all health facilities to:

- Adults, adolescents, or children who present in clinical settings with signs and symptoms or medical conditions that could indicate HIV infection, including tuberculosis\*.
- HIV-exposed children or children born to HIV-positive women.
- Children with suboptimal growth or malnourished children, in generalized epidemics, who are not responding to appropriate nutritional therapy.
- Men seeking circumcision as an HIV prevention intervention.

\* If data show that HIV prevalence in patients with tuberculosis is very low, the recommendation of HIV testing and counseling to these patients may not remain a priority.

#### **Generalized epidemic settings**

HIV testing and counseling should additionally be recommended to all patients in all health facilities, including medical and surgical services, public and private facilities, inpatient and outpatient settings and mobile or outreach medical services.

In the case of phased implementation of provider-initiated HIV testing and counseling, an approximate order of priority, depending on local conditions, may be as follows:

- Medical inpatient and outpatient facilities, including TB clinics
- Antenatal, childbirth, and postpartum health services
- STI services
- Services for most-at-risk populations
- Services for children under 10 years of age
- Services for adolescents
- Surgical services
- Reproductive health services, including family planning

## **Concentrated and low-level epidemic settings**

Implementation of provider - initiated HIV testing and counseling should additionally be considered in:

- STI services
- Services for most-at-risk populations
- Antenatal, childbirth, and postpartum health services
- TB services

Provider-initiated HIV testing and counseling should be accompanied by a recommended package of HIV-related prevention, treatment, care and support services. Although not all the services need necessarily be available in the same facility as where the HIV test is performed, they should be available through local referral. Although access to antiretroviral therapy should not be an absolute prerequisite for the implementation of provider-initiated HIV testing and counseling, there should at least be a reasonable expectation that it will become available within the framework of a national plan to achieve universal access to antiretroviral therapy for all who need it.

## **Section – B: Post Exposure Prophylaxis (PEP)**

### **PURPOSE:**

In this session, participants will learn about occupational exposure to HIV, how to manage it, HIV PEP, and drug selection for PEP.

### **OBJECTIVES:**

By the end of this session, the participants will be able to:

1. Explain the definitions and principles of providing PEP.
2. Understand what type of Health Care Providers at risk of blood and/ or body fluid exposures
3. Describe how to preventing exposure and Transmission of HIV and other Viruses.
4. Explain how to manage exposed person to HIV effectively.
5. Understand the various PEP regimens and when to use which.
6. Describe ways of helping healthcare workers overcome their fears and biases about working with HIV infected persons.
7. Describe the implementation of PEP in the Health Care Facilities

### **1. Definitions and Principles of Providing PEP**

**Occupational exposure:** refers to exposure to potential blood-borne infections (HIV, HBV and HCV) during performance of duties in relation to provision of health care.

**Non-occupational exposure:** refers to exposure to potential blood-borne infections (HIV, HBV, and HCV) outside of the health care setting.

**Post exposure prophylaxis (PEP):** refers to the comprehensive management given to minimize the risk of infection following potential exposure to blood-borne pathogens (HIV, HBV, and HCV). This includes counseling, risk assessment, relevant laboratory investigations based on informed consent of the source and exposed person, first aid and depending on the risk assessment, the provision of short term (4 weeks) prophylactic course of antiretroviral drugs, with follow up and support.

The term "**Health Care Personnel (HCP)**" is defined as any person, paid or unpaid; working in healthcare settings who are potentially exposed to infectious materials (e.g. blood, tissue, and specific body fluids and medical supplies, equipment, or environmental surfaces contaminated with these substances). HCP include: emergency care providers, laboratory personnel, autopsy personnel, hospital employees, medical and nursing students and health care professionals of all levels. If required, PEP can also be given to public safety workers, including law enforcement personnel, prison staff, fire-fighters, workers in needle exchange programs and workers in international HIV programs.

**"Exposure"** which may place an HCP at risk of blood-borne infection is defined as: a percutaneous injury (e.g. needle-stick or cut with a sharp instrument) or, contact with the mucous membranes of the eye or mouth, or contact with non-intact skin (particularly when the exposed skin is chapped, abraded, or afflicted with dermatitis), or contact with intact skin when the duration of contact is prolonged (e.g. several minutes or more) with blood or other potentially infectious body fluids.

**Non-discrimination:** The decisions about whether to provide PEP should be based on clinical consideration of risk (risk assessment). Providers should give information, services and education without discrimination.

**Confidentiality:** The provision of information regarding PEP should be confidential including information about HIV testing, PEP provision and the reasons for seeking PEP.

**Informed consent:** For prescribing PEP informed consent to be obtained as for any other medical procedure. Consent for HIV testing in context of HIV exposure and/or taking PEP, needs to be done according to national counseling and testing guidelines.

In special situations where the individual has limited/no capacity to provide valid consent (e.g. children, or unconscious or mentally ill adults), a proxy may be able to provide consent e.g. parents/guardian/caretaker.

## **2. Who is at Risk?**

### **Health Care Providers at risk of blood and/ or body fluid exposures;**

- Interns and medical students
- Nursing staff and students
- Physicians
- Surgeons

- Emergency care providers
- Dentists & staff of Dental care facilities
- Labour and delivery room personnel
- Laboratory Staff
- Health facility cleaning staff and clinical waste handlers
- Health care providers dealing with autopsies

**Table 41: Potentially infectious body fluids**

Exposure to body fluids considered 'at risk'	Exposure to body fluids considered 'not at risk'	
Blood		
Semen	Tears	unless these secretions
Vaginal secretions	sweat	contain visible blood
Cerebrospinal fluid	Urine and faces	
Synovial, pleural, peritoneal, pericardial fluid	saliva	
Other body fluid Contaminated with visible blood		

Any direct contact (i.e., contact without barrier protection) to concentrated virus in a research laboratory or production facility requires clinical evaluation. For human bites, clinical evaluation must include the possibility that both the person bitten and the person who inflicted the bite were exposed to blood-borne pathogens.

### **3. Preventing Exposure to and Transmission of HIV and other Viruses**

The average risk of acquiring HIV infection after different types of occupational exposure is low compared to risk of infection with HBV or HCV. In terms of occupational exposure the important routes are needle stick exposure (0.3% risk for HIV, 9–30% for HBV and 1–10% for HCV) and mucous membrane exposure (0.09% for HIV).

**Table 42: Risk of HIV transmission from different routes**

Exposure route	Estimated risk of transmission
Blood transfusion	90-100%
Perinatal	20-45%
Sexual intercourse	
◆ Anal receptive_____	0.1 to 3%
◆ Anal insertive_____	up to 0.06%
◆ Vaginal receptive_____	
◆ Vaginal insertive_____	0.1 to 0.2%
◆ Oral receptive_____	0.03 to 0.09%
	up to 0.04%
Sharing injecting equipment	0.7%
Occupational Needle stick injury	0.3%
Mucous membrane contact	0.1%

Certain work practices increase the risk of needle stick injury such as:

- Recapping needles (Most important).
- Transferring a body fluid between containers.
- Failing to dispose of used needles properly in puncture-resistant sharps containers.
- Poor healthcare waste management practices

*How to protect health care personnel from needle stick/sharp injuries:*

- Avoid the use of needles where safe and effective alternatives are available.
- Avoid recapping needles.
- Plan for safe handling and disposal of needles before using them.
- Promptly dispose of used needles in appropriate sharp disposal containers.
- Report all needle stick and sharp-related injuries promptly to ensure that you receive appropriate follow-up care.
- Participate in training related to infection prevention.

- Help your institute selects and evaluate devices with safety features that reduce the risk of needle stick injuries.
- Use devices with safety features provided by the institute (wherever possible).
- Record and monitor injuries and exposures to potentially infected body fluids by maintaining a register on accidental injuries and mucous membrane exposures to potentially infected body fluids in each section of the health care facility.

**Staff information:** All categories of HCP within the hospital should be informed about how to protect themselves against HIV and other pathogens transmitted by blood or body fluids. The information must be reinforced on a regular basis. All staff shares an individual and collective responsibility in this regard. The Medical Superintendent (MS)/Dean/Principal/In-charge of the Hospital must constitute a hospital infection control committee which will conduct regular trainings and monitor hospital infection control including universal precaution and post-exposure prophylaxis implementation and quality control. The MS must ensure that the hospital has a written protocol and Standard Operational Procedures (SOP) to handle occupational exposures and are disseminated to all relevant personnel/departments.

The Medical Superintendent of the hospital has the responsibility of informing all staff about:

- The universal / standard precautions to be followed in health care facility.
- Use of personal protective equipment.
- Other preventive measures to be taken against these viruses (including vaccination).
- SOPs to be followed in case of accidental exposure to blood and body fluids.

All hospital staff must know whom to report for PEP in case of occupational exposure

### **Universal precautions**

Universal precautions are intended to prevent the exposure of health-care workers and patients to blood-borne pathogens in a health care facility. These must be practiced in regard to the blood and body fluids of all patients, regardless of their infection status.

#### **Universal precautions include:**

- hand-washing before and after all medical procedures
- safe handling and immediate safe disposal of sharps: not recapping needles; using special containers for sharp disposal; using needle cutter/destroyers; using forceps instead of fingers for guiding sutures; using Vacutainers where possible
- safe decontamination of instruments;
- use of protective barriers whenever indicated to prevent direct contact with blood and body fluid

such as gloves, masks, goggles, aprons, and boots. A HCP who has a cut or abrasion should cover the wound before providing care

- safe disposal of contaminated waste

#### **4. Management of the Exposed Person**

##### **Management of Exposure Site - First Aid**

For skin—if the skin is broken after a needle-stick or sharp instrument:

- Immediately wash the wound and surrounding skin with water and soap, and rinse. Do not scrub.
- Do not use antiseptics or skin washes (bleach, chlorine, alcohol, betadine).

##### **After a splash of blood or body fluids:**

- To unbroken skin:
  - i) Wash the area immediately
  - ii) Do not use antiseptics
- For the eye:
  - a) Irrigate exposed eye immediately with water or normal saline. Sit in a chair, tilt head back and ask a colleague to gently pour water or normal saline over the eye.
  - b) If wearing contact lens, leave them in place while irrigating, as they form a barrier over the eye and will help protect it. Once the eye is cleaned, remove the contact lens and clean them in the normal manner. This will make them safe to wear again
- Do not use soap or disinfectant on the eye.
- For mouth:
  - a) Spit fluid out immediately
  - b) Rinse the mouth thoroughly, using water or saline and spit again. Repeat this process several times
  - c) Do not use soap or disinfectant in the mouth

Consult the designated physician of the institution for management of the exposure immediately.

##### **Establish eligibility for PEP**

On an average the HIV sero-conversion rate is 0.3% after an Accidental Exposure to Blood or Body Fluids through a needle stick injury. The real risk of transmission depends on the amount of HIV transmitted (= amount of contaminated fluid and the viral load).

A designated person/trained doctor must assess the risk of HIV and HBV transmission following an accidental exposure. This evaluation must be made rapidly, so as to start any treatment as soon as possible after the accident (ideally within 2 hours but certainly within 72 hours). This assessment must be made thoroughly (because not every accidental exposure requires prophylactic treatment).

The first dose of PEP should be administered within the first 72 hours of exposure and the risk evaluated as soon as possible. If the risk is insignificant, PEP could be discontinued, if already commenced.

**PEP must be initiated as soon as possible, preferably within 2 hours**

Two main factors determine the risk of infection: the nature of exposure and the status of the source patient.

**Assessing the nature of exposure and risk of transmission**

Three categories of exposure can be described based on the amount of blood/fluid involved and the entry port. These categories are intended to help in assessing the severity of the exposure but may not cover all possibilities.

**Table 43: Categories of exposure**

Category	Definition and example
<b>Mild exposure :</b>	mucous membrane/non-intact skin with small volumes E.g. : a superficial wound (erosion of the epidermis) with a plain or low caliber needle, or contact with the eyes or mucous membranes, subcutaneous injections following small-bore needles
<b>Moderate exposure:</b>	mucous membrane/non intact skin with large volumes Or percutaneous superficial exposure with solid needle E.g. : a cut or needle stick injury penetrating gloves
<b>Severe exposure :</b>	percutaneous with large volume e.g. : <ul style="list-style-type: none"><li>• an accident with a high caliber needle (<math>\geq 18</math> G) visibly contaminated with blood;</li><li>• a deep wound (hemorrhagic wound and/or very painful);</li><li>• transmission of a significant volume of blood;</li><li>• an accident with material that has previously been used intravenously or intra-arterially</li></ul>
The wearing of gloves during any of these accidents constitutes a protective factor.  <i>Note:</i> In case of an AEB with material such as discarded sharps/needles, contaminated for over 48 hours, the risk of infection becomes negligible for HIV, but still remains significant for HBV. HBV survives longer than HIV outside the body.	

**Assessing the HIV status of the source of exposure**

PEP needs to be started as soon as possible after the exposure and within 72 hours. In animal studies, initiating PEP within 12, 24 or 36 hours of exposure was more effective than initiating PEP 48 hours or 72 hours following

exposure. PEP is less effective when given more than 72 hours after exposure. A baseline rapid HIV testing should be done before starting PEP.

Initiation of PEP where indicated should not be delayed while waiting for the results of HIV testing of the source of exposure. Informed consent should be obtained before testing of the source as per national HIV testing guidelines.

**Table 44: Categories of situations depending on results of the source**

source HIV status	Definition of risk in source
HIV negative	Source is not HIV infected but consider HBV and HCV
Low risk	HIV positive and clinically asymptomatic
High risk	HIV positive and clinically symptomatic (see WHO clinical staging)
Unknown	Status of the patient is unknown, and neither the patient nor his/her blood is available for testing (e.g. injury during medical waste management the source patient might be unknown). The risk assessment will be based only upon the exposure (HIV prevalence in the locality can be considered)

HIV infection is not detected during the primary infection period by routine-use HIV tests. During the “window period”, which lasts for approximately 6 weeks, the antibody level is still too low for detection – but infected persons can still have a high viral load. This implies that a positive HIV test result can help in taking the decision to start PEP, but a negative test result does not exclude HIV infection. In districts or some population groups with a high HIV prevalence, a higher proportion of HIV-infected individuals are found in the window period. In these situations, a negative result has even less value for decision-making on PEP.

#### **Assessment of the exposed individual**

The exposed individual should have confidential counseling and assessment by an experienced physician. The exposed individual should be assessed for **pre-existing HIV infection** intended for people who are HIV negative at the time of their potential exposure to HIV. Exposed individuals who are known or discovered to be HIV positive should not receive PEP. They should be offered counseling and information on prevention of transmission and referred to clinical and laboratory assessment to determine eligibility for antiretroviral therapy (ART). Besides the medical assessment, **counseling** exposed HCP is essential to allay fear and start PEP (if required) at the earliest.

#### **Prescribe PEP**

**There are two types of regimens:**

**Basic regimen: 2-drug combination**

**Expanded regimen: 3-drug combination**

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### Evaluation Prior to PEP

The decision to initiate the type of regimen depends on the type of exposure and HIV sero status of the source person.

- HIV testing of the source patient should not delay the decision about whether or not to start PEP. Start 2-drugs first if required, then send for consultation or refer.
- In the case of a high risk exposure from a source patient who has been exposed to or is taking antiretroviral medications, consult an expert to choose the PEP regimen, as the risk of drug resistance is high. Refer/consult expert physician. Start 2 drug regimen first

## HIV post-exposure prophylaxis evaluation

### Initiate HIV chemoprophylaxis

Because post-exposure prophylaxis (PEP) has its greatest effect if begun within 2 hours of exposure, it is essential to act immediately. There is little benefit if >72 hours later. The prophylaxis needs to be continued for 4 weeks.

- Report exposure immediately to appropriate authority.
- Fill in the medical form.
- Never delay start of therapy due to debate over regimen. Begin with basic 2-drug regimen, and once expert advice is obtained, change as required.

**Table 45: HIV post-exposure prophylaxis evaluation**

exposure	status of source		
	HIV +	HIV+ and clinically symptomatic	HIV status unknown
Mild	Consider 2-drug	Start 2- drug PEP	Usually no PEP or consider 2-drug PEP
moderate	Start 2-drug PEP	Start 3-drug PEP	Usually no PEP or consider 2-drug PEP
severe	Start 3-drug PEP	Start 3-drug PEP	Usually no PEP or consider 2-drug PEP

- The 3<sup>rd</sup> drug can be added after consultation with an expert.

**Table 46: Dosages of the drugs using for pep**

Medication	2-drug regimen	3-drug regimen
Zidovudine (AZT)	300 mg twice a day	300 mg twice a day
Stavudine (d4T)	30 mg twice a day	30 mg twice a day
Lamivudine (3TC)	150 mg twice a day	150 mg twice a day

<b>protease inhibitors</b>	<p><b>1<sup>st</sup> choice:</b> Lopinavir/ritonavir (LPV/r) 400/100 mg twice a day or 800/200 mg once daily with meals</p> <p><b>2<sup>nd</sup> choice :</b> Nelfinavir (NLF) 1250 mg twice a day or 750 mg three times a day with empty stomach</p> <p><b>3<sup>rd</sup> choice :</b> Indinavir (IND) 800 mg every 8 hours and drink 8-10 glasses of water daily</p>
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Note: If protease inhibitor is not available and the 3rd drug is indicated, one can consider using Efavirenz (EFV 600 mg once daily). Monitoring should be instituted for side effects of this drug eg CNS toxicity such as nightmares, insomnia etc.

\* Fixed Dose Combination (FDC) are preferred, if available. Ritonavir requires refrigeration.

#### Antiretroviral drugs during pregnancy

If the exposed person is pregnant, the evaluation of risk of infection and need for PEP should be approached as with any other person who has had an HIV exposure. However, the decision to use any antiretroviral drug during pregnancy should involve discussion between the woman and her health-care provider (s) regarding the potential benefits and risks to her and her fetus. Data regarding the potential effects of antiretroviral drugs on the developing fetus or neonate are limited. There is a clear contraindication for Efavirenz (first 3 months of pregnancy) and Indinavir (pre natal). In conclusion, for a female HCP considering PEP, a pregnancy test is recommended if there is any chance that she may be pregnant. Pregnant HCP are recommended to begin the basic 2-drug regimen, and if a third drug is needed, Nelfinavir is the drug of choice.

#### Side-effects and adherence to PEP

Studies of HCP taking PEP have reported more side effects than PLHAs taking ART, most commonly nausea and fatigue. Possible side-effects occur mainly at the beginning of the treatment and include nausea, diarrhoea, muscular pain and headache. The person taking the treatment should be informed that these may occur and should be dissuaded from stopping the treatment as most side-effects are mild and transient, though possibly uncomfortable. Anaemia and/or leucopenia and/or thrombocytopenia may occur during the month of treatment. A complete blood count and liver function tests (transaminases) may be performed at the beginning of treatment (as baseline) and after 4 weeks.

In practice and from HCP studies, many HCP did not complete the full course of PEP because of side effects. Side effects can be reduced by prescribing regimens that do not include a protease inhibitor (PI), by giving medications to reduce nausea and gastritis and by educating clients about how to reduce side

effects eg. taking PEP medications with food. It is important that side effects should be explained before initiating PEP so that the symptoms are not confused with symptoms of seroconversion to HIV. Adherence information is essential with psychological support. More than 95% adherence is important in order to maximize the efficacy of the medication in PEP.

**Table 47: Counseling for PEP**

Key information to exposed person (client)	Specific Details include
<ul style="list-style-type: none"> <li>The risk of acquiring HIV infection from the specific exposure</li> </ul>	<ul style="list-style-type: none"> <li>Ask client for understanding of HIV transmission risk after exposure</li> <li>The risk of getting HIV infection from a person known to be HIV positive is estimated to be <ul style="list-style-type: none"> <li>Sharps injury: 3 in 1000 exposures (0.3%)</li> <li>Mucous membrane splash: 1 in 1000 exposures (0.1%)</li> <li>the risk is increased with large exposure eg needle-stick from hollow bore needles with visible blood, from artery or vein and from source patients with high viral load (usually very sick persons with OIs)</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>What is known about PEP efficacy</li> </ul>	<ul style="list-style-type: none"> <li>Ask client's understanding of PEP</li> <li>PEP is provided to prevent potential transmission of the HIV virus</li> <li>PEP is not 100% effective and should be given within 72 hours (ideally as soon as possible, if eligible).</li> <li>Balance risk and benefits of PEP: PEP <i>may</i> prevent HIV transmission, versus possible risk of side effects</li> </ul>
<ul style="list-style-type: none"> <li>Information about client's risk of HIV infection based upon a risk assessment (if she/he has not had a recent HIV test)</li> <li>The importance of being tested and receiving appropriate post-test counseling (although HIV testing can be delayed if needed)</li> <li>That PEP medicines will be discontinued if their initial (baseline) HIV test is positive</li> </ul>	<ul style="list-style-type: none"> <li>Client's possibility of prior HIV infection should be assessed</li> <li>Counsel for HIV testing and follow-up psychosocial support - where possible rapid testing should be used based on national testing guidelines</li> <li>Inform if the baseline HIV test is positive, then the PEP will be discontinued</li> <li>Arrange referral to ART centers for assessment if found HIV positive</li> </ul>
<ul style="list-style-type: none"> <li>Importance of adhering to medication once started</li> <li>Duration of the course of medicine (4 weeks)</li> </ul>	<ul style="list-style-type: none"> <li>Discuss dosing of the PEP medicine eg pill should be taken twice a day for 28 days, once in the morning and once in the evening Depending on the nature and risk of exposure, 2 drugs or 3 drugs may be used <ul style="list-style-type: none"> <li>Side effects may be important with use of 3 drugs</li> <li>Expert opinion/consultation by phone or referral may be needed with a HIV specialist if 3<sup>rd</sup> drug is to be used</li> </ul> </li> <li>Arrange for special leave from work (2 weeks initially)</li> </ul>
<ul style="list-style-type: none"> <li>Common side effects</li> </ul>	<ul style="list-style-type: none"> <li>Discuss possible side effects of the PEP medicines eg. nausea,</li> </ul>

that may be experienced	<p>fatigue, headache (depending on which drugs given)</p> <ul style="list-style-type: none"> <li>Side effects often improve over time. It is often minor and do not need specialized supervision. Symptomatic relief can also be given by using other drugs</li> </ul>
<ul style="list-style-type: none"> <li>That they can stop at any time but will not get the benefit of PEP - if the source is HIV positive</li> </ul>	<ul style="list-style-type: none"> <li>Animal studies suggest that taking less than 4 weeks of PEP does not work</li> <li>If client decides to stop at any time, s/he needs to contact the physician before stopping the medications</li> <li>Arrange for follow-up visit and decide further course of action/follow-up</li> </ul>
<ul style="list-style-type: none"> <li>Prevention during the PEP period eg sexual intercourse and unplanned pregnancy</li> </ul>	<ul style="list-style-type: none"> <li>After any AEB, the exposed person should not have unprotected sexual intercourse until it is confirmed, 3 months after the exposure, that s/he is not HIV infected. It is also advised to avoid pregnancy. Use of condoms is essential</li> </ul>
<ul style="list-style-type: none"> <li>If client is pregnant - she can still take PEP during pregnancy</li> </ul>	<ul style="list-style-type: none"> <li>The PEP drugs used are safe for pregnancy</li> <li>If the client gets HIV during the pregnancy due to the exposure, the baby will have some risk of becoming HIV infected</li> </ul>
<ul style="list-style-type: none"> <li>Safety of PEP if the client is breastfeeding</li> </ul>	<ul style="list-style-type: none"> <li>The PEP drugs used are safe during breast-feeding. May consider stopping breastfeeding if PEP is indicated.</li> </ul>
<ul style="list-style-type: none"> <li>Educate client on the possible signs and symptoms of early HIV sero-conversion</li> </ul>	<ul style="list-style-type: none"> <li>Signs and symptoms of early HIV sero-conversation: fever, rash, oral ulcers, pharyngitis, malaise, fatigue, joint pains, weight loss, myalgia, headache (similar to flu-like symptoms)</li> </ul>
<ul style="list-style-type: none"> <li>Risk of acquiring Hepatitis B and C from a specific exposure and availability of prophylaxis for this</li> </ul>	<ul style="list-style-type: none"> <li>Risk of Hepatitis B is 9-30% from a needle stick exposure - the client can be given vaccinations</li> <li>Risk of Hepatitis C is 1-10% after needle stick exposure - there is no vaccinations for this</li> </ul>

*Note:* Provider should correct misconceptions at all times during the counseling sessions

### Laboratory Evaluation

The reason for HIV testing soon after an occupational exposure is to establish a "baseline" against which to compare future test results.

If the HCP is HIV-negative at the baseline test, it is in principle possible to prove that subsequent infection identified by follow-up testing is related to the occupational exposure (depending on the timing of infection and consideration of other risks or exposures). When offered HIV testing, the exposed person should receive standard pre-test counseling according to the national HIV testing and counseling guidelines, and should give informed consent for testing. Confidentiality of the test result must be ensured. Do not delay PEP if HIV testing is not available.

**Table 48: Recommended baseline laboratory evaluation**

Timing	In persons taking PEP (Standard regimen)	In persons not taking PEP
Baseline (Within 8 days after AEB)	HIV, HCV, anti-HBs* Complete blood count transaminases	HIV, HCV, anti-HBs*

\*HIV,HBV and HCV testing of exposed staff within 8 days of an AFB if required (baseline serostatus). Offer on HIV test in case of an AFB, as a positive HIV status may indicate the need to discontinue PEP. The decision on whether to test for HIV or not should be based on informed consent of the exposed person.

**Other laboratory testing** such as hemoglobin estimation should be available, especially when AZT is used for PEP in areas where anemia is common.

**Testing for other blood-borne diseases** such as syphilis, malaria and kala-azar may also be useful, depending on the nature of risk, symptoms of the source patient, local prevalence and laboratory capacity.

#### **Follow-up of an Exposed Person**

Whether or not PEP prophylaxis has been started, follow up is indicated to monitor for possible infections and provide psychological support.

The exposed person must be monitored for the eventual appearance of signs indicating an HIV seroconversion: acute fever, generalized lymphadenopathy, cutaneous eruption, pharyngitis, non-specific flu symptoms and ulcers of the mouth or genital area. These symptoms appear in 50%-70% of individuals with an HIV primary (acute) infection and almost always within 3 to 6 weeks after exposure. When a primary (acute) infection is suspected, referral to an ART centre or for expert opinion should be arranged rapidly.

An exposed person should be advised to use precautions (e.g., avoid blood or tissue donations, breastfeeding, unprotected sexual relations or pregnancy) to prevent secondary transmission, especially during the first 6–12 weeks following exposure. Condom use is essential. Adherence and side effect counseling should be provided and reinforced at every follow-up visit. Psychological support and mental health counseling is often required.

#### **Laboratory follow-up**

**Table 49: Recommended follow-up laboratory tests**

Timing	In person taking PEP standard regimen)	In persons not taking PEP
Weeks 2 and 4	Transminases* Complete blood count	Clinical Monitoring for hepatitis
Weeks 6	HIV-AB	HIV-AB
Month 3	HIV-AB, anti-HCV, HBsAg, Transminases	HIV-AB, anti-HCV, HBsAg
Month 6	HIV-AB, anti-HCV, HbsAg, Transminases	HIV-AB, anti-HCV, HBsAg

\* Transminases should be checked at week 2 and 4 to detect hepatitis in case the exposed person contracted HBV from the AFB & for persons started on AZT containing PEP regimens.

#### **5. Implementation of PEP in the Health Care Facility**

### **Responsibility of the Medical Superintendent of the Hospital:**

As with all other functions of a healthcare facility, the ultimate responsibility for prevention and control of infection rests with the hospital administrator. The Medical Superintendent (MS)/Dean/Principal/In-charge of the Hospital must constitute a hospital infection control committee which will oversee and monitor hospital infection control including universal precaution and post-exposure prophylaxis implementation.

The Medical Superintendent of the hospital has the responsibility of informing all staff about:

- the universal precautions to be followed in health services
- use of personal protective equipment
- other preventive measures to be taken against these viruses (including vaccination) especially Hep B vaccine
- procedures to be followed in case of accidental exposure to blood and body fluids

Each institution should designate a team of persons who has the authority to ensure that confidentiality of the HCP is maintained and the required care is given in any case of occupational exposure.

### **Infection control committee**

The infection control committee is responsible for the development of policies for the prevention and control of infection and to oversee the implementation of the infection control program. This includes:

- Electing one member of the committee as chairperson (who will have direct access to the head of the hospital administration)
- Appoint an infection control practitioner as secretary (Health care provider trained in principles and practices of infection control e.g. physician, microbiologist or infection control nurse)
- Meet regularly – ideally monthly but minimum three times a year
- Develop for the hospital, the infection control manual/standard operating procedures, injury register etc.
- Monitor and evaluate the performance of the infection control programme
- Appoint an infection control core group

**Infection control core group/working group:** is responsible for the day-to-day activities of the infection control programme. They will have a direct reporting responsibility to the hospital administration. The infection control team will:

- Assess training needs of the staff and provide required training through the awareness program, in-service education and on-the job training
- Organize regular training programme for the staff for essential infection control practices appropriate for their nature of work

- Provide periodic re-training or orientation of staff and review the impact of training
- Review and monitor practices of infection control in the healthcare facility with feedback to the hospital infection committee and hospital administration

#### **Access and Availability to PEP at the Healthcare Facility**

In order to ensure that an exposed person has access to prophylactic therapy in a timely manner, it is recommended that PEP drugs be kept available round-the-clock in any one location where a doctor is on-call 24-hours a day (e.g. casualty, ICU). All health staff should know through in-house trainings where to get PEP as required.

The following are the minimum provisions of PEP in health care facilities:

- A minimum of 72 hours worth of 2 drugs in the basic regimen should be included in the HIV exposure-response kit
- Reporting/written consent forms
- Information sheet for the exposed person
- Maintain confidentiality
- Rapid HIV test kit to be used to test the source patient/exposed person should be available in the hospital or if not, referral to next level (eg from PHC to district hospital) should be possible.
- List of referral persons and nearest laboratory testing sites for HIV, HBV,HCV
- The names and contact details of at least 3 trained doctors for PEP should be displayed in the casualty of the hospital

## Module-IV: Public Private Partnership for ART

### PURPOSE:

In this session, participants will learn about Public Private Partnership for ART.

### OBJECTIVES:

By the end of this session, the participants will be able to:

1. Explain the responsibilities of National HIV AIDS Control Programme and NGO/Corporate/Private sectors.
2. Describe how to select private organization for PPP.
3. Understand about support of NGOs and positive networks to HIV prevention.

#### **1. Expansion of ART programme to private sector**

It has been seen that many patients approach various NGO/Trust/Charitable Hospitals for HIV care including ART. In addition, there are a number of hospitals under organizations, which are already providing some services to HIV infected persons including ART in some of these hospitals. These services need to be streamlined as per National ART Guidelines in country context.

In this regard a **Memorandum of Understanding (MOU)** for starting ART in NGOs/Corporate Sector need to be developed at National Programme level and approved by the Department of Legal Affairs, Ministry of Law and Justice of the country.

#### **The Salient Features of MoU are:**

##### **I. Responsibilities of National HIV AIDS Control Programme**

- 1) To provide support for one time training of personnel of these organizations.
- 2) To provide regular updates on National ART guidelines from time to time.
- 3) For private sectors, National Programme may provide diagnostic kits, ART and OI drugs for a specified number of patients for a specified period of years. (Depending on Country Context)

##### **II. Responsibilities of NGO/Corporate/Private sectors**

- 1) To provide all health services related to provision of ART and treatment of opportunistic Infections, free of cost to patients who require treatment and shall not deny services to any person living with HIV on any ground.
- 2) To comply with all the laws for the time being in force in COUNTRY in the running of the ART center.
- 3) To follow the National ART guidelines (drug regimen as well as physical standards) issued by National AIDS Control Programme from time to time.
- 4) To bear the costs related to the staff's salary (doctors, counselors, nutritionist, pharmacist, nurses, medical records officer and administrative staff) and the cost related to the infrastructure.

5) It shall conform to any guidelines issued by programme.

## **2. Selection of NGO/ Private Sectors for PPP**

The selection criteria for NGO are:

- It should be run by a registered organization in country.
- It should have sound financial position and should give commitment to support services for 3-5 years;
- It should have at least 2 years experience in ART provisioning;
- They should have facilities for CD4 and other lab. Tests needed at center or should have clear workable linkages for the same;
- They should follow the same man-power for ART centers as is done at government run centers;
- They should follow National ART guidelines and report to National AIDS Control Programme using M&E tools.

Before start/signing of MOU, the center shall be visited by an expert team of 3-5 persons including Programme officer at National programme and Ministries.

## **3. Supports from NGOs and positive networks:**

In order to improve the quality of care provided to HIV/AIDS patients, the hospital should have effective linkages with Community Based Organizations (CBO), Faith Based Organizations (FBO) and with Positive Network Groups in the region.

Rapport building and development of positive relationships with these organizations will also help reduce the burden on the hospital. Such NGOs may provide vocational (or occupational) rehabilitation to deserving PLHA and family members, support children affected with AIDS (CAA) and children infected with AIDS (CIA) by providing educational support and/or care homes.

They could also provide legal support when PLHA or their family members are deprived of their rights. In addition, they are often well equipped to provide psychosocial support and even nutritional support to the patients and, if necessary, their families.

## Module-V: Standard Operating Procedures, Research, Monitoring and Evaluation

### Section – A: Standard Operating Procedures

#### PURPOSE:

In this session, participants will learn about entry into HIV care and flow of patients at the ART center. To discuss the current issues of stigma and discrimination, look at the causes of stigma and the consequences of discrimination. To brainstorm and arrive at some concrete suggestions and plans for the way forward to decrease stigma and discrimination of all those infected or affected by HIV.

#### OBJECTIVES:

By the end of this session, participants will be able to:

- Understand the enrollment of patient into HIV care.
- Explain about the flow of patient at the ART center
- Better understand the issues of stigma and discrimination;
- Be aware of the situation locally;
- Brainstorm ideas to combat stigma and discrimination in their local setting;
- Arrive at a plan of what they can do personally to help combat stigma and discrimination.

#### Standard Operating Procedures (SOP)

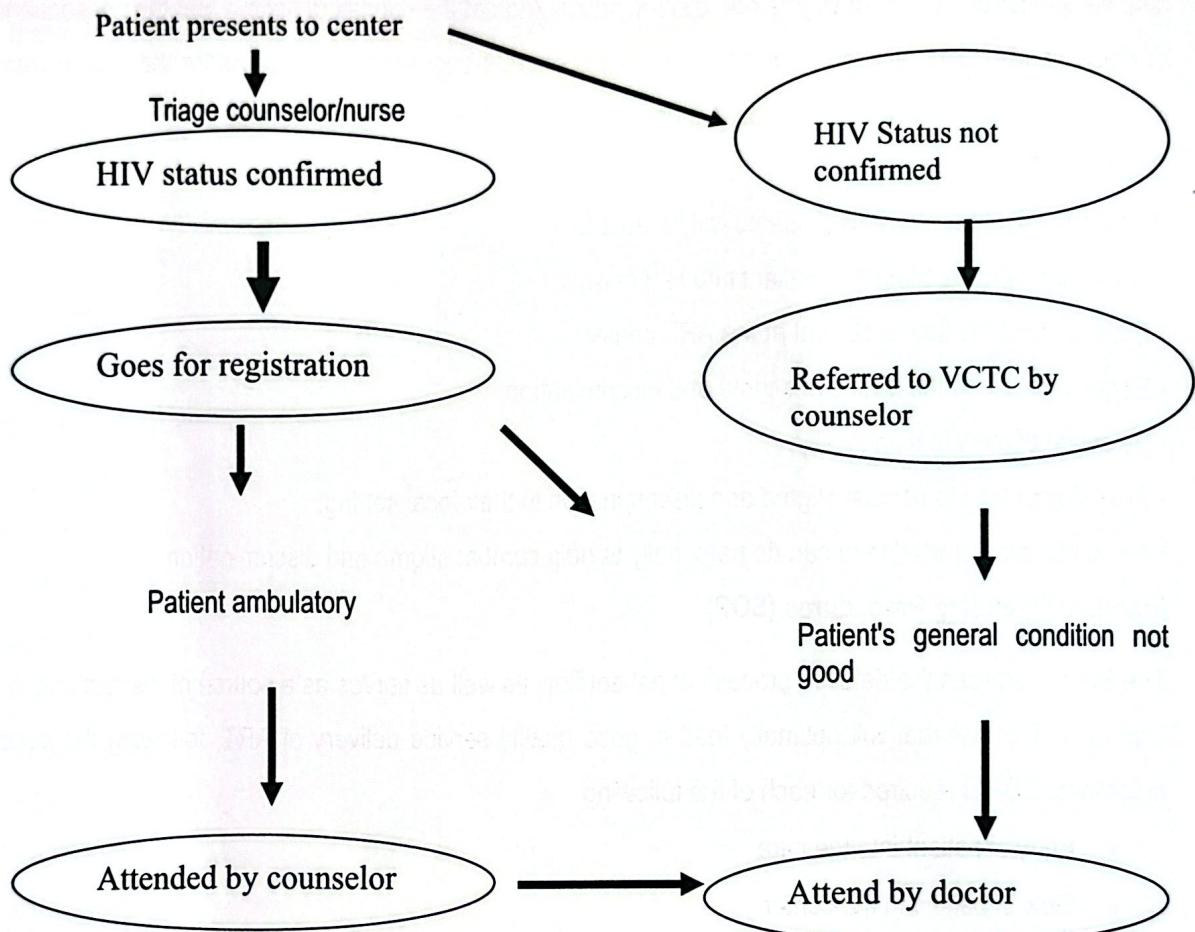
The SOP addresses the detailed process of patient flow as well as serves as a source of instructions to the staff of ART center that will optimally lead to good quality service delivery of ART, following the national guidelines. SOP is required for each of the following:

- Entry of patient into the care
- Flow of patient in the center
- Referral system for the patients

## 1. Entry into HIV care

The ART center should enroll the person once he has a confirmed HIV test result. If a person has Suggestions of the HIV disease but is not serologically confirmed, the person should be referred for HIV testing at VCTC. The common referral form should be used for all referrals in the program.

## 2. Figure 27: Flow of Patient at the ART center



In order to ensure good adherence and for tracking the patients lost to follow up , it is desirable that patient is enrolled at ART center nearest to his current place of stay. He should be asked to furnish the documentary evidence of address proof. The ART Medical officer should get full contact details of patient including phone numbers before starting ART.

Having confirmed the HIV status, the patient is registered in the Pre-ART care by the counselor.

The counselor also makes patient ID card and refers to the doctor. The principles of 5 A's in any chronic illness should be followed (Assess, Advise, Agree, Assist and Arrange).

These SOP should address the detailed process of patient flow as well as serves as a source of instructions to the staff of ART center.

### **3. Stigma and Discrimination**

#### **Definitions of Stigma and Discrimination**

Stigma: an undesirable or discrediting attribute that a person or group possesses that results in the reduction of that person's or group's status in the eyes of society. Stigma can result from a physical characteristic such as the visible symptoms of a disease or from negative attitudes toward the behavior of a group, such as homosexuals or prostitutes.

Discrimination: Can be expressed as both negative attitudes or particular behavior or actions. It is often described as a distinction that is made about a person that results in their being treated unfairly and unjustly on the basis of their belonging, or being perceived to belong, to a particular group. For example, stigma can lead to prejudice and active discrimination directed toward persons who are actually, or are simply perceived to be, infected with HIV, and the social groups and persons with whom they are associated.

#### **PLHIV Perspective on Stigma and Discrimination**

- 2 PLHIV to share personal experiences of stigma and discrimination.
- Request that they offer some suggestions of how to improve this.
- Large group question and answer period on issues raised by PLHIV.

#### **Small Group Activity:**

Divide into small groups made up of local teams if possible. Invite PLHIV to participate in groups.

Discuss experiences that they have seen, heard of or experienced of stigma and discrimination.

Specifically discuss the following settings:

- Family/Home
- Community
- School/work
- Healthcare settings

### **Section – B: Research and Monitoring and Evaluation**

#### **1. Introduction to Strategic information of HIV Services (monitoring, evaluation, surveillance and research)**

##### **PURPOSE:**

This section is designed to allow participants to clarify their concepts about monitoring (primarily) and about evaluation (secondarily), to share their feelings about M&E, and to discuss the value of M&E and the particular opportunities and barriers they will confront when conducting M&E activities.

##### **OBJECTIVES:**

At the end of this session, participants will be able to:

- Understand key terms and concepts of Monitoring & Evaluation (M&E);
- Understand basic elements in SI system –components of strategic information, difference between M&E, Surveillance and Research;
- Provide general overview of M&E framework and M&E data needs;
- Familiarization with 12 components of functional M&E system;

### **Basic Elements of Strategic Information (SI) System**

A functional Strategic Information system is one of the cornerstones of a country's response to fighting a disease. It provides the strategic information (SI) needed to make good decisions for managing and improving program performance, formulating policy and advocacy messages and planning programs better.

#### **Thus, the main purpose of SI is**

- To improve programs by identifying those aspects that:
  - are working according to plan; and
  - those in need of mid-course correction;
- To understand the characteristics of epidemics;
- To track changes in the services provided, and in the desired outcomes;
- To reach informed decisions regarding the effective and efficient use of programme resources;
- Ultimately, to better the human condition.

#### **We Invest In SI In order to:**

- Strengthen programme design, improve implementation;
- Justify allocation of limited resources - Improve use of allocated resources (thereby increasing cost-effectiveness);
- Generate knowledge: Identify factors (individual, community, programmatic) that influence health outcomes;
- Meet an organizational requirement.

### **Four components of Strategic Information- Monitoring, Evaluation, Surveillance and Research**

#### **1. Monitoring**

Monitoring is the routine process of data collection and measurement of progress toward program objectives.

There are **three main domains** of information required in a monitoring system:

**Inputs**— Resources going into conducting and carrying out the project or program. These could include staff, finance, materials, and time.

**Process**— Set of activities in which program resources (human and financial) are used to achieve the results expected from the program (e.g., number of workshops or number of training sessions).

**Outputs**— Immediate results obtained by the program through the execution of activities (e.g., number of commodities distributed, number of staff trained, number of people reached, or number of people served). Monitoring addresses the following questions:

- To what extent are planned activities actually realized? Are we making progress toward achieving our objectives?
- What services are provided, to whom, when, how often, for how long, and in what context?
- How well are the services provided?
- What is the quality of the services provided?
- What is the cost per unit service?

## 2. Evaluation

Evaluation is the use of social research methods to systematically investigate a program's effectiveness.

Evaluation is used for the following:

- To assess the changes in the target group (e.g., changes in risk behavior)
- To assess the extent to which the objectives have been met. It is the process of determining the effectiveness of a program or a project.
- To track the **outcomes** and **impacts** of programs or projects at the larger population level, as opposed to the program or project level:
  - **Outcomes**—Short-term or intermediate results obtained by the program through the execution of activities.
  - **Impact**—Long-term effects (e.g., changes in health status). This can be through special studies with wide district, regional, or national coverage.

Evaluation addresses the following questions:

- What outcomes are observed?
- What do the outcomes mean?
- Does the program make a difference?

## 3. Surveillance

Surveillance is the routine tracking of diseases (disease surveillance) or risk behavior (behavioral surveillance) using the same data collection system over time. Surveillance helps describe the epidemic and its spread, and can contribute predicting future trends and targeting needed prevention programmes. In the case of HIV, surveillance typically tracks impact in terms of HIV and sometimes STI prevalence, and outcomes in terms of risk behavior.

Surveillance systems provide the basis for understanding current HIV epidemics, their potential for spread across populations and geographic areas, and the implications for prioritization and implementation of prevention and care interventions that will best mitigate the impact of the epidemic.

The multiple objectives and uses of surveillance include:

- To gain an understanding of how HIV is spreading within countries:
- Who is infected with HIV and where? (HIV surveillance)
- Who is being exposed to HIV and where? (Behavioral surveillance)
- What is the size of high-risk subpopulations in different areas? (Population size estimation)
- What is the source of new infections and how is it changing over time? (Case reports, surveillance, models)
- To help prioritize the need for interventions in terms of risk populations and geographic locations
  - an understanding of the behavioral linkages between high-risk groups and link with qualitative studies is critical.
- To provide information to advocate for interventions and guide resource allocation.
- To provide data that is useful to monitor and evaluate the national response.

**Key Components of Surveillance are:**

- HIV and AIDS Case Reporting
- STI Case Reporting
- HIV Surveillance
- STI surveillance
- Behavioral surveillance
- Population Size Estimation
- National HIV Estimations and Impact

#### **What is second generation surveillance?**

Traditional surveillance systems typically tracked HIV or STIs. However, they did not concurrently track the sexual practices that lead to STI/HIV transmission. This made it difficult to corroborate and explain STI/HIV trends. To address these limitations, second generation surveillance evolved. Second generation surveillance seeks to combine biological and behavioral data, to increase explanatory power. The concordance of diverse biological, behavioral and qualitative insights not only enhances confidence in trends, but it permits meaningful explanations of these trends.

#### 4. Research

Research is a systematic activity that focuses primarily on hypothesis testing, aiming to contribute to generalizable knowledge. Research typically attempts to make statements about relationships among specific variables under controlled circumstances and at a given point in time.

#### Framework suggested for M&E

Varying frameworks are applied to M&E. During the past few years, one largely agreed framework has commonly been used: **Logical Framework**: the input–process–output–outcome–impact framework. This reflects the indicators used at different levels to measure what goes into a program or project and what results are achieved.

Effective M&E is based on a clear, logical pathway of results, in which results at one level are expected to flow towards results at the next level, leading to the achievement of the overall goal. If there are gaps in the logic, the pathway will not flow towards the required results.

For a program or project to achieve its goals, inputs such as money and staff time must result in outputs such as new or improved services, trained staff, people reached with services, etc.

These outputs are the result of specific activities, such as training for staff. If these outputs are meaningful and are achieved in the populations intended, the program or project is likely to have positive effects or outcomes in the medium or longer term, such as increased condom use with casual partners, adherence to HIV drugs or later age at first sex among young people. These positive outcomes should lead to changes in the long-term impact of programs, measured in fewer new cases of HIV, and related burden of disease among those infected and affected (such as orphans and vulnerable children or widows). For HIV, a desired impact among those infected includes quality of life and life expectancy.

**Table 51: Major levels of the M&E framework**

<b>Inputs</b>	People, training, equipment and resources that we put into a project, in order to achieve outputs.
<b>Process</b>	Set of activities in which program resources (human and financial) are used to achieve the results expected from the program (e.g., number of workshops or number of training sessions).
<b>Outputs</b>	Activities or services we deliver, including HIV/AIDS prevention, care and support services, in order to achieve outcomes. The processes associated with service delivery are very important. The key processes include quality, unit costs, access and coverage. <i>Example: % HIV-infected pregnant women receiving a complete course of antiretroviral prophylaxis to reduce the risk of MTCT</i>
<b>Outcomes</b>	Through good-quality, economical, accessible and widespread services, key outcomes should occur. Outcomes are changes in behaviour or skills, especially safer HIV prevention practices and increased ability to cope with AIDS. <i>Example: % of young people aged 15–24 reporting use of a condom during sexual</i>

	<i>intercourse with a non-regular sexual partner</i>
<b>Impacts</b>	These outcomes are intended to lead to major health impacts. Impacts refer to measurable health impacts, particularly reduced STI/HIV transmission and reduced AIDS impact. <i>Example: % young people aged 15–24 who are HIV-infected</i>

### Understanding M&E Data needs

The main purpose of M&E is to provide the data required to guide the planning, coordination, and implementation of the HIV response; assess the effectiveness of the HIV response; and identify areas for program improvement. In addition, M&E data are needed to ensure accountability to those infected/affected by HIV and AIDS, as well as those providing financial resources for the HIV response.

The investigation of any public health problem starts by asking pertinent questions that serve to organize the response. Such questions include:

- What is the problem?
- What factors are contributing to the problem?
- What can be done?

Once a program response has been determined and has been implemented for a sufficient period of time, we want to know:

- Is the program working?
- Is it reaching enough people to resolve the problem or at least decrease the severity of the problem?

### Components of a Functional M&E system

To support efforts to build better national M&E systems for HIV, countries and global partners have developed and endorsed an organizing framework for a functional national HIV M&E system. This framework describes the 12 components of a functional, national, multisectoral HIV M&E system and provides a benchmark against which to assess progress.

Intended to facilitate:

- Identification of strengths and weaknesses of existing M&E systems;
- Development of a national plan for M&E system implementation;
- Coordination of investments in M&E;
- Monitoring of progress toward a fully functional national HIV M&E system.

**Table 52: Twelve components of a functional M&E system**

1 Organizational structures with M&E functions	Establish and maintain a network of organizations responsible for M&E at the national, subnational and service delivery levels.
2 Human capacity for M&E	Ensure adequate skilled human resources at all levels of the M&E

	system to ensure completion of all tasks defined in the annual M&E work plan. This includes sufficient analytical capacity to use the data and produce relevant reports.
3 Partnerships to plan, coordinate and manage the M&E system	Establish and maintain partnerships among in-country and international stakeholders involved in planning and managing the national M&E system.
4 National, multisectoral M&E plan	Develop and regularly update the national M&E plan, including identified data needs, national standardized indicators, data collection procedures and tools and roles and responsibilities for implementation.
5 Annual, costed, national M&E work plan	Develop an annual, costed, national M&E work plan including specified and costed M&E activities of all relevant stakeholders and identified sources of funding and use this plan for coordination and for assessing the progress of M&E implementation throughout the year.
6 Advocacy, communication and culture for M&E	Ensure knowledge of and commitment to M&E and the M&E system among policy-makers, program managers, program staff and other stakeholders.
7 Routine program monitoring	Produce timely and high-quality (valid, reliable, comprehensive and timely) routine program monitoring data.
8 Surveys and surveillance	Produce timely, valid and reliable data from surveys and surveillance.
9 National and subnational databases	Develop and maintain national and subnational databases that enable stakeholders to access relevant data for formulating policy and for managing and improving programs.
10 Supportive supervision and data auditing	Monitor data quality periodically and address obstacles to producing high-quality (that is, valid, reliable, comprehensive and timely) data.
11 Evaluation and research	Identify evaluation and research questions, coordinate studies to meet the identified needs and enhance the use of evaluation and research findings.
12 Data dissemination and use	Disseminate and use data from the M&E system to guide the formulation of policy and the planning and improvement of programs.

### Monitoring & Evaluation (M&E) Plan

The national M&E plan of a country describes the organization of its M&E system and the related M&E activities and thus forms the basis for implementing a functional M&E system. The M&E plan includes identified data needs and standardized national indicators to monitor the achievement of program objectives and goals. It includes indicator baselines and targets to be achieved, methods of data collection, data sources, frequency of data collection and the partners responsible for data collection and management. The national M&E plan covers all components of the M&E system, including evaluation needs and how they will be addressed: data analysis and data use at different levels of the system.

The national M&E plan should be linked to the national disease control strategy and usually covers M&E activities over 3–5 years. It should be developed and regularly updated in consultation with various stakeholders involved in the program, including subnational authorities and representatives from civil society. It should define how each of the 12 components of a functional M&E system will be implemented and strengthened if necessary, ideally based on a national M&E assessment. The plan should also indicate the resources needed for implementing the M&E plan, both technical and financial, and outline a strategy for mobilizing resources.

The different sectors, development partners and subnational entities involved in program implementation may develop their own M&E plans that detail their data collection and reporting schedule. All these plans should be linked to the national multisectoral M&E plan and contribute to one national M&E system.

Standard indicators for which data collection and analysis have been field-tested and validated are recommended so that risks linked to their measurement are minimized and utility maximized. The consistent use of standard indicators based on agreed global standards provides national programs with valuable comparable measures for trend analysis. It also allows comparability across countries, regions and populations. In some cases however, standard indicators specific to some service delivery areas may not be available. In such cases, countries may use national or regional indicators or additional indicators proposed in this toolkit that were developed through various consultative processes. When data from different sources are combined for analysis, this triangulation of data allows national, regional or local evaluation of program efforts.

To implement a national M&E system based on a national M&E plan, a national, costed M&E work plan should be developed to direct investment in high priority M&E activities. The period covered by the M&E work plan depends on the country context and could range from one year to several years. The M&E work plan should be based on the national M&E plan and should describe the key M&E activities during the time frame covered by the plan and include the following elements:

- Performance goals for the M&E system and results to be achieved;
- M&E activities with a time frame for implementation (start date and end date);
- Defined responsibilities for implementing each activity; and
- Cost for each activity and identified funding sources (including secured funding sources but also funding gaps and how these will be addressed).

The M&E work plan should cover M&E activities and the agreed roles and responsibilities of all relevant stakeholders. It may address the health sector and other relevant multisectoral activities or may be disease-specific. It is good practice to integrate the M&E work plan in the overall M&E work plan and

budget of the health sector to ensure appropriate linking of various data collection, management and analysis efforts as part of one national M&E system.

### **Monitoring and Evaluation Questions**

**Is this the information that we would be responsible for collecting?**

**If this is the information we will collect, at what level of M&E does this belong—Input, Process, Output, Outcome, or Impact?**

### **Monitoring and Evaluation Questions**

- How well-trained and prepared are the peer educators?
- How many staff members are available to do the work?
- What percent of the target population is using condoms with non-regular partners?
- Has the prevalence of HIV decreased?
- Has the target population increased its use of STI clinics in the target area?
- How supportive of HIV prevention work is the institution's policy environment?
- Have the STI rates decreased among the target population?
- Have referrals to voluntary counseling and testing sites increased?
- How appropriate is the media campaign for this target population?
- Has the social structure improved to support people living with HIV?
- How many condoms have been distributed in the past 6 months?
- Has correct knowledge of HIV/STI transmission increased among the target population?

## **2. Overview of ART Recording and Reporting**

### **PURPOSE:**

To introduce the national forms for HIV care and monitoring including the provision of ART. To discuss record keeping, flow charts and organizational systems to provide services with a high standard of care in the participant's local setting.

### **SESSION OBJECTIVES**

At the end of the session participants will be able to:

- Understand the importance of standard recording and reporting tools;
- List key information collected; and
- Identify the different forms to be used in a paper-based recording and reporting system.

## **1. Objective of Programme Monitoring**

With the increasing access to antiretroviral treatment (ART), a strong monitoring system is required at facility, district, provincial, national and international levels.

At facility level, the objectives of programme monitoring are to:

- Support patient management by regularly recording and storing of key individual information for lifelong care and follow-up;
- Facilitate an accurate patient tracking system to identify those missing or lost to follow-up; and
- Support drug supply management at the facility.

At all levels, programme monitoring will help to:

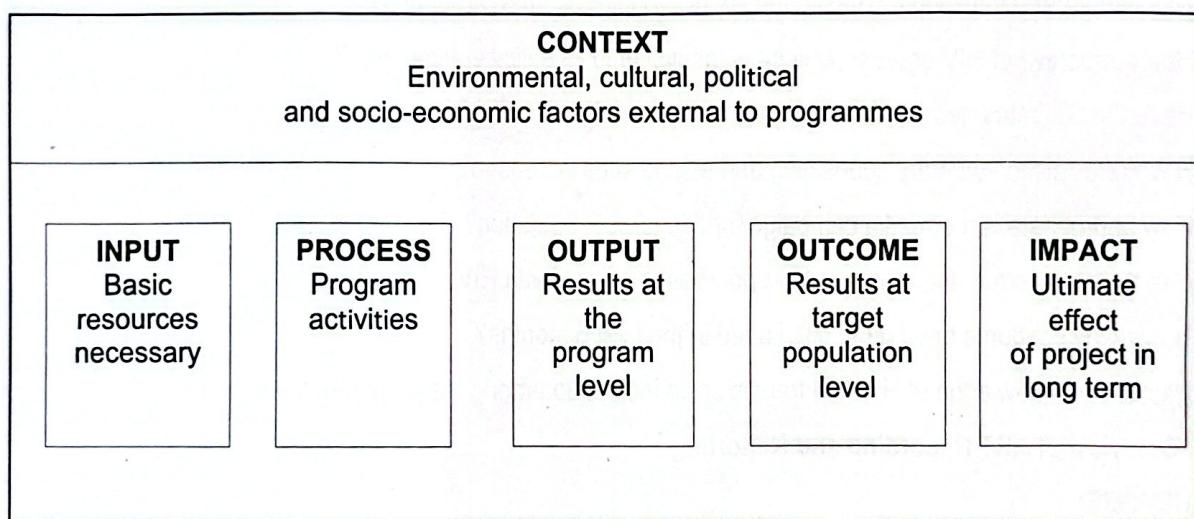
Document the progress in equitable access to HIV care and ART programmes; and

Identify the successes and gaps over time and modify the programmes accordingly.

## 2. Indicators at National/international levels

The following indicators, based on the M&E framework were developed for national programs to demonstrate progress in scaling up ART programs

**Figure 33: Monitoring and Evaluation Framework**



### Input indicators

- Existence of national policies, strategy and guidelines for ART programmes.

### Process indicators

- Percentage of districts or local health administration units with at least one health facility providing ART services in line with national standards.
- Percentage of ARV storage and delivery points experiencing stock-outs in the preceding 6 months.
- Number of health workers trained on ART delivery in accordance with national or international standards.

### Output indicators

- Percentage of health facilities with systems and items to provide ART services.

- Percentage of health facilities with ART services that also provide comprehensive care, including prevention services, for HIV-positive clients.

#### Outcome indicators

- Percentage of adults and children with advanced HIV infection receiving ART.
- Percentage of patients initiating ART at the site during a selected period who are taking an appropriate first line regimen 12 months later.

#### Impact indicators

- Percentage of adults and children with HIV known to be on treatment 6, 12, 24, 36, 48 months after initiation of ART.

**Table 54: Indicators at the facility level**

Indicators No.	Indicators	Recommended reporting frequency
1.	Cumulative number ever enrolled for HIV care	Monthly
2.	Number started on ART during the reporting period	Monthly
3.	Cumulative number ever started on ART	Monthly
4.	Cumulative number medically eligible for ART but have not been started on ART	Monthly
5.	Cumulative number on ART	Monthly
6.	Cumulative number on substituted 1st line regimen	Monthly
7.	Cumulative number switched to 2nd line regimen	Monthly
8.	Proportion of patients with >95% adherence	Monthly
9.	Proportion of patients alive and on treatment 6, 12, after start of treatment	Bi-annual or annual and 24 months
10.	Proportion of patients continuing initial 1st line regimen, substituting 1st line, switched to 2nd line at 6, 12, 24 months of ART	Bi-annual or annual
11.	Proportion of patients with >200 cells/mm <sup>3</sup> CD4 cells after 6, 12, 24 months of ART	Bi-annual or annual
12.	Proportion of patients on ART whose performance scale at 6, 12, 24 months is "normal activity."	Bi-annual or annual
13.	Proportion of patients who have picked up their ARV drugs 6/6 months or 12/12months	Bi-annual or annual

#### Standardized recording and reporting system

- To generate the above listed indicators, it is important to have a uniform data collection and reporting system. Standard recording and reporting ensures that key information gets stored.

This helps in:

- Easily retrieval by care providers to get an overview of the patient's progress over time;

- Exchange of information between the different health care providers (such as, doctor, nurse, counselor, psychologist) as well as with other ART centres when the patient is referred or transferred to another clinic; and
- Facilitate compilation and comparison of indicators at province, national and international levels.

### 3. List of records and reports at the facility

#### Recording forms

- Patient HIV Care and ART Record
- Pre-ART Register
- ART Register
- ARV Drug Dispensing Register
- ARV Drug Stock Register.

#### Reporting forms

1. ART Monthly Report
2. Cohort Analysis Report.

Table 55: Quick guide for Recording and reporting formats

Form	What information?	For what purpose?	When to complete	Who will complete
Patient HIV Care / ART Record	Demographic, HIV care, Antiretroviral treatment and monthly follow-up clinical information	<i>Patient management:</i> to ensure appropriate lifelong follow-up <i>Patient monitoring:</i> to obtain key individual variables for future analysis	At each patient visit, starting from the 1st visit to the clinic	Health care providers during each patient visit
Pre-ART Register	Standardized and systematic key variables on each patient before ART started	<i>Patient monitoring:</i> to report key variables on each patient <i>Program monitoring:</i> to facilitate calculation of indicators	At the 1st visit At start of tuberculosis treatment and cotrimoxazole prophylaxis At ART eligibility At start of ART At end of follow up, if needed	Health care providers during each patient visit Or Trained staff using patient record after the visit
ART Register	Standardized and systematic key variables on each patient under ART	<i>Patient monitoring:</i> to report key variables on each patient <i>Program monitoring:</i> to	At each visit once ART is started	Health care providers during each patient visit Or

		facilitate calculation of indicators		Trained staff using patient record after the visit
ARV Drug Dispensing and Stock Registers	Drugs and no. of tablets dispensed Drug stocks	<i>Patient monitoring:</i> accounting for no. of tablets dispensed <i>Program monitoring:</i> drug consumption and available stocks	At the time of drug dispensing to each patient Daily basis	Pharmacist or officer in charge of dispensing drugs
Monthly ART Report	Indicators	<i>Program monitoring:</i> to calculate and analyse indicators	Every month	Facility manager Or Trained staff under supervision of the facility manager
Cohort Analysis Report	Indicators	<i>Program monitoring:</i> to calculate and analyse indicators at 6, 12, 24 months of start of ART	Every 6 months or during yearly assessment	Facility manager Or Trained staff under supervision of the facility manager

#### 4. Storage of records and reports

Correct storage of records and reports is important and ensures:

- That forms are available at each next visit;
- The confidentiality and security of the forms;

In numerous settings, records are transferred from outpatient services to the administrative section in charge of storage. This system is often not suitable for the lifelong follow-up required in HIV care because of the elaborate procedures and efforts required in requesting and obtaining the patients' records on time, as well as the possibility of difficulty in finding or losing records.

The best method is to store the client record within the clinic. Ensure that:

- Records are kept in the locked cabinet with access limited to the authorized staff.
- Records are arranged serially by registration number. Alternatively, they may be arranged by name, or date/month of next appointment. This will help in quickly locating the medical records just before the consultation, as well as in identifying those patients who missed an appointment.

## 5. Confidentiality and security

*Confidentiality* is the assurance that medical information will be used only for appropriate care and treatment of the individual.

*Security* is defined as the protection that assures that no breaches in confidentiality will occur.

Stigma and discrimination regarding HIV/AIDS still remain very high in most countries. Lack of confidentiality within health services is often a major obstacle in access to care for people who need it. Strict rules of confidentiality between the clients and their health care providers have to be developed to protect clients' rights. Protecting confidentiality is part of the professional code to conduct to the health care providers.

When recording and compiling individual information, ART clinic managers should ensure that confidentiality of records is mentioned. Breaches in confidentiality may easily occur if the clients' records aren't stored properly (as these may be accessed by unauthorized persons like friends or family members).

In establishing the monitoring system all aspects of confidentiality should be addressed, such as:

- Has the medical team, including the non technical staff, handling the patients' information been briefed on the principles of confidentiality?
- Where will the patient records be stored and who are the designated persons authorized to access the records?
- Who will be in charge of the registers and where will this register be stored?
- How will the medical information be transferred between services, such as for blood samples and laboratory results?
- In the **paper based system**, the most sensitive documents are records and registers with the patient information. Usually, only one copy should be available directly under the responsibility of the facility manager. The registers should be kept in the locked cabinet after the day's activities are over or when the clinic closes.
- In **computerized systems**, the individual patient information represents even a higher risk for breaches in confidentiality as electronic files can be easily reproduced and shared. Besides all the protection required for securing the database (e.g., computer dedicated for this purpose only, access limited to authorized persons, regular change in password), individual patient information should be computerized by registration number to maintain anonymity.

