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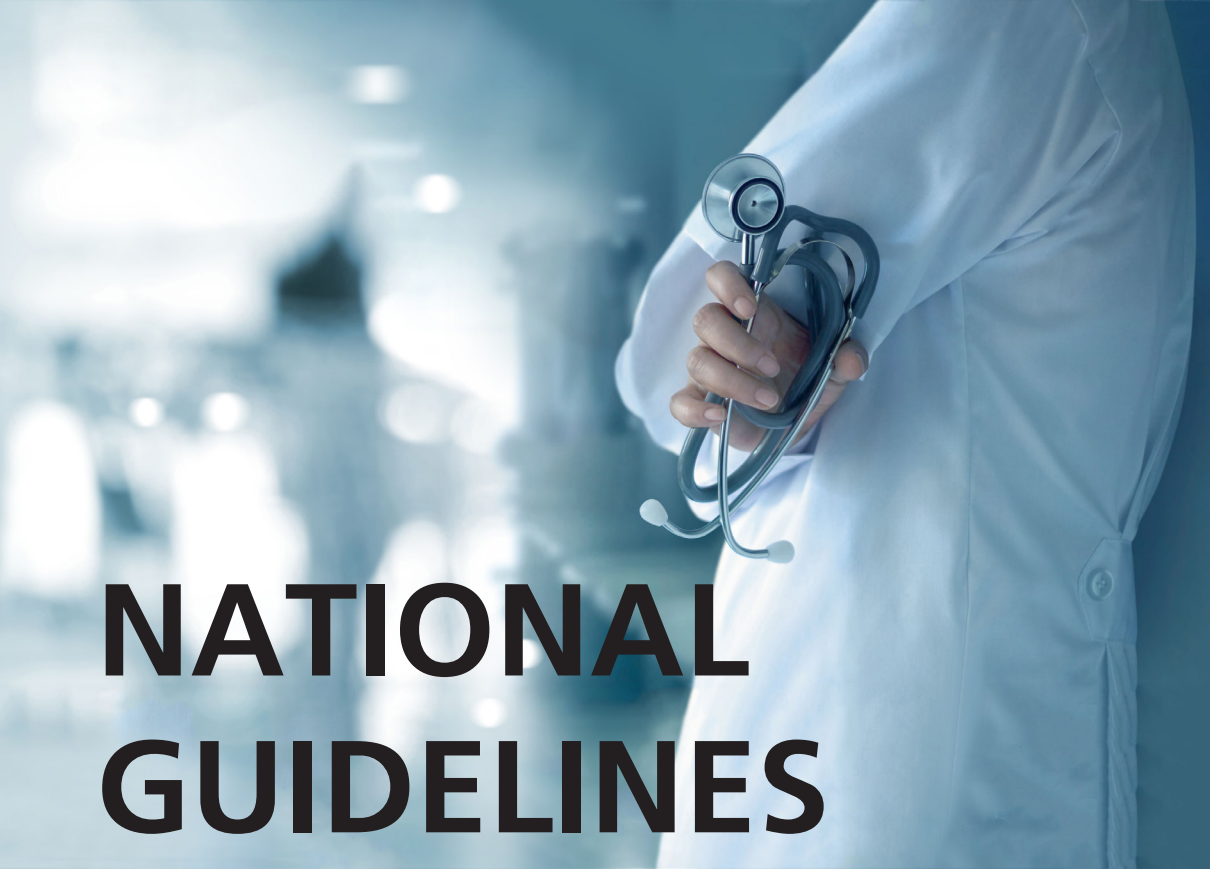

NATIONAL GUIDELINES

ON CLINICAL CARE AND ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION 2021

منظمة الصحة العالمية
جمهورية مصر العربية

وزارة الصحة والسكان
Ministry of Health & Population

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NATIONAL GUIDELINES ON
CLINICAL CARE AND ANTIRETROVIRAL DRUGS FOR TREATING AND
PREVENTING HIV INFECTION

Dr. Hala Zaid
Minister of Health and Population , Egypt

Since 1986, with the detection of the first HIV/AIDS case in Egypt, the Ministry of Health has committed to providing care and treatment to people living with HIV/AIDS. It ensures the quality of provided services to cope with the international guidelines.

Antiretrovirals have proved to be crucial in reducing the physical, psychological and economic burden of this disease on both individual and community basis. ARVs not only improve the quality of life for people living with HIV/AIDS but also plays a critical role in reducing the transmission of infection, which was the main pillar in the global ambitious target 90-90-90 aiming to end HIV/AIDS as a public health problem by 2030.

Egypt is working to cover the gap between the registered and estimated number of HIV/AIDS cases through scaling up testing and early detection of patients and instant linkage to care and treatment through quality stigma-free health care services.

These Guidelines come to scale up treatment regimens offered to PLHIV in line with the latest WHO guidelines, updating testing guidelines ensuring a continuum of care and rapid ART initiation.

I would like to present my great appreciation to HIV scientific Committee, Ministry of Health team and to introduce my gratitude to WHO and all partners for all their great efforts to support the National HIV response in Egypt

I am looking forward to more achievements in the health services provided to People living with HIV/AIDS and all Egyptians.

Forward

Dr. Naeema Al Gasser
WHO Representative to Egypt

WHO is pleased to support Egypt's commitment towards achieving the Sustainable Development Goals (SDGs) and in line with the Government of Egypt's national priorities towards achieving 'Zero HIV/AIDS '.

In accordance with the latest updated WHO HIV clinical guidelines and recent scientific advances in HIV clinical care and treatment , WHO appreciates all the efforts exerted to develop these updated national HIV clinical guidelines with national authorities led by Ministry of Health and in collaboration with partners. Egypt's clinical guidelines comes at a time to ensure high quality case management and treatment together with continuous streaming of care for all People living with HIV PLHIV with the lens of equity including refugees, migrants , prisoners and most vulnerable for both women and men. The aim is enhance prevention and control of HIV epidemic in Egypt in alignment with the global health sector strategy for ending the AIDS epidemic as a public health threat by 2030.

Moreover, the new guideline will be fully utilized by a team of clinicians and health care providers on case management in Egypt as part of strengthen the HIV national response in Egypt through series of capacity building courses and close monitoring and follow up.

WHO will continue collaboration with GOE and partners to achieve effective, efficient and innovative solutions based on evidence for any priority health problems. Our mandate as WHO Egypt country office to support national HIV clinical management with high quality of care and document the out come including the value for money.

Finally , I would like to appreciate Her Excellency Minister of Health and Population 's leadership to ensure expansion of HIV/AIDS Voluntary Counselling in all governorates under Universal Health Coverage . Further, recognize the thanks to Egypt's HIV Scientific Committee for their cooperation and efforts to deliver this comprehensive updated clinical guidelines to achieve better health outcomes for PLHIV towards achieving Universal health coverage for all and by all under an umbrella of leaving no one behind.

Forward

ACKNOWLEDGEMENTS

The HIV Scientific Committee would like to acknowledge the Egyptian Drug Authority for their contribution in finalizing this National Guidelines and the National AIDS Program Central and Peripheral teams for their efforts in providing health care services to PLHIV.

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I. ABBREVIATIONS AND ACRONYMS

3TC	lamivudine	**HTLV**	human T-cell lymphotropic viruses
ABC	abacavir	**INH**	isoniazid
AIDS	acquired immunodeficiency syndrome	**INSTI**	Integrase strand transfer inhibitor
ART	antiretroviral therapy	**IRIS**	immune reconstitution inflammatory syndrome
ARV	antiretroviral (drug)	**LPV**	lopinavir
ATV	atazanavir	**LPV/r**	lopinavir/ritonavir
ATV/r	atazanavir/ritonavir	**MAC**	Mycobacterium avium complex
AZT	zidovudine	**MSM**	Men who have Sex with Men
CBC	complete blood count	**MTCT**	Mother to Child Transmission
CD4	T–lymphocyte cell bearing CD4 receptor	**NAP**	National AIDS Program
CD8	T-lymphocyte cell bearing CD8 (cluster of definition 8) receptor	**NNRTI**	Non–nucleoside reverse transcriptase inhibitors
CDC	United States Centers for Disease Control and Prevention	**NRTI**	nucleos(t)ide reverse transcriptase inhibitor
CMV	cytomegalovirus	**NVP**	Nevirapine
CNS	central nervous system	**OIs**	opportunistic infections
CSF	cerebrospinal fluid	**PAP smear**	Papanicolaou smear
CXR	chest x-ray	**PCP**	Pneumocystis pneumonia
DNA	deoxyribonucleic acid	**PEP**	Post-exposure prophylaxis
DRV	darunavir	**PGL**	persistent generalized lymphadenopathy
DRV/r	darunavir/ritonavir	**PI**	Protease inhibitor
DTG	dolutegravir	**PLHIV**	people living with HIV
EFV	efavirenz	**PMTCT**	Prevention of Mother to Child Transmission
eGFR	estimated glomerular filtration rate	**PPD**	purified protein derivative
ELISA	enzyme-linked immunosorbent assay	**PrEP**	pre-exposure prophylaxis
FTC	emtricitabine	**PWID**	People Who Inject Drugs
HAART	highly active antiretroviral therapy	**RAL**	Raltegravir
Hb	haemoglobin	**STIs**	sexually transmitted infections
HBsAg	hepatitis B surface antigen	**TAF**	Tenofovir Alafenamide
HBV	hepatitis B virus	**TB**	Tuberculosis
HCV	hepatitis C virus	**TDF**	Tenofovir Disproxyl Fumarate
HIV	human immunodeficiency virus	**VCT**	voluntary counseling and testing
HPV	human papilloma virus	**WHO**	World Health Organization
HSV	herpes simplex virus	**XTC**	3TC or FTC

II. DEFINITION OF KEY TERMS

HIV refers to human immunodeficiency virus. There are two types of HIV; HIV-1 and HIV-2. HIV-1 is responsible for the majority of HIV infections globally.
In this guideline 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 18 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 18 years inclusive.

A child is a person 18 years or younger unless national law defines a person to be an adult at an earlier age. However, in this guideline when a person falls into the 10 to 18 age category they are referred to as an adolescent (see adolescent definition).

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

A neonate: is newborn till 28 days after birth.

Key populations 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.

Most-at-risk populations as people who inject drugs, men who have sex with men, sex workers, transgender people. 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 centers), 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.

Sero-discordant 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.

ARVs (ANTIRETROVIRAL DRUGS)

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

ART (ANTIRETROVIRAL THERAPY)

ART refers to the use of a combination of ARVs drugs to achieve viral suppression. This generally refers to lifelong treatment. Synonyms are combination ART and HAART.
ART for prevention is used to describe the HIV prevention benefits of ART.

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.

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 epidemic: 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- ART uptake refers to settings in which the uptake of ART among people living with HIV is less than 50%, 50-80% and greater than 80%, respectively.

High burden of TB and HIV setting refers to settings with adult HIV prevalence ≥1% or HIV prevalence among people with TB ≥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.

COMBINATION PREVENTION

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

1. Introduction

Despite the dramatic improvement in understanding HIV/AIDS epidemiology, natural history of HIV/AIDS and the emergence of effective antiretroviral therapies, AIDS continues to initiate fear, stigma and confusion. As part of the NAP strategy updating, these guidelines are delivered with great concern issued to the local epidemiological situation and special circumstances, as well as country-specific demographic nature of PLHIV, taking into consideration the previous national experience.

This process started by reviewing the previous national guidelines of clinical care and that of ARVs through the scientific national HIV committee by reviewing the epidemiological situation and considering the recent evidence and recommendation of the WHO consolidated guidelines.

These guidelines have been developed to provide guidance and support for physicians, as accurate information and appropriate management is the backbone for safe and competent care and treatment for persons suffering from AIDS.

These guidelines describe strategies for managing PLHIV at different levels of care provision, in order to ensure a continuum of comprehensive care. It also provides a guide for the use of ART using the different lines according to the national protocol. A strategy is proposed for each level of care, as well as the necessary equipment and drugs for responding to the health needs of PLHIV.

NAP provides clinical care and ARVs for all people living with HIV/AIDS free of charge according to the national guidelines and WHO recommendations.

Egypt epidemic update

By the end of 1986 the Ministry of Health in Egypt reported the first HIV/AIDS case, since that time there is a steady increase in PLHIV number in Egypt.

This steady increase is expected with the advent of counseling and testing services in different settings and with the expansion of the awareness activities to focus more on reaching those at risk in different governorates.

Scaling up the surveillance system and giving more attention to the care and support services provided to PLHIV, all these factors give a strong indicator of increasing epidemic.

People requiring care and support are thus on the rise. Accordingly, AIDS will become a public health problem of primary importance as health of one individual affects all the community.

Although, Egypt is still a low prevalence country with prevalence of 0.02% among the general population.

There are signs that indicate the presence of concentrated epidemic among two of the most at risk groups namely PWIDs and MSMs in addition to findings of IBBSS 2006 and 2010 with an urgent need to conduct new IBBSS.

Data collection and analysis for 2019 show that about 14% of the new cases were female and about 86% of the PLHIV at this year were 15-50 years.

1- Etiology of AIDS:

AIDS is caused by a lentivirus named Human Immuno Deficiency Virus (HIV). It belongs to the family of retroviridae and is one of the human T-cell lymphotropic viruses (HTLV).
The virus is 1/10000 millimeter in diameter and it is composed of:

1. An outer lipoprotein studded coat (the envelope). The outer protein coat is termed P18. It has a glycoprotein GP 120.
2. A core genome composed of ribonucleic acid (RNA), surrounded by a protein P 24 forming the inner coat. The inner layer of glycoprotein is termed GP-41.
3. Three enzymes named reverse transcriptase, integrase, and protease enzymes. These enzymes have a role in the replication of the virus.

Types and Subtypes of HIV:

There are currently two types of HIV: HIV-1 and HIV-2.
Worldwide and in Egypt the predominant type is HIV-1.

HIV-2 is different from HIV-1 in some points:

- HIV-2 is less pathogenic than HIV-1 and is associated with lower viral burden and a lower rate of both cell decline and clinical progression.
- HIV-2 is less easily transmitted than HIV-1
- The incubation period in HIV-2 is longer
- The transmission from mother to baby in HIV-2 is rare.

Because of its higher rate of replication HIV-1 mutates rapidly into subtypes. There are at least 10 genetically distinct subtypes of HIV-1 within group M (from A-J) and a distinct group of very heterogeneous viruses within group O.

2- HIV Replication:

The replication cycle includes the following steps:

- Attachment: the viral glycoprotein GP 120 is attached to the cell wall receptors (CD4) and the co-receptors (CCR5 and CXCR4).
- Fusion: complete fusion occurs between the virus and CD4 cell.
- Penetration: the virus enters into the CD4 cell.
- Uncoating: the virus loses its protein coat leaving RNA genome.
- Reverse transcription: the viral RNA is transformed into proviral DNA using reverse transcriptase enzyme.
- Integration: proviral DNA integrates into the T4 cellular genome using the integrase enzyme.
- Replication: proviral DNA replicates concomitantly with the replication of cellular DNA
- Transcription: messenger RNA is transcribed from proviral DNA.
- Translation: viral RNA is translated into viral precursor protein.
- Assembly: viral components form new viruses using the protease enzyme.
- Budding: viruses bud out of the cells killing it.

3- HIV transmission

Modes of transmission: Sexual transmission:

HIV may be transmitted from an infected person to the partner through any form of unprotected sexual activity (vaginal, rectal, and/or oral). It is the predominant mode of transmission worldwide and in Egypt. Transmission can occur from: male to female, female to male, male to male and female to female.
Penetrative intercourse has been associated with more risk of HIV infection. Receptive rectal and vaginal intercourse appears to present the greatest risk of infection. Oral sex has a much lower risk than anal or vaginal sex.

Parenteral transmission:

HIV may be transmitted through infected blood and blood products, as in sharing contaminated injecting equipment's (as needle, syringe and preparing tools) in intravenous drug use and needle stick and sharp injury in health care settings. Contaminated surgical and skin piercing instruments may play a role in HIV transmission.
N.B: HIV transmission does not occur by use of albumin, immunoglobulin, Rh factor or hepatitis B vaccine because the manufacturing process of these items kills the virus.

Mother to Child transmission (MTCT):

Also called perinatal transmission as HIV infection can occur from an infected mother to her infant in utero, during labor and delivery or postpartum through breastfeeding.

Factors Affecting HIV Transmission:

Biological factors:

Infectiousness of the host which depends on the stage of disease as stages in which high viral load is present - at the initial stage of infection and in more advanced stages - , there is increased risk of transmission. Also viral properties have a role as HIV-1 is more virulent than HIV-2 and certain virus may be resistant to antiretroviral drugs.

Increased Susceptibility of the recipient due to Inflammation or disruption of genital or rectal mucosa, lack of circumcision, and sex during menstruation.

Socioeconomic factors:

These include social mobility, stigma and denial, people in conflict, cultural factors as traditions, beliefs, religion, poverty, gender and drug use.

4- Natural Course of HIV/AIDS

Once HIV enters the human body it infects and replicates in the body cells (mainly CD4 cells). Significant viral replication induces the immune system to produce antibodies to HIV.

The period between acquisition of infection and production of antibodies, called "sero- conversion". It usually lasts between 2 and 12 weeks but may continue for as long as six months. This is known as the "window period". During this time, a person is infectious but may not test positive on HIV antibody tests.

At the time of infection, a small number of people may have a recognizable acute illness, with symptoms such as fever, lymphadenopathy (enlarged lymph nodes), night sweats, skin rash, headaches, and cough. These symptoms are usually ignored and/or passed off as general flu- like symptoms or as malaria in malaria endemic areas.

After sufficient induction of the antibody response, viral replication is kept in check. The infected person is asymptomatic and may remain so for a period varying from few weeks up to 10 years or more.

After a time, which varies from one individual to another, viral replication resumes and intensifies. Other infections may play a role in facilitating viral replication.
Viral replication leads to destruction of CD4 cells and progressive immunodeficiency.
As immune depression progresses, infected person becomes increasingly susceptible to opportunistic infections.
Clinical syndrome at this stage depends on the level of immune depression and on previous or current exposure to antiretroviral drugs.

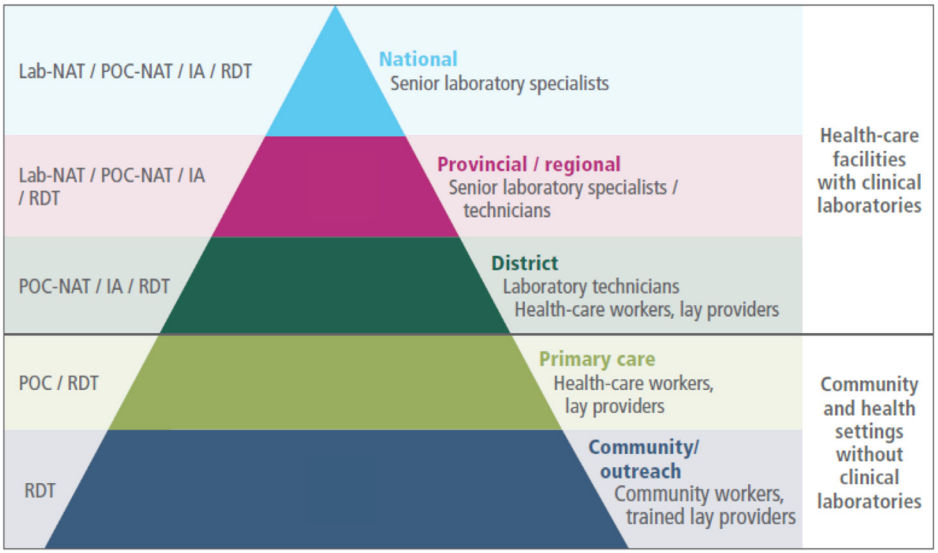
HIV co-morbidities with other infections are common among people living with HIV and have implications for natural course of HIV/AIDS and their treatment and care, including the timing and choice of ARV drugs.

2. HIV Testing and Counseling

1- General considerations

Different models of HIV testing and counseling services are available to increase and access to HIV diagnosis, including:

- Community based testing and counselling
- Provider initiated testing and counseling in health care facilities
- Testing and counseling for specific populations
- Wife of positive person has to be tested for HIV as to be provided with the PMTCT package or to stick to use very potent contraceptive method.



IA: enzyme immunoassay; Lab-NAT: laboratory-based nucleic acid testing; POC-NAT: nucleic acid testing at point-of-care; RDT: rapid diagnostic test, including HIV self-testing.

Source: WHO, 2012 (13).

All forms of HIV testing should be **in line with the WHO 5 C's: consent, confidentiality, counselling, correct results and connection**

- Consent
- Confidential
- At quality level of pre-test information and post -test counseling
- Monitored for correct test result
- Connection and linkage to other care, treatment and prevention services

In community-based testing and counseling, HIV test is offered on 'opt-in' basis which simply means that patients need to specifically ask to have an HIV test themselves. Nonetheless healthcare workers may still discuss the benefits of testing or make patients aware that tests are available. On the other hand, in healthcare settings, people are offered an HIV test on 'opt-out' basis. This simply means that healthcare worker demonstrates the benefits of having an HIV test, and that it will be carried out unless the patient refuses to do it.

2- HIV Laboratory testing

The current advancement in HIV testing technology availed different types of tests with high sensitivity and specificity exceeding 99% and 98% respectively. Samples yielding a negative Ab result are reported as negative provided that they are taken after the window period; the time between initial infection with HIV and when the body builds a measurable antibody response to it. HIV infection is diagnosed through a series of three consecutive tests which should be all positive to yield a confirmed HIV positive result. These tests may be any combination of three serological tests including rapid diagnostic tests (RDTs), ELISA, chemiluminescence, and combined HIV antigen/antibody tests. Western blot is also available for a minority of cases. The tests are described below:

Detection of viral antibodies:

- Rapid diagnostic tests (RDTs)

Various tests are available and can provide results in about 20 minutes. Their accuracy is analogous to ELISA screening tests. Reported negative tests are considered definitely negative; positive results should be confirmed with two other successive standard serology tests. RDTs can be performed in community settings by community health workers. They are useful for triage or for initial screening of patients. The use of RDTs for Ag/Ab combination for both HIV-1 and HIV-2 is preferred. After ruling out negative serostatus, reactive tests need to be sent for further confirmation with further tests. Samples from patients with reactive rapid tests should be sent to the laboratory for further confirmation with ELISA and/or chemiluminescence, preferably with an Ag/Ab combination assays.

It is recommended if available to the use of a combination rapid test (combo) for assessing three infectious diseases (HIV, Hepatitis B, and Hepatitis C). For pregnant women, rapid test for syphilis should be added as part of triple elimination mother-to-child transmission of HIV/HBV/Syphilis.

- Enzyme Linked Immunosorbent Assay (ELISA)

This is performed on a patient's serum to identify HIV antibodies. ELISA is performed in the laboratory by trained personnel. Negative ELISA Ab test results imply that a patient is HIV negative, provided that they are taken after the window period. Reactive tests should be confirmed with further tests (Chemiluminescence test, HIV PCR). Fourth generation combined HIV antigen/antibody tests are available nowadays and are preferred especially as they may shorten the window period.

- Western Blot test

It detects antibodies to a number of specific HIV proteins and is considered to be highly specific for HIV. After the two initial positive test results, samples yielding a positive result by Western Blot imply a confirmed positive HIV status. Negative results are reported as negative provided that they are taken after the window period. Western Blot is not currently recommended.

Detection of Antigen or its component:

DNA PCR (Qualitative)

This test detects the intracellular virus and can be used primarily for early viral infection, neonatal infection and indeterminate serology. It is not currently available in Egypt.

Reverse transcriptase (RT)-RNA PCR (Quantitative)

Plasma RNA is routinely used at baseline and to monitor the course and treatment of HIV infection. These tests report the number of copies of virus per milliliter of plasma.

Fourth generation combined antigen/antibody detection assays

These assays provide an enhanced level of seroconversion sensitivity in early infection over antibody-only assays by reducing the serological window period.

Minimum requirements suggested for the performance characteristics of different tests

Test	Requirements
Rapid diagnostic tests	Sensitivity ≥99% specificity ≥98% Include HIV-1/ HIV-2 Ab Preferred to detect Ag/Ab
Enzyme immune assays	Sensitivity 100% Specificity ≥98% Include HIV-1/ HIV-2 Preferred to detect Ag/Ab (4th generation)
PCR	Lower detection limit ≤50 IU

3- National Protocol for HIV testing

Adult and children more than 18 months:

In Egypt, diagnosis of HIV infection in adult and children more than 18 months is done through a series of 2 consecutive serological tests that detect viral antibodies and / or antigen in the following sequence:

Step (1): Ag/Ab Rapid test:

- If test result is negative: declare as negative considering the window period (2 -3 weeks).
- If test result is positive: refer to next step.

Step (2): HIV Chemiluminescence/ELISA Immunoassay

- If positive declare as positive.
- If negative declare as negative : repeat step 1 after 2 weeks.
- If inconclusive perform HIV PCR after 3 months:
  - If positive declare as positive.
  - If negative declare as negative.
  - If still inconclusive declare as negative.

Test 1: should be an RDT which detects Ag/Ab combination to shorten the window period, If Test 1 is an Ab RDT, confirmation with another type of Ab RDT or ELISA is needed before moving to step 2.

Tests 2: should include a serological test using ELISA or chemiluminescence technique which could detect HIV Ab. A test which can detect the Ag/Ab combination would be preferred.

If the patient is reported as inconclusive twice, PCR for HIV RNA could be used to help in the diagnosis.

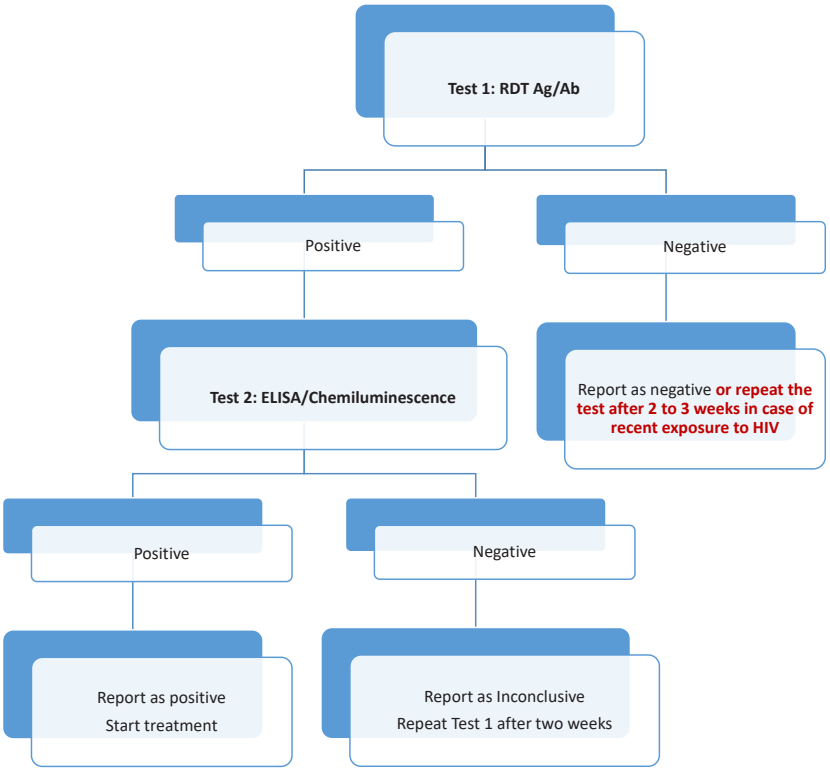


Figure 1. Algorithm of testing and reporting the test result

4 - Post-Test Counseling

Goals of counseling

- To educate people on how HIV is transmitted and how it can be prevented.
- To provide risk reduction strategies for all persons.
- To identify HIV infected individuals and provide them with proper clinical, psychological and social care and support.
- To provide counseling for HIV positive persons on how to prevent potential transmission onto others and on how to live a productive and healthy life.

Components of HIV post-test counseling

One aim of post-test counseling is to help clients understand and accept their test results. Post-test counseling is also a chance for counselors to help clients make choices based on their test results. Messages will differ for those who test positive and those who test negative.

First ensure that the client is ready to receive the result – mentally and physically – then disclose and interpret the test results according to the following:

For HIV–seronegative patients:

- Redress and reinforce the personalized risk-reduction plan
- Discuss the need to repeat the test for those with recent exposure (<3 months) or ongoing risk behavior

For persons with inconclusive results:

- Discuss prevalence and causes of inconclusive test results.
- For persons with high risk behavior, discuss the possibility of acute HIV infection and the need to repeat the test after the window period.

For HIV seropositive persons:

- Differentiate between being HIV-infected and developing AIDS.

Counsel patients that they are HIV-positive and discuss ways to avoid transmitting HIV onto others.
Emphasize the importance of medical referrals and the rapid initiation of ARTand adherence on ART as well to avoid progression to AIDS stage, if necessary

- Assess needs for psychological and social support and provide adequate referrals.
- Assess possibility of domestic violence and provide referrals.
- Encourage clients to return for follow-up services.

3. HIV prevention based on ARV drugs

1-Introduction

ARV drugs play a key role in HIV prevention, but they should be used in combination with an appropriate mix of other preventive measures.

Combining approaches may also result in synergies that have greater impact than single interventions alone. For example, other approaches having an important role in HIV prevention or used as harm reduction measures are:

Behavioral interventions

Reduce the frequency of potential transmission events through targeted information and education. A program that uses a variety of communication approaches to promote behavioral messages designed to encourage people to reduce behavior that increases the risk of HIV and increase the behavior that is protective.

Biomedical interventions

Reduce HIV risk practices and/or the probability of HIV transmission per contact event, including the following.

- Male and female condoms: Male condoms reduce transmission to a great extent if used consistently and correctly. Fewer data are available for the efficacy of female condoms, but evidence suggests they can have a similar prevention effect.
- Using clean needles and syringes each time is highly associated with a reduction in HIV transmission among injecting drug use.
- Opioid substitution therapy with methadone or buprenorphine is used as treatment for opioid dependence and has the additional benefit of effectively reducing HIV risk behavior and transmission among people who inject drugs.

2-Prevention of Mother to Child Transmission (PMTCT)

Mother to Child Transmission (MTCT) of HIV infection is the vertical transmission of HIV from mother who is HIV-infected to her infant. MTCT is the main transmission route for HIV infection in infants and children. Programs for the prevention of MTCT (PMTCT) can reduce MTCT and link women who are HIV- infected, their children and their families to treatment, care and support. PMTCT programs are comprehensive and follow national protocols and policies.

MTCT

HIV infection can be transmitted from an HIV-infected mother to her child during pregnancy, labor and delivery or breastfeeding
High maternal viral load in new or advanced HIV/AIDS is responsible for increased risk of MTCT.

MTCT risk factors during pregnancy

- Viral, bacterial or parasitic placental infection (especially malaria).
- Sexually transmitted infections.
- Maternal malnutrition (indirectly).

MTCT risk factors during labor and delivery

- Chorioamnionitis.
- Rupture of membranes for more than 4 hours before labor begins.
- Invasive delivery procedure.
- First infant in a multiple birth.

MTCT risk factors during breastfeeding

- Duration of breastfeeding.
- Early mixed feeding of infant (breast milk with replacement feeding).
- Breast abscesses/inflammation or cracked nipples.
- Maternal malnutrition.
- Infant oral diseases (e.g. Thrush or mouth sores).

2-PMTCT program

Prevention of primary HIV infection

- Promote safer and responsible sexual practices.
- Provide access to condoms.
- Provide early diagnosis and treatment of Sexually Transmitted Infections (STIs).
- Make HIV testing and counseling widely available.
- Provide suitable counseling for HIV-negative women.

Prevention of unintended pregnancies among women who are HIV-infected

- Provide effective family planning.
- Promote access to safe and effective contraception.
- Promote safer sex practices.

Prevention of HIV transmission from HIV-infected pregnant mothers to their infants "PMTCT core interventions"

- Provide HIV testing and counseling.
- Provide lifelong antiretrovirals for the mother (option B +).
- Promote safer delivery practices
- Provide prophylaxis for the infant.
- Educate and support safe infant feeding practices.

PMTCT strategies

Providing treatment, care and support to women who are HIV-infected, their infants and their families

- Provide HIV-related treatment, care and support services for women.
- Provide early diagnosis, care and support to the infant and child who are HIV-infected.
- Promote linkage to community-based services for comprehensive family care.

Antiretroviral treatment for pregnant women

Antiretroviral (ARV) drugs suppress the viral replication and viral load in the mother and thus protect to a great extent the infant against HIV exposure. ARV drugs effectively treat maternal HIV infection and prevent MTCT.

All pregnant and breastfeeding women with HIV should initiate ARVs, which should continue lifelong ,
The ART regimen is determined according to physician case assessment and National treatment guidelines recommendations , Mostly common ARVs regimens are not contraindicated with pregnancy.

Antenatal care of women who are HIV-infected and women of unknown HIV status

Antenatal care of women who are HIV-infected and women of unknown status includes the following:

- Health information and education.
- Education about safer sex practices and HIV.
- Safe motherhood including malaria and TB treatment.
- HIV testing and counseling.
- Partner HIV testing and counseling.
- Interventions to reduce the risk of MTCT.
- Infant feeding counseling and support.
- Diagnosis and treatment of Sexually Transmitted Infections (STIs).

In March 2020, Egypt initiates routined HIV testing for all pregnant women in antenatal care centers include in package of routine testing for pregnant women which also include HBV & syphilis screening.

- **Recommendations during labor and delivery**
  Reduce risk in women who are HIV-infected

Adherence to standard practices for delivery and to procedures that reduce fetal contact with maternal blood and secretions can reduce the risk of MTCT.
Interventions that reduce MTCT risk in labor and delivery include:

- Mother initiates and adhere to Antiretroviral treatment and infant prophylaxis both according to the national protocols.
- Universal precautions.

- Avoidance of:
  - Repeated unnecessary cervical examination.
  - Prolonged labor.
  - Routine rupture of membranes.
  - Unnecessary trauma such as episiotomies and fetal scalp monitoring.
- Minimizing the risk of postnatal hemorrhage.

Risk reduction in the obstetric setting

The potential for exposure to HIV-contaminated blood and body fluids is greatest during labor and delivery. The following can help reduce risk:

- Cover broken skin or open wounds with watertight dressing.
- Wear suitable gloves, including long cuffed gloves for manual removal of placenta.
- Wear impermeable plastic apron for delivery.
- Modify surgical practice to use needle holders, and use appropriately sized needles for suturing.
- Wear eye shield as needed.
- Wash blood splashed on skin with soap and water; rinse eyes with clear water only.
- Safely dispose of solid waste, including placenta and blood soaked dressing.

Reduce MTCT risk in women with unknown HIV status

Even when a woman's HIV status is unknown, there are steps healthcare workers can take to prevent MTCT:

- Offer rapid HIV testing with right to refuse during labor.
- Provide post-test counseling.

Recommendations during infant feeding
For mothers with HIV-infection

- Avoid all breastfeeding and should be replaced by replacement feeding
- Mothers who are HIV-infected should exclusively breastfeed when replacement feeding is not an option.
- Discontinue breastfeeding as soon as feasible. There is no evidence indicating a specific time for early cessation of breastfeeding. It depends on each mother's individual situation.
- All mothers who are HIV-positive should receive infant feeding counseling.

For infants born to HIV mothers

- Infants born to positive mothers are given ARVs (Nevirapine and/or Zidovudine) as prophylaxis for 6 weeks.

It is important to note that NAP recommends caesarian section for pregnant HIV women and normal delivery can be considered if the mother adhere to treatment and reaches undetectable viral load at 36 weeks of gestation and recommends the use of replacement feeding for their infants.

3-Post-exposure prophylaxis (PEP)

Post-exposure prophylaxis is short-term use of ARVs to reduce the probability of acquiring HIV infection after potential exposure

PEP after occupational exposure

A set of actions aimed at preventing infection in a person who may have been exposed to the HIV infection in health care setting.

An occupational exposure is defined as a percutaneous, mucous membrane or non-intact skin exposure to blood or body fluids that occurs during the course of an individual's employment.

Provision of antiretroviral drugs for post-exposure prophylaxis (PEP) for health care staff is important in case of any potential exposure, such as needle stick injuries. PEP is a part of a comprehensive package of universal precautions that reduces the exposure of personnel to infectious hazards at work. The issuing of PEP should be considered after an exposure with the potential to transmit HIV, based on the type of body fluid or substance involved, and the route and severity of exposure.

Accidents at work

- In case of injury with a sharp instrument, the wound should be washed thoroughly with water or soap and water and then covered with a waterproof dressing
- If a person receives splashes of blood or other body fluid into the mouth, the mouth should be rinsed out thoroughly with water and if the splash occurs to the eyes, they should be bathed either with saline or plain water.
- Any accident should then be reported to the health officer in charge to ensure appropriate follow-up and possible treatment with post-exposure prophylaxis
- PEP should be started as soon as possible after potential exposure to HIV.

The current recommended duration of post-exposure prophylaxis for HIV infection is 28 days, and the first dose should be offered as soon as possible within 72 hours after exposure. The choice of post-exposure prophylaxis drugs is as follows:

DTG + (TDF+FTC)
Or
LPV/r + (TDF+FTC)

1.First aid interventions of the injury:

- Wash the exposed site (e.g. wound or intact skin) liberally with soap and water, but without scrubbing.
- Flush exposed mucous membranes with water. If saline is available, flush eyes with saline.
- Do not apply caustic agents, including antiseptics or disinfectants, to the exposed areas.

2.Reporting:

- Immediate reporting to the Infection Control team and filling the reporting form.
- Reporting to the HIV governorate focal person.

3.Evaluate the exposed person and the source patient:

- To confirm the risk of the injury.
- To know the serostatus of the exposed person (only negative persons offered ARVs as PEP).
- To confirm the serostatus of the source person. Only contamination from a confirmed. positive source is applied to receive prophylactic ARVs.

4.ARVs:

- It is better to start ARVs within 2 hours of exposure if possible.
- The ARVs prescribed are based on the 1st line regimen. (6.3.1.1)
- ARVs are not supplied if a delay occurs more than 72 hours of exposure.
- Administer ARVs regimen for 28 days.

5.Testing protocol:

Antibody test is performed for exposed persons at definite intervals and its interpretation is:

- Zero point: to know the sero-status of the exposed person and if positive refer to care services as PLHIV, if negative proceed to all PEP steps.
- After one month: 2nd antibody test is performed, if positive refer to care services as PLHIV, if negative repeat after 2 months.
- After 3 months: 3rd antibody test is performed, if positive refer to care services as PLHIV, if negative declare as negative.

PEP after non occupational exposure "in case of sexual assault"

NAP recommends the use of post-exposure prophylaxis in case of sexual assault (rape) provided that there are existing legal documents such as availability of police record.
The same steps described under occupational exposure should be followed.

If it is not possible for the person to receive PEP in your setting, refer her to the HIV/AIDS focal person in the corresponding governorate as soon as possible (within 72 hours of the rape), then she can be referred to a service center where PEP can be supplied. If she presents after 72 hours, provide information on voluntary counseling and testing (VCT) services available in your area.
Consultation for psychological support is important in case of sexual assault.

4-Oral pre-exposure prophylaxis (PrEP)

Pre-exposure prophylaxis (PrEP) is a form of HIV prevention that uses ARVs for HIV-negative people without recent exposure to HIV.

- Adherence on ART for PLHIV and reaching undetectable viral load makes the risk for HIV transmission minimal anyway.
- People who are able to consistently use condoms and other HIV prevention strategies substitute the use of PrEP.

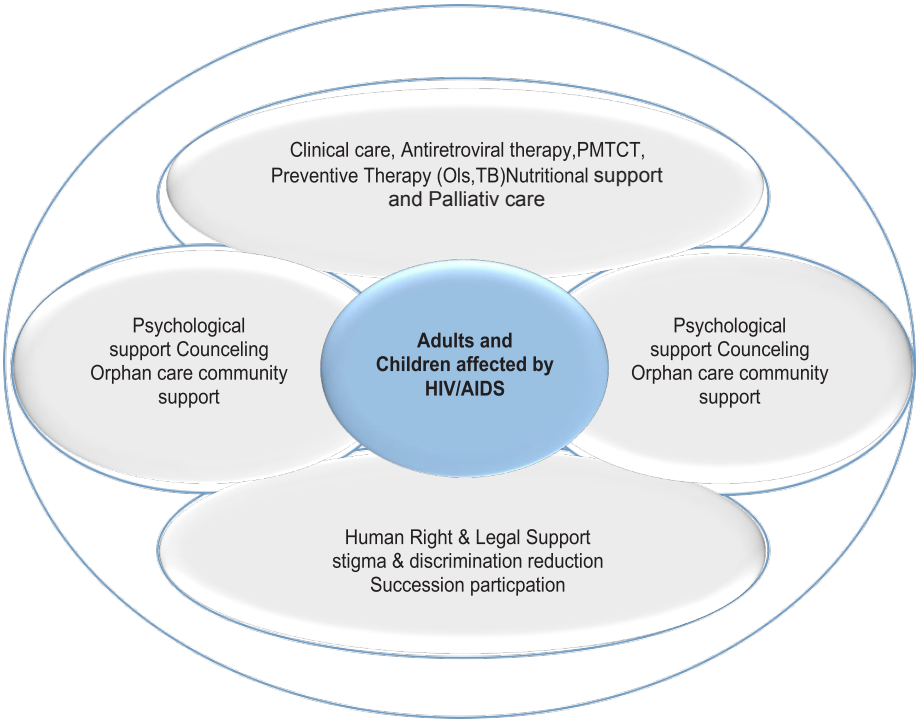
4. Linking people diagnosed with HIV infection to HIV care and treatment

Once people diagnosed with HIV from different entry points they should be linked to an integrated process of clinical care and treatment.

1-HIV/AIDS Continuum of Care

The different elements of comprehensive care should complement and strengthen one another at all stages of the disease. For example, managing a clinical condition is easier and more effective if worries about infecting a partner and planning for the family's future can be addressed through referral to counseling services that provide legal or social support.

The different elements of comprehensive care may not come from the same institution, but can be provided through networking with other services, institutions, and projects in the community.



The human needs of HIV infected people will continue for as long as they live, just like everyone else. Those physical, social, emotional and sexual needs must be actively managed for those infected and affected by HIV. Continuum of care should include timely referral between home, community and a hospital (and vice versa) with effective discharge planning and follow-up at each level.

Functional and confidential referral systems must be in place to build on previous care efforts.

Important components of referral include:

- Medical referral between a central hospital and community health center.
- Psychosocial referral between counselors and psychological care facilities.
- Referral to a home based care program.

Such coordination permits a continuum of care from the institutional level to the community and home based care level.

The support group's ability to make these linkages, exchange information, and offer emotional and moral support has been found to be essential all over the world. The HIV care continuum illustrates how linkages should function in a referral system.

Many people can be affected by HIV, not only through infection due to their own or their partner's risk behavior, but also through infection or risk behavior of a family member. The HIV virus does not discriminate; it will affect and infect anyone.

2-Comprehensive care of PLHIV

Care for PLHIV should cover all stages of HIV infection, from asymptomatic infection to end- stage disease.

Awareness of HIV serostatus allows for early access to HIV specific health care services. However, the stigma associated with HIV often discourages people from determining their HIV status. The longer it takes someone to find out that he/she is infected with HIV, the more chances there are for passing the infection onto others. Ideally, people should be informed of their serostatus through VCT in a confidential manner.

Comprehensive care for PLHIV includes:

- Clinical care to manage HIV- related illnesses
  - Emotional, psychological and spiritual care to help PLHIV, their families and friends to cope with the impact of HIV/AIDS. This is called impact alleviation.
  - Sexual education on managing sexual needs while protecting partners from infection is of paramount importance
  - Social care to maintain a nutritional and economical balance when repeated health expenditures deplete the family's income, which in turn affects planning for the family's future and securing basic support for survivors, particularly orphans

The type of care and support to be emphasized within a comprehensive approach will vary as the disease progresses. Early-stage infection requires an emphasis on counseling and behavior change while late-stage disease requires an emphasis on palliative care (to alleviate symptoms) and social support. Medical interventions are needed at all stages to prevent and treat opportunistic infections (OIs) and HIV-related diseases.

1-Clinical assessment

Patient's History

A comprehensive database is essential in assessing the patient's current situation and formulating a plan of care. Always remember that the patient may be anxious and frightened. The physician should be able to empathize with the patient, gain his/her trust, have a non- patronizing attitudes, show acceptance and provide reassurance.

In Patient's history, should fulfill the following:

- History of HIV diagnosis: why the patient was tested, when did he/she test positive, possible mode of transmission, the presence of any classic symptoms
- History of HIV treatment: if the patient has been treated for any HIV disease and his/her response to treatment. History of other medications
- Complete medical history including:
  - STIs: including a complete gynecological history.
  - Other infections: such as tuberculosis (TB), hepatitis A, B and/or C, pneumococcal infections, etc.
- Sexual practices and substance use evaluation.
- Mental health: past and current problems, especially assessement and management of depression and other psychiatric diseases.
- Comorbidities (diabetes, renal impairment, chronic liver disease, chronic pulmonary disease, cardiovascular risk assessment, etc.).
- Family history.
- Social history including sources of social support.

Physical Examination

A complete examination should be performed focusing on HIV/AIDS related clinical manifestations for early detection of any complications. Components of physical examination include:

General appearance:
may denote problems related to HIV infection. Weight loss is a common manifestation in an HIV infected person due to many causes such as chronic diarrhea, loss of appetite, dysphagia.

Fever:
important to record patient temperature and if he/she is feverish, ask about associated symptoms. If fever is associated with respiratory symptoms, TB or pneumonia is suspected. If fever is associated with neurological symptoms cryptococcal meningitis is suspected.

Eyes:
should be examined for anemia, jaundice, visual disturbances.

Mouth:
Any examination of an HIV infected person should include careful assessment of the oropharynx. There are many oral complications that may occur in an HIV infected person such as oral candidiasis, oral thrush, hairy leukoplakia, oral ulcers such as herpes simplex ulcers and even Kaposi Sarcoma.

Lymph nodes:
Lymphadenopathy may be the only presenting symptom in the acute stage of HIV infection. Persistent Generalized Lymphadenopathy (PGL) should be checked for.

Skin:
Careful examination of the skin often yields early clues of HIV infection. Mucocutaneous manifestations can occur in the second clinical stage e.g., prurigo, angular stomatitis, oral ulcers, seborrheic dermatitis, Molluscum contagiosum, etc.

Chest:
Chest manifestations, such as dyspnea, persistent cough (productive or dry), respiratory distress should be looked for. These might denote TB, bacterial pneumonia, and/ or PCP. Chest problems may be an indication for starting TB or PCP prophlaxis.

Gastrointestinal (GI):
Approximately half of AIDS patients suffer from diarrhea for numerous reasons such as: Salmonellosis, Shigellosis, Campylobacteriosis, Giardiasis, Amoebiasis and Cryptosporidiosis. Diarrhea may be the leading cause of death in AIDS patients. Hepatosplenomegaly should be looked for as it may reflect disseminated infections such as Mycobacterium avium complex (MAC) or TB.

Central nervous system (CNS):
The CNS should be examined carefully as HIV can affect the immune system and the nervous system. HIV can affect the CNS very early causing acute aseptic meningitis and in the terminal stage in the form of AIDS dementia. Neuropathy, numbness, loss of memory, diminished concentration and sensory motor retardation should be kept in mind while examining the patient.

Genital organs:
Genital organs should be examined for STIs as the increase the vulnerability to and the transmission of HIV infection. Pelvic examination and Papanicolaou (PAP) smears are required for women.

3-Routine Investigations for HIV- infected Patients

Basic Investigations	Indication
CD4 count	Baseline and every 6-12 months , In case of availability of routine viral load monitoring , it is enough to perform CD4 count every 12 months.
CD8 count	Baseline and every 6/12 months especially for children under 5 years
Viral load	Baseline, then 3 months after ART initiation or regimen shifting or manifestations of regimen failure., Thereafter, it is recommended to perform viral load testing every 6-12 months.(12 months for people stable on ART) , It is recommended to perform viral load monitoring more frequently during pregnancy every 3 months.
Complete blood count (CBC)	Baseline, then every 6 months; more frequently with taking marrow toxic drugs
Liver function tests Anti-HCV (HCV Ab) HBsAg Anti-HBc IgG HCV RNA	Baseline, then if history, symptoms or signs suggest liver diseases and done regularly if taking hepatotoxic drugs.
Hepatitis serology B, C	Baseline, before initiation of ART and then every 6 months for PWID.
Renal function tests (Urea, Creatinine)	Baseline, then if taking renal toxic drugs.
Pregnancy test	Baseline for all married women living with HIV and if pregnancy is suspected, for early PMTCT.
Tuberculin skin test (PPD)	Baseline, then annually if previous PPD- negative.
TB Testing	GeneXpert if symptomatic.
Chest X- ray (CXR)	Indicated for symptoms or signs suggesting pulmonary disease or newly- detected PPD- positive.

4-Preparing people living with HIV for ART

One of the important steps in the process of linking people diagnosed with HIV infection to care and treatment is counseling and educating them regarding ARVs initiation and continuity.

Previous to start ART, it is important to provide people living with HIV/AIDS with a suitable counseling regarding the benefits of ARVs and rapid ART initiation as well as the importance of adherence and some probable side effects of ARV are temporary and the required follow up and monitoring plan.

PLHIV whom will start ARVs should be informed that first line ART regimen offers the best opportunity for effective viral suppression and immune recovery.

Also they should be informed that while the ARV drugs reduce the risk of HIV transmission, they cannot be relied on to prevent other people from acquiring infection they should be given advice on safer sex (including condom use) and avoidance of other high-risk activities, such as sharing of injecting equipment, to prevent transmitting HIV to other people.

What to expect in the first 6 months of ART

Although taking ART is a lifelong commitment, the first six months of therapy are especially important. Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART, but opportunistic infections and/or immune reconstitution inflammatory syndrome (IRIS) may develop, as well as early adverse drug reactions, such as drug hypersensitivity, especially in the first three months of ART.

ART significantly decreases mortality overall however in case of late ART initiation death rates may be high as in this case people starting ART already have advanced HIV disease (AIDS stage) with severe immunodeficiency and existing confections and/or comorbidities, severely low hemoglobin, low body mass index and very low CD4 counts or are severely malnourished.

CD4 recovery

In most adults and children, CD4 cell counts rise when ART is initiate and immune recovery starts. Generally, this increase occurs during the first year of treatment, plateaus, and then continues to rise further during the second year.

However, severe immunosuppression may persist in some individuals who do not experience a significant rise in CD4 cell count with treatment, especially those with a very low CD4 cell count when initiating ART.

Failure to achieve some CD4 recovery should alert the health care provider to potential adherence problems or primary non-response to ART, and consideration should be given to continue prophylaxis for opportunistic infections such as co-trimoxazole preventive therapy.

Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is a spectrum of clinical signs and symptoms thought to be associated with immune recovery brought about by a response to ART.

It is a widely recognized phenomenon that occurs among 10–30% of the people initiating ART, usually within the first 4–8 weeks after initiating therapy.

It may present in two different ways: paradoxical IRIS, when an opportunistic infection or tumor diagnosed before ART initially responds to treatment but then deteriorates after ART starts; or unmasking IRIS, in which initiating ART triggers disease that is not clinically apparent before ART. It should be considered only when the presentation cannot be explained by a new infection, expected course of a known infection or drug toxicity.

The clinical spectrum is diverse, and IRIS has been reported for many different infections, tumors and non-infectious conditions.

The most serious and life-threatening forms of paradoxical IRIS are for TB, cryptococcosis, Kaposi's sarcoma and herpes zoster. BCG vaccine–associated IRIS (localized and systemic) may occur in infants infected with HIV in settings where BCG immunization is routine.
A low CD4 cell count (<50 cells/mm^3) at ART initiation, disseminated opportunistic infections or tumors and a shorter duration of therapy for opportunistic infections before ART starts are the main risk factors. IRIS is generally self-limiting, and interruption of ART is rarely indicated, but people may need to be reassured in the face of protracted symptoms to prevent discontinuation of or poor adherence to ART.

The most important steps to reduce the development of IRIS include:

- Earlier HIV diagnosis.
- nitiation of ART before a decline to below 200 CD4 cells/mm^3.
- Improving screening for opportunistic infections before ART, especially TB and Cryptococcus; and optimal management of opportunistic infections before initiating ART.
- Timing of ART in people with opportunistic infections requires balancing a greater risk of IRIS after early initiation against continuing high mortality if ART is delayed.

Opportunistic infections	ART initiation
Pneumocystis pneumonia	As soon as possible (within 2 weeks of initiation of co-trimoxazole.
Toxoplasmic encephalitis	3 weeks from the initiation of anti-toxoplamic therapy.
Cryptococcal meningitis	4-6 weeks from the initiation of antifungal therapy according to induction and consolidation therapy (4 weeks for amphotericin B-containing regimen and 4-6 weeks for fluconazole) containing regimen.
Tuberculosis	Within the first 2 weeks if CD4 count < 50/mm^3 Within the first 8 weeks if CD4 count > 50/mm^3.
	TB meningitis: initiating ART 2 months after the start of TB treatment.

5. Antiretroviral Therapy

1-Introduction to ARVs

Antiretroviral drugs are medications for the treatment of infections by retroviruses. When several such drugs, typically three or four, are taken in combination, the approach is known as highly active antiretroviral therapy "HAART".
There are different classes of antiretroviral drugs that act on different stages of the HIV life cycle.

Many antiretroviral drugs are available for the treatment of HIV infection; however, none of these medications can cure HIV. Medications used to treat HIV only reduce the ability of the virus to replicate (or reproduce itself). When the virus is unable to replicate, the immunity is restored and symptoms experienced by a person infected with HIV are reduced. Individuals receiving ART are less susceptible to OIs, cancers and other illnesses.

The goals of ART include the following:

- Improve and maintain the quality of life for people living with HIV and improve life expectancy.
- To maximally suppress viral replication.
- To achieve immune reconstitution that is quantitative (CD4 count in normal range) and qualitative (pathogen specific immune response).
- To decrease onward transmission of HIV.

Provide an ARV regimen that not only achieves reduced viral loads, but also preserves future therapeutic options, is relatively free of side effects and is tailored to individual needs for adherence.

Classes of Drugs:

Antiretroviral (ARV) drugs are broadly classified by the phase of the retrovirus life – cycle that the drug inhibits.

- Entry inhibitors (or fusion inhibitors) interfere with binding, fusion and entry of HIV host cell by blocking one of several targets.
- CCR5 receptor antagonists are the first antiretroviral drugs which do not target the virus directly. Instead, they bind to the CCR5 receptor on the surface of the T-Cell and block viral attachment to the cell. Most strains of HIV attach to T – Cells using the CCR5 receptor. If HIV cannot attach to the cell, it cannot gain entry to replicate.
- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI) inhibit reverse transcription by being incorporated into the newly synthesized viral DNA strand as a faulty nucleotide. This causes a chemical reaction resulting in DNA chain termination.
- Non – nucleoside reverse transcriptase inhibitors (NNRTI) inhibit reverse transcriptase directly by binding to the enzyme and interfering with its function.
- Protease inhibitors (PIs) target viral assembly by inhibiting the activity of protease, an enzyme used by HIV to cleave proteins for the final assembly of new virions.
- Integrase inhibitors inhibit the enzyme integrase, which is responsible for integration of viral DNA into the DNA of the infected cell.
- Maturation inhibitors inhibit the last step blocking the conversion of the polyprotein into the mature capsid protein (p24). "Not on the market yet"

Combinations of antiretroviral create multiple obstacles to HIV replication and reduce the possibility of a superior mutation.

Antiretroviral combination therapy defends against resistance by suppressing HIV replication as much as possible. If a mutation that convey resistance to one of the drugs being taken arises, the other drugs continue to suppress reproduction of that mutation. These agents must be taken in combination in order to have a lasting effect. Fixed-dose combination is recommended according to availability.

2-When to start

As a National Policy , Antiretrovirals should be introduced to all HIV confirmed cases regardless their immunological or virological status – Treat all or * Test and Treat Policy*.

Rapid initiation of ART is recommended for all PLHIV, on the same day to people who are ready to start ART or within 7 days, in order to reduce the number of (LTFU) Lost to follow up.

*In case of ARVs unavailability, ARVs will be prioritized to those with severe /advanced HIV disease and/or a CD4 count of 350 cells /mm^3 or less, people with active TB disease, HBV and/or HCV co-infection especially with severe liver disease, all pregnant and breastfeeding women with HIV and all children younger than five years living with HIV.

3- What to start

1- 1st line

1 Adults

Preferred 1st line ART regimen	Alternative 1st line ART regimen	Special circumstances
TDF + FTC (or 3TC) + DTG	TDF+FTC+EFV 400mg TDF+FTC+EFV600mg	AZT + 3TC + EFV 600 mg ABC + 3TC + DTG ABC + 3TC + EFV 600mg ABC + 3TC + EFV 400mg TDF + FTC (or 3TC) + RAL TAF+ FTC (or 3TC) + DTG TDF + FTC (or 3TC) + PI/r

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; PI/r: protease inhibitor boosted with ritonavir; RAL: raltegravir; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

DTG-based ART is preferred, and if DTG is unavailable, EFV 400mg or EFV 600mg can be used as alternative.

TAF may be considered for people with established osteoporosis and/or impaired kidney function.
Approved DTG dosing age and weight groups should be considered.

2- Second line ART

1. Adults and Adolescents

Failing First line regimen	Preferred Second Line regimen	Alternative Second line regimen
TDF + FTC (or 3TC) + DTG	AZT + 3TC + LPV/r or (ATV/r)	AZT + 3TC + DRV/r
TDF + FTC (or 3TC) + EFV (or NVP)	AZT + 3TC + DTG	AZT + 3TC + LPV/r or (ATV/r) or (DRV/r)
AZT + 3TC + EFV (or NVP)	TDF + FTC (or 3TC) + DTG	TAF+FTC+DRV/r TDF + FTC (or 3TC) + ATV/r TDF + FTC (or 3TC) +LPV/r TDF + FTC (or 3TC) + DRV/r

3TC: lamivudine; ABC: abacavir; ATV/r: atazanavir/ritonavir; AZT: zidovudine; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; RAL: raltegravir; TDF: tenofovir disoproxil fumarate.

TAF (tenofovir alafenamide) can be used as an alternative NRTI in special situations for adults and adolescents.

Second-line ART in case of HIV co-infection with either T.B. or Hepatitis B is explained in the following table.

HIV and TB	AZT + 3TC + LPV/r	LPV/r should be used by doubling the dose (800mg/200mg twice daily) or by using a super-boosted dose (ratio 1:1 LPV and ritonavir) with anti-TB treatment containing rifampicin.
	AZT + 3TC + DTG	It is recommended to prescribe AZT/3TC+DTG with doubling the dose of DTG (extra dose of DTG 50 mg at 12 hours interval), if the failing first line was TDF/XTC/EFV
HIV and HBV	AZT + TDF + FTC (or 3TC) + (ATV/r or LPV/r)	

2-Pregnant or breast feeding women

considering any drug contraindications , kindly return to the chapter of HIV Drug Formulary.

3-Third line

Third line ART should be guided by genotype testing and Stanford scores that inform ART regimen sequencing; robust regimen selection is key to ensure treatment optimization. DRV/r is PI and is effective in treatment for patients with LPV/r resistance.

Recommendation: RAL/DTG + DRV/r ± 1-2 NRTIs

However , Shifting to third line can be done without performing genotype testing in case of initiation with EFV. (In case genotype testing is not available)

Third-line ART in adults should consist of one or two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a Darunavir/ritonavir (DRV/r) plus Dolutegravir (DTG).
For NRTIs, it is recommended to recycle TDF/XTC.
For PI experienced people, the recommended DRV/r dose should be 600 mg/100 mg twice daily.
For INSTI experienced people, the recommended DTG dose should be 50 mg twice daily.
So, the preferred third line regimen is TDF/XTC+DTG+DRV/r with using higher dose of DTG or DRV/r or both according to their use or not in first and second line.

Recommendation for Third Line: RAL/DTG + DRV/r ± 1-2 NRTIs

4-Monitoring the response to ART and the diagnosis of treatment failure

Clinical assessment and laboratory tests play a key role in assessing individuals before ART is initiated and then monitoring their treatment response and possible toxicity of ARV drugs.

1-Recommended clinical & laboratory monitoring before starting and on first line ART

Evaluation	At start	Week 4	Week 12	Every 6 months
Clinical				
Clinical evaluation	√	√	√	√
Weight	√	√	√	√
Concomitant medication	√	√	√	√
Adherence support	√	√	√	√
Laboratory				
CD4	√		√	√
HIV RNA (viral load)	√		√	√
Hemoglobin	√		√	√
Pregnancy test	√			√
ALT- AST	√			√
Pregnancy test	√			
Creatinine	√			√
Fasting glucose	√			√

2-Recommended clinical & laboratory monitoring before starting and on second line ART

Evaluation	At start	Week 4	Week 8	Week 12	Every 6 months
Clinical					
Clinical evaluation	√	√	√	√	√
Weight	√	√	√	√	√
Concomitant medication	√	√	√	√	√
Check ART adherence	√	√	√	√	√
Laboratory					
CD4 count	√			√	√
HIV RNA (viral load)	√			√	√
Hemoglobin	√	√	√	√	√
Pregnancy test	√				√
ALT- AST	√				√
Creatinine	√				√
Fasting glucose	√				√

3-Desirable Laboratory monitoring before and after initiating ART

Phase of HIV	Desirable (if feasible)
HIV diagnosis	HBV (HBsAg) serology HCV serology
Follow-up	HIV Viral load (every 6–12 months)
ART	Haemoglobin test regularly for AZT Urine dipsticks for glycosuria and estimated glomerular filtration rate (eGFR) and serum creatinine for TDF Alanine aminotransferase for NVP
Receiving ART	Urine dipstick for glycosuria and serum creatinine for TDF
Treatment failure	HBV (HBsAg) serology (before switching ART regimen if this testing was not done or if the result was negative at baseline)

4- Monitoring the response to ART and the diagnosis of treatment failure

Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure. If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure.

Viral load testing strategies to detect or confirm treatment failure and switch ART regimen in adults, adolescents and children are explained in the following algorithm:

WHO definitions for ART failure

▸ Clinical failure

Adults and adolescents
New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment

Children
New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment

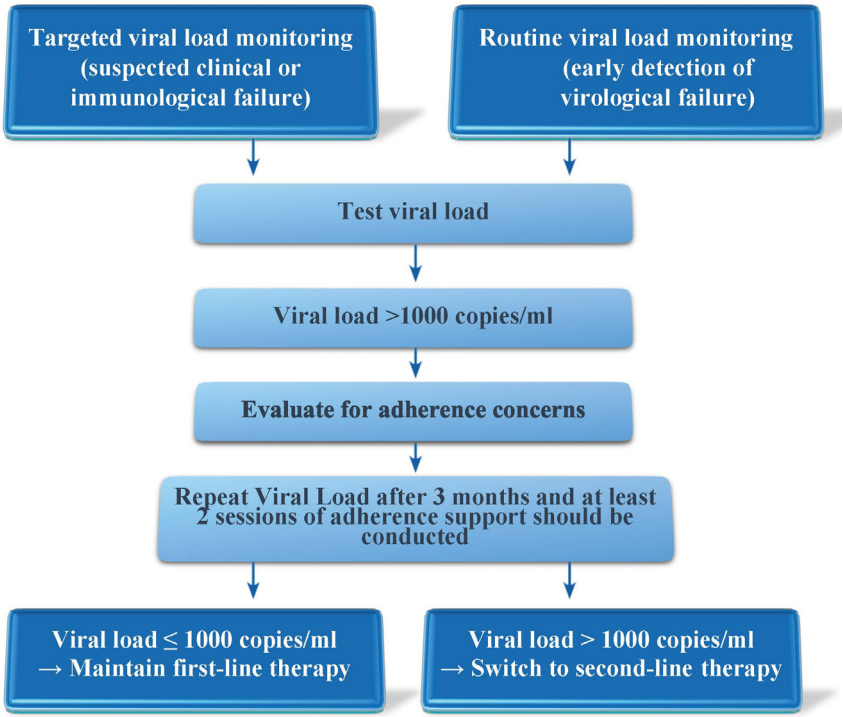
▸ Immunological failure

Adults and adolescents
CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm3

Children
Younger than 5 years: Persistent CD4 levels below 200 cells/mm3 or <10% Older than 5 years: Persistent CD4 levels below 100 cells/mm3

► Virological failure

Plasma viral load above 1000 copies/ ml (based on two consecutive viral load measurements within a 3-month interval, with adherence support) after at least 6 months of using antiretroviral drugs.



5-Adherence to ART

Adherence is defined as a patient's ability to follow a treatment plan, take medications at prescribed times and frequencies, and follow restrictions regarding food and other medications. Both patients and health care providers face significant challenges with respect to adherence to ART.

It is widely appreciated that adherence to highly active antiretroviral therapy (HAART) is one of the most critical determinants of the success of HIV care. Consequences of less-than- optimal adherence have been reported since the earliest days of the HAART era and include increased risk for disease progression, treatment failure, emergent drug-resistant HIV, and death.

Strategies to promote adherence were broken into categories discussed in the following table:

Area	Recommendation
General	Assess factors that influence adherence/assess barriers and suggest strate- gies to over- come them (social context, professional and familial conflicts, non-disclosure of HIV status, limited financial resources, etc.)
	Provide group education/group counseling support in a format and to cov- er content relevant to a specific patient population
	Target and enhance self-efficacy for adherence
	Assess and address common misconceptions and cultural beliefs regarding ART
	Mobilize community support
	Stigma and discrimination in HIV care centers in the main barrier to retention in care and ART adherence
Education	Explain the regimen and discuss side effects and management
	Use of material (figures, pictures, so on) to promote transfer of informa- tion and pro- mote memory and understanding
	Explain the importance of adherence for the success of ART, consequences on nonad- herence, and resistance
	Provide brochure or written information (general and specific to one's regi-men for when to take what
Regimen	Simplify regimen—effective once-daily or co-formulated regimens are pre- ferred
Access	Ensure consistent access to ART medications
Navigation	Link to services; treat concomitant conditions
	Navigation

Patient-centered care	Adopt regimens that are tailored to patient's lifestyle and as "simple" as possible
	Establish readiness for antiretroviral therapy (ART) before prescribing
	Use multidisciplinary treatment team approaches to consolidate treatment of multiple conditions and use of combined services
	Avoid judgmental or punishing interactions in discussing and reacting to nonadherence
	Support maintenance of high rates of adherence
	Ask about experiences with taking ART and refrain from "solving" or fixing reported barriers; allow patients to tell you their strategies
	Follow-up with adherence plans or difficulties with adherence between ap- (pointments (eg, via phone
	Increase resources of care through task shifting so that more ART prescrib- ers are available
	Establish a care team that is accessible and is perceived as trusted (estab- (lish trusting relationships with patients). Building trust from the visit is very important for adherence and retention in care
Engage-ment	Invite patients to actively contribute to care and treatment planning
	Facilitate positive interactions at point of care (positive patient–provider (relationships
Social	Support development of social support/enlist support of those in social networks
	Facilitate connections with peers who are on ART
	Encourage adherence (communication and messages delivered to support (adherence
Tools	Reminder devices
	(Communication technologies (interactive text messaging
	Encourage use of pillboxes, diaries, cell phone alarms as needed and as ad- juncts to other adherence support strategies
Skills	Plan ahead for changes in routine, weekends, and holidays
	Establish a routine; plan dose taking around routine, daily events, and cues; develop medication-taking schedules
	Recommend storing/carrying extra dose/doses

Targeted in-terven-tion	Increase intensity of intervention and follow-up for those struggling with adherence
	Tailor intervention approaches to stage of ART use (prior to initiation, ini- (tiation, and long-term use
	Incorporate routine HIV testing amongst expecting mothers and provision of ART for PTMTCT
	Treat comorbid conditions, screen and treat for mental health conditions such as de-pression as part of routine care and offer directly observed ther- apy for substance using populations
Monitor	Monitor levels of adherence
	Presence of adverse events when starting ART and over time
	Collect self-report data and medication refill data routinely (pill counts, drug concentra-tion, and electronic drug monitoring not recommended for (routine use in practice
	Ask about adherence at each clinical visit using open-ended questions ((Please tell me how you took your medications over the last 3 days

Questionnaires evaluating medication adherence in general can be used in healthcare settings for measuring ART adherence

Morisky 8-Item Medication Adherence Questionnaire

Question	Patient Answer (Yes/No)	Score Y=1; N=0
Do you sometimes forget to take your medicine?		
People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?		
Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?		
When you travel or leave home, do you sometimes forget to bring along your medicine?		
Did you take all your medicines yesterday?		
When you feel like your symptoms are under control, do you sometimes stop taking your medicine?		
Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		
How often do you have difficulty remembering to take all your medicine? A. Never/rarely B. Once in a while C. Sometimes D. Usually E. All the time		
	Total score	

Scores: >2 = low adherence 1 or 2 = medium adherence 0 = high adherence
Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence.
Med Care. 1986;24:67-74.

6. Neonatal and Pediatric HIV/AIDS

Neonatal and pediatric HIV/AIDS

Epidemiology

- The early diagnosis is sometimes difficult since the signs and symptoms are not specific.
- By one year of age one-third (1/3) of cases will have died, and half (1/2) of cases will die by 2 years of age.
- Worldwide, in 2013 an estimated 240,000 new infections occurred in infants and children (WHO) versus 290,000 new infections in 2010.
- More than 90% of new infections were acquired through mother to child transmission (MTCT).
- HIV testing and ART for pregnant women is very important to prevent MTCT and reduce the number of infected children.

Main modes of transmission

- MTCT (more than 90%):
  - During pregnancy (in 3rd trimester).
  - During delivery.
  - Breast-feeding.
- Other modes of transmission 10%

HIV diagnosis in children

- **Children at 18 Months and non-perinatal exposure:**
  - Testing as adult.

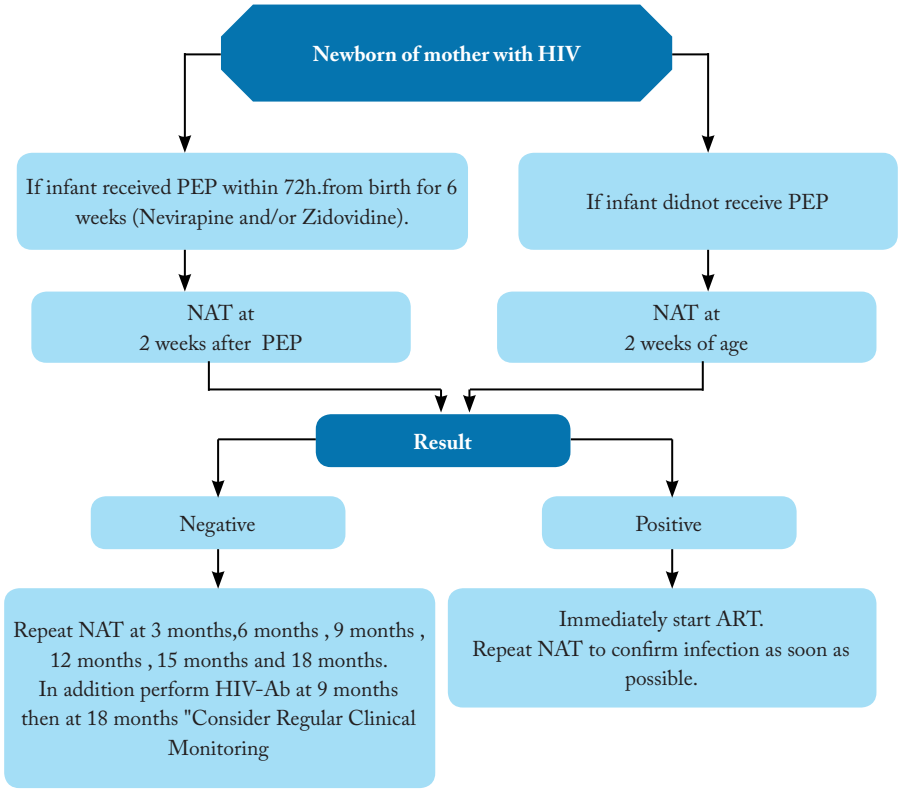
- **Infant and children under 18 months:**
  - Mortality is very high among untreated infants infected with HIV in the first year of life, making early HIV testing, prompt return of results and rapid initiation of treatment essential.
  - In this population, HIV infection can be definitively confirmed only
  - with virological testing using nucleic acid testing (NAT) technologies
  - (DNA/RNA-PCR). This is because transplacentally transmitted maternal HIV antibody may persist in the child up to 6-9 months of age, preventing the use of serological testing to diagnose HIV infection. In rare cases, maternal HIV antibody may persist in the child up to 18 months of age
  - HIV antibody (Ab) assays reliably detect HIV antibodies in children but cannot distinguish persisting maternal HIV antibody from antibodies produced by the child: They can only assess HIV exposure. In contrast, the presence of HIV Ab is a quick and reliable means of definitively diagnosing HIV infection in children older than 18 months because maternal HIV Ab are usually no longer detectable.
  - Virological tests include assays to detect viral nucleic acid (HIV DNA, RNA or total nucleic acid) or p24 antigen. Currently, assays to detect viral nucleic acid for early testing is recommended in Egypt.

- **Rapid Detection Tests (RDTs) in infant younger than 4 months:**
  - RDTs may be used to assess HIV exposure when testing mothers is not possible.
  - Children who are started on ART early are unlikely to develop an antibody response to the virus and may falsely test HIV-negative using a serological assay. Antibody testing should not be used to confirm or rule out infection in children who are already receiving ART.

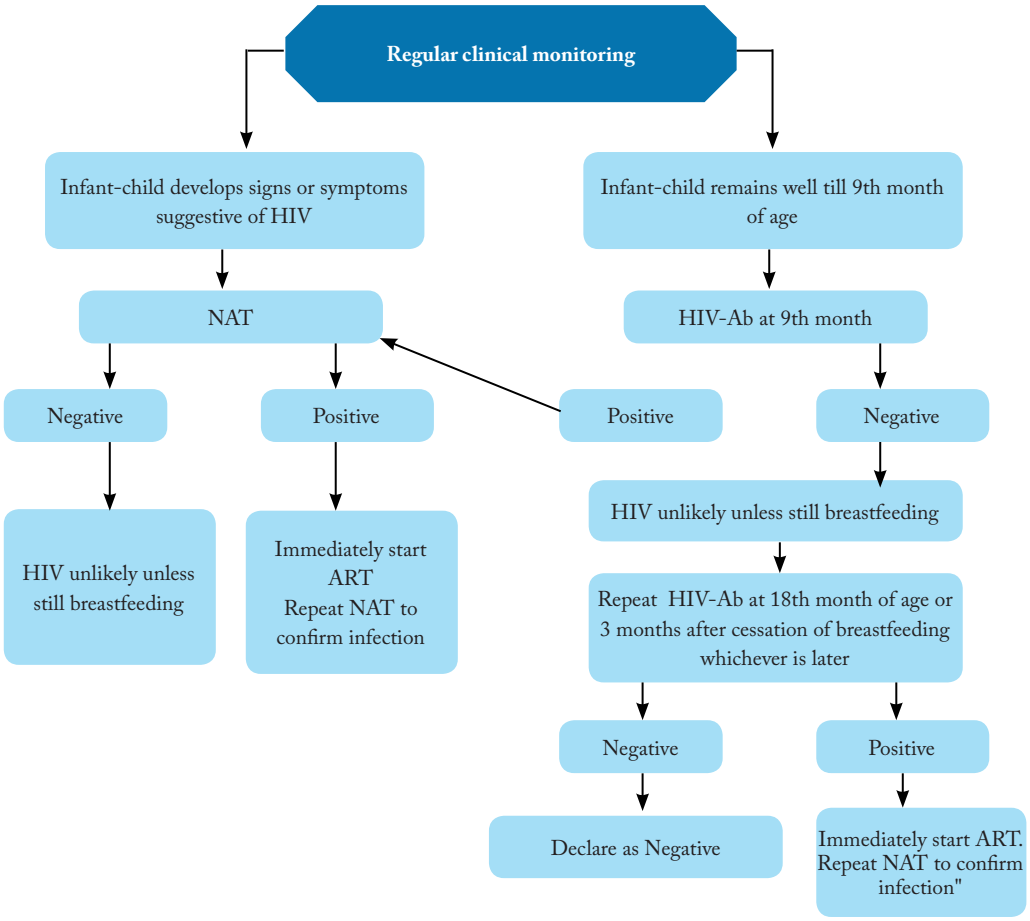
- **Protocol of testing:**
  - HIV-exposed infants (both infants born to HIV mother a n d breast feeding from HIV woman) should be tested.
  - Newborn of mother with HIV should be tested according to the following steps:
    1. When the newborn take post exposure prophylaxis (PEP) within 72h.from birth, do a virological testing using nucleic acid testing technologies (NAT) at 2 weeks after PEP:
       a. If negative, you should perform NAT every 3 months until 18 months and HIV-Ab at 9 months then at 18 months (considering also regular clinical monitoring)
       b. If positive, you must immediately start ART and repeat NAT at the same time to confirm infection. Do not delay ART, immediate initiation of ART saves lives and should not be delayed while waiting for the results of the second sample.
    2. When the newborn haven't received PEP, do NAT at 2 weeks of age and proceed as previous steps.

Algorithms of HIV testing in newborn and children:

a) HIV exposed infant:



b) Regular clinical monitoring:



c) Children with non-perinatal exposure: as adult

Clinical manifestations

There are two important clinical forms of HIV in pediatrics:

- Early severe form.
- Slowly progressive form.

	Early severe form	Slowly progressive form
Rate	15-20%	80-85 %
Contamination	In utero	Intrapartum
Onset of AIDS stage	3 to 15 months	2 -10 years
Manifestations	► Opportunistic infections and/or bacterial infections. ► HIV encephalopathy: 70 to 80% ► Haematological: anemia, neutropenia, thrombocytopenia.	► Bacterial infections, interstitial pneumonia, parotitis. ► Behavioral disorders, cognitive delay (10-20%).
5 year survival rate, in the absence of ART	Less than 10%	95%

Factors that promote occurrence of a severe form

- Maternal factors:
  1. Severe clinical form.
  2. CD4 < 200/mm3
  3. Viral load > 100 000 copies/ml

- Infantile factors :
  1. A virologic assay (PCR) positive at birth.
  2. Early clinical symptoms < 2 months
  3. High Viral load after 3 months.
  4. Co-infection HIV- CMV.

The most common co-morbidities and co-infections in pediatrics

1. Otitis media, sinusitis and pneumonia are more frequent and more severe than in healthy children.
2. Recurrent fungal infections, such a candidiasis (thrush), that do not respond to standard antifungals.
3. Recurrent or unusually severe viral infections, such as recurrent or disseminated herpes simplex or zoster infection or CMV retinitis, are seen with moderate-to severe immune deficiency.
4. Cancers:
    - Less frequent than in adults.
    - Kaposi's sarcoma is rare. It is due to human herpes virus 8 (HHV8).
    - Lymphomas: mostly non-Hodgkin lymphoma type B (role of EBV).
5. Lymphoid interstitial pneumonia (LIP)
6. Dilated cardiomyopathy
7. Renal lesions: proteinuria, nephrotic syndrome, renal failure.
8. Ocular lesions: asymptomatic micro-vascular ischemia.
9. Delayed puberty (endocrine disruption).
10. Early HIV encephalopathy: Start: 6-12 m, death before 4 years, no seizures and no peripheral neuropathy and CSF examination is normal. Diagnosis by MRI.

What is the cause of death in a child with HIV?

The most common causes of death in HIV infected children were:

- Pneumonia (30%),
- Pyrexia (22%),
- diarrhea (16%) and
- Wasting syndrome (16%).

If early use of ART in children, prognosis of HIV infection will be good.

Virological and immunological parameters in pediatric HIV infection

- In children <5 years, the risk of disease progression is based on CD4 % or CD4 count and plasma HIV RNA level.
- The absolute number of CD4 cells is much higher than in adults because of the physiological lymphocytosis and slowly decline to adult levels by age of 5 years.
- Younger children (especially <12 months) have higher risk of disease progression.
- Below 5 years of age, we depend on CD4 percentage while in adults we depend on CD4count.
- A higher VL (> 7 log10) characterizes the initial period of infection in the first months of life and a slower decrease at 12 to 24 months.
- Without treatment, the reduction of VL is very slow. HIV RNA generally low at birth, increases to high values by 2 months, then decreases slowly over several years (in untreated children).

Copies/ml	Log10 scale
1	1o
2	1oo
3	1ooo
4	10,000
5	100,000
6	1,000,000
7	10,000,000

Estimation of immunodeficiency based on CD4 count and CD4 % according to age

Normal value of CD4 %: 25 – 40

	<12 months	1-5 years	6-12 years
No immune deficiency			
- percentage	≥ 25%	≥ 25%	≥ 25%
- absolute value (/mm3)	≥ 500	≥ 1000	≥ 1500
Immunedeficiency Moderate			
- percentage	15-24%	15-24%	15-24%
- absolute value (/mm3)	750-1499	500-999	200-499
immune deficiency Severe			
- percentage	< 15%	< 15%	< 15%
- absolute value (/mm3)	< 750	< 500	< 200

Guidelines for the use of antiretroviral agents in pediatric HIV infection. MMWR, 1998, 47 (RR-4): 1-38.

WHO clinical staging of HIV/AIDS for children with confirmed HIV infection

Clinical stage 1

Asymptomatic
Persistent generalized lymphadenopathy

Clinical stage 2

Unexplained persistent hepatosplenomegaly Popular pruritic eruptions
Fungal nail infection Angular chelates
Lineal gingival erythema Extensive wart virus infection
Extensive molluscum contagiosum Recurrent oral ulcerations
Unexplained persistent parotid enlargement Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)

Clinical stage 3

Unexplained moderate malnutrition or wasting 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 one month)
Persistent oral candidiasis (after first 6–8 weeks of life) Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis or periodontitis Lymph node tuberculosis
Pulmonary tuberculosis
Severe recurrent bacterial pneumonia Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 109 per liter) and or chronic thrombocytopenia (<50 × 109 per liter)

Clinical stage 4
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy Pneumocystis pneumonia Recurrent severe bacterial infections (such as empyema, pomposities, bone or joint infection or meningitis but excluding pneumonia) Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site) Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extra pulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month Central nervous system toxoplasmosis (after one month of life) Extra pulmonary cryptococcosis (including meningitis) HIV encephalopathy Disseminated endemic mycosis (coccidiomycosis or histoplasmosis) Disseminated non-tuberculous myco-bacterial infection Chronic cryptosporidiosis (with diarrhea) Chronic isosporiasis Cerebral or B-cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Antiretroviral Therapy (ART)

When to start

Initiate ART to all HIV positive children regardless of WHO clinical stage and CD4 Cell count . For infants < 18 months when NAT is positive immediate initiation of ART should be considered while repeating NAT to confirm infection.

What to start

Baseline assessment: entry into care

- History and Physical examination.
- Weight, height, head circumference and other measures of growth.
- Tests for Co-infections: routine tests for hepatitis B and C infection and if suspected other coinfections e.g., TB testing (Tuberculin skin test, Chest X-ray , gene x pert), Toxoplasmosis Ab., CMV serology.
- CD4 and HIV RNA.
- Routine Lab-tests: CBC with differential leukocytic count. Chemiseries : SGOT, SGPT, Creatinine, Blood glucose, lipids: cholesterol and triglycerides
- Urinalysis.
- HLA-B*5701 test: This test is not necessary to initiate an ABC-based treatment. Only counseling and close clinical assessment is needed during the 6 first weeks of ART. In effect, according to systematic review among children exposed to ABC the estimated incidence of HSR was low (2.2%) with none of the deaths reported was being associated with ABC toxicity. So, ABC can be safely used for first-line or second-line antiretroviral regimens in children.

Monitoring the response to ART and the diagnosis of treatment failure: See general guidelines

Regimens of ART:

First line ART: (2NRTIs + 1 PI or INSTI or 1 NNRTI)
Recommended Regimens for newly initiating Children and Adolescents:

Key considerations for Optimizing Pediatric ART Formulations are the following:

- Solid formulations of LPV/r as soon as possible
- Transition to DTG-containing regimens as soon as possible based on child's weight, 20kgs at minimum
- Rapid phase-out of NVP-Based regimens based on child's weight

Preferred and alternative first-line antiretroviral therapy regimens for Pediatrics

	Preferred regimen	Alternatives	Special circumstances
Neonates			
	AZT + 3TC + RAL[a]	AZT + 3TC + NVP	AZT + 3TC + LPV/r[b]
Children			
< 20 kg	ABC/3TC + LPV/r	ABC/3TC + RAL AZT + 3TC + NVP	ABC/3TC + EFV400
20-30 kg	ABC/3TC + DTG	ABC/3TC + LPV/r ABC/3TC + RAL	ABC/3TC + EFV400 AZT/3TC + EFV400 AZT/3TC + LPV/r
> 30 kg	TDF/3TC/DTG		
Special considerations	► BLPV/r is not recommended for infants < 2 weeks of age ► If initiated at < 4 weeks of age or has weight <3 kg for ART initiation, see figure 2 below ► LPV/r tablets should not be cut, split, dissolved, chewed or crushed as bioavailability is seriously reduced when not swallowed whole ► Transition from LPV/r solution/ granules to LPV/r 100mg/25mg tablets as soon as the child is safely able to swallow tablets to reduce pill burden		

a. Neonates starting ART with an RAL-based regimen should transition to LPV/r as soon as possible.
b. LPV/r syrup or granules can be used after 2 weeks of age.

Considerations for Timing of ARVs for Pediatrics

ARVs	Time for use
Zidovudine	At birth
Lamivudine	At birth
Abacavir	Since 3 months (4,6-6 Kg)
Tenofovir	Since 2 years or (12 kg)
Nevirapine	At birth
Efavirenz	Since 3 years or ≥ (14 kg)
Lopinavir/r	Since 2 weeks
Atazanavir/r	Powder (since 3 months or 6 Kg) capsules (since 6 years or 20 Kg).
Darunavir+Ritonavir	Since 3 years or ≥ (10 kg)
Raltegravir	At birth
Dolutegravir	Since 20 kg
Etravirine	Since 10 kg

Recommendations for co-administering antiretroviral drugs with rifampicin

- For infants and children infected with HIV weiging less than 20 kg , E F V based regimen or RAL based regimen (For infant from 4 weeks, when raltégravir is associated to rifampicin based anti-TB treatment, it should be used at the dose of 12 mg/kg twice daily) or triple nucleoside regimen (ABC + 3TC + AZT) is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. (superboosted LPV/r (a 1:1 ratio between LPV and Ritonavir) can also be used as an option) Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted.

- Non-nucleoside reverse transcriptase inhibitors
  - Efavirenz: No interaction.
  - Etravirine: should not be used together with rifampicin

- Integrase inhibitors
  - Dolutegravir: Increase dose to 50 mg twice daily. This extra dose of DTG is well tolerated, with equivalent efficacy in viral suppression.
  - Raltegravir: should be given at a higher dose of 12 mg/kg twice daily as an oral chewable formulation (maximum dose: 800 mg twice daily).

- Ritonavir boosted protease inhibitors
  - Lopinavir / ritonavir (Kaletra™): double the dose according age dosing. This may cause hepatotoxicity and more common GI adverse effects.
  - Super-boosted lopinavir / ritonavir: Suggested RTV dose for super-boosting to achieve the same dose as LPV in mg, in a ratio equal or approaching to 1:1. This dosing approach is supported by a study which explored this approach in young children receiving LPVr. The standard boosting ratio in HIV treatment is 4:1.
  - Darunavir/ritonavir, Atazanavir/ritonavir: They should not be used with rifampicin.

Second line ART

Failing First Line	Preferred Second-line regimen	Alternative Second Line
ABC/3TC + DTG	AZT/3TC + LPV/r	AZT/3TC + ATV/r
ABC/3TC + LPV/r	AZT/3TC + DTG ABC/3TC + DTG	AZT/3TC + RAL ABC/3TC + RAL
AZT/3TC + LPV/r		
ABC/3TC + EFV	AZT/3TC + DTG ABC/3TC + DTG	AZT/3TC + ATV/r ABC/3TC + ATV/r AZT/3TC + LPV/r ABC/3TC + LPV/r
AZT/3TC + EFV		
AZT/3TC + NVP	ABC/3TC + DTG	ABC/3TC + LPV/r ABC/3TC + ATV/r

- 3TC: lamivudine; ABC: abacavir; ATV/r: atazanavir/ritonavir; AZT: zidovudine; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ ritonavir; NVP: nevirapine; RAL: raltegravir; TDF: tenofovir disoproxil fumarate.

For age and weight groups with approved DTG dosing.
ATV/r can be used as an alternative to LPV/r for children older than three months, but the limited availability of suitable formulations for children younger than six years, the lack of a fixed-dose formulation and the need for separate administration of the ritonavir booster should be considered when choosing this regimen.
DRV should not be used for children younger than three years and should be combined with appropriate dosing of ritonavir.

- After failure of a first-line regimen containing AZT + XTC, the preferred NRTI backbone option for second-line ART is ABC or TDF + XTC according to the weight.
- After failure of a first-line regimen based on DTG, children should be switched to a boosted PI-based regimen. LPV/r (can be used from 14 day or 4 kg) or ATV/r (from 20 kg) are the preferred boosted PIs.

Third line Regimen

There is a limitation of third-line ARVs for children.

For older children and adolescents who have more therapeutic options available, constructing third-line ARV regimens with drugs used in treating adults such as DRV, DTG may be possible. It is recommended to use the following combination: TDF/FTC+DTG+DRV/r. The doses of DTG and DRV/r should be adjusted according to their use on first- and second line therapy.
For younger children (<20 kg), RAL may replace DTG.
For children weighing ≥10 kg, Etravirine may be used
Children on a second-line regimen that is failing with no new ARV drug options should continue with a tolerated regimen.

Considerations for transition to optimal ART regimens for children who are considered stable on ART based on national guidelines

Considerations	Weight	Optimal regimen for transition	Considerations
AZT + 3TC + NVP AZT + 3TC + EFV ABC + 3TC + NVP	<20 kg	ABC + 3TC + LPV/r	If stable, children can be transitioned to DTG when they reach 20 kg
	20–30kg	ABC + 3TC + DTG	If stable, children can be transitioned to TDF + 3TC + DTG when they reach 30 kg
	> 30 kg	TDF + 3TC + DTG	-

ABC + 3TC + EFV	<20 kg	No change until they reach 20 kg unless treatment failure occurs	Transition to optimal regimens for these children is of value once they reach 20 kg and DTG can be used maintaining once-daily administration
	20–30kg	ABC + 3TC + DTG	If stable, children can be transitioned to TDF + 3TC + DTG when they reach 30 kg
	> 30 kg	TDF + 3TC + DTG	-
ABC + 3TC + LPV/r AZT + 3TC + LPV/r	<20 kg	No change until they reach 20 kg unless treatment failure occurs	Ensure the use of tablets as soon as possible to reduce pill burden. Transition from AZT + 3TC + LPV/r to ABC + 3TC + LPV/r can also be considered to reduce the pill burden and preserve the antiviral advantage of NRTI's sequencing
	20–30kg	ABC + 3TC + DTG	If stable, children can be transitioned to TDF + 3TC + DTG when they reach 30 kg
	> 30 kg	TDF + 3TC + DTG	=

Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing in infants and children 4 weeks of age and older

Drug	Strength of paediatric tablets	Number of tablets by weight band morning and evening										Strength of adult tablet	Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
AZT/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg/150 mg	1	1
AZT/3TC/ NVP	Tablet (dispersible) 60 mg/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg/150 mg/ 200 mg	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600 mg/300 mg	0.5	0.5
ABC/3TC	Tablet (dispersible) 120/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600 mg/300 mg	0.5	0.5

Each AZT/3TC/ NVP tablet can be melt in 3cm water

Simplified dosing of child-friendly solid formulations for once-daily dosing in infants and children 4 weeks of age and older

Drug	Strength of paediatric tablets	Number of tablets or capsules by weight band once daily					Strength of adult tablet	Number of tablets or capsules by weight band once daily
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg		25–34.9 kg
EFV	Tablet (scored) 200 mg	–	–	**1**	**1.5**	**1.5**	–	**2**
DTG	Tablet 50 mg	–	–	–	–	1	50 mg	1

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or MLS by weight-band morning (AM) and evening(PM)										Strength of adult tablet	Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
Solid formulations														
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
NVP	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200 mg	1	1
LPV/r	Tablet 100 mg/25 mg	–	–	–	–	2	1	2	2	2	2	–	3	3
	Pellets 40 mg/10 mg	2	2	3	3	4	4	5	5	6	6	–	–	–
DRV	Tablet 75 mg	–	–	–	–	–	–	5	5	5	5	400 mg	1	1
RTV	Tablet 25 mg	–	–	–	–	–	–	2	2	2	2	100 mg	1	1
	Tablet 50 mg	–	–	–	–	–	–	1	1	1	1			
RAL	Chewable tablets 25 mg	1	1	2	2	3	3	4	4	6	6	400 mg	1	1
	Chewable tablets 100 mg	–	–	–	–	–	–	1	1	1.5	1.5	400 mg	1	1
Liquid formulations														
AZT	10 mg/ml	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	–	–	–	–	–	–	–
ABC	20 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	–	–	–	–	–	–	–
3TC	10 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	–	–	–	–	–	–	–
NVP	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	–	–	–	–	–	–	–
LPV/r	80/20 mg/ml	1 ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml	–	–	–
DRV	100 mg/ml	–	–	–	–	2.5 ml	2.5 ml	3.5 ml	3.5 ml	–	–	–	–	–
RTV	80 mg/ml	–	–	–	–	0.5 ml	0.5 ml	0.6 ml	0.6 ml	–	–	–	–	–
RAL	10 mg/mL (Oral granules for suspension: 100 mg/ sachet)	3 mL	3 mL	5 mL	5 mL	8 mL	8 mL	10 mL	10 mL	–	–	–	–	–

Drug dosing of liquid formulations in infants less than 4 weeks of age

Drug	Strength of oral liquid		2-3 kg		3-4 kg		4-5 kg	
			AM	PM	AM	PM	AM	PM
AZT	10 mg/mL		1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL
NVP	10 mg/mL		1.5 mL	1.5 mL	2 mL	2 mL	3 mL	3 mL
3TC	10 mg/mL		0.5 mL	0.5 mL	0.8 mL	0.8 mL	1 mL	1 mL
LPV/r	80/20 mg/mL		0.6 mL	0.6 mL	0.8 mL	0.8 mL	1 mL	1 mL
RAL	10 mg/mL (Oral granules for suspension: 100 mg/ sachet)C	<1 week	0.4 mL (once daily)		0.5 mL (once daily)		0.7 mL (once daily)	
		>1 week	0.8 mL	0.8 mL	1 mL	1 mL	1.5 mL	1.5 mL

Dosing for ritonavir (RTV) super-boosting of LPV/r for children receiving rifampicin-containing TB treatment

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or MLS by weight-band morning (AM) and evening (PM)										Strength of adult tablet	Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
For children able to swallow tablets														
LPV/r	Tablet 100/25 mg	–	–	–	–	2	1	2	2	2	2	–	3	3
RTV	Tablet 100 mg	–	–	–	–	1	1	1	2	1	2	100 mg	2	2
	Tablet 50 mg	–	–	–	–	2	2	3	3	3	3			
	Tablet 25 mg	–	–	–	–	4	4	6	6	6	6			
For children unable to swallow tablets														
LPV/r	Oral solutionc 80/20 mg/ml	1 ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml	-	-	-
	Pelletsd 40 mg/10 mg	2	2	3	3	4	4	5	5	6	6	-	-	-
RTV	Oral solution 80 mg/ml	0.8 ml	0.8 ml	1.2 ml	1.2 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.3 ml	2.3 ml	-	-	-
RTV	Powder 100 mg/ packet	-	-	1	1	1	1	1	2	1	2	-	-	-

7. Vaccines and HIV

Vaccines and HIV

Introduction

- Vaccination recommendations are determined by weighing the benefits of vaccination against the risks.
- Although vaccination recommendations for HIV-infected patients are similar to those for HIV-uninfected patients in many respects, HIV can alter the efficacy and safety of vaccines and affect the susceptibility of the patient to the diseases for which immunization can confer protection.
- No effect of vaccination on HIV disease progression has been found.
- Generally, vaccination is safe and effective before HIV infection causes significantly immune suppression.
- Protective immunity to vaccines received before HIV infection is usually maintained, certain exceptions such as measles vaccine.
- The risk increases with severe immune suppression.
- Reconstitution of the immune system and control of HIV replication using ART before immunization should result in improved responses to vaccination.
- In general, it is preferable to avoid live-virus vaccines if an alternative inactivated vaccine is available, as in the case of influenza.
- Live-virus vaccines generally are contraindicated because of a proven or theoretical increased risk of vaccine virus disease.
- Live-virus vaccination should be avoided during and 3 months after intravenous immunoglobulin (IVIG) treatment, if possible, because passive antibodies in IVIG may impair response to live-virus vaccination with MMR or varicella for up to 3 months after IVIG infusion.

Types of vaccines

- **Inactivated vaccines:**
  3. Tetanus toxoid, diphtheria toxoid, acellular pertussis vaccines
  4. Pneumococcal vaccine
  5. Haemophilus influenza vaccine
  6. Influenza vaccine
  7. Hepatitis A vaccine
  8. Hepatitis B vaccine
  9. Meningococcal vaccine
  10. Human papilloma virus vaccine
  11. Inactivated Poliovirus vaccine(IPV)
- **Live vaccines:**
  1. Rotavirus vaccine
  2. Measles, mumps, and rubella vaccine
  3. Varicella vaccine
  4. Zoster vaccine
  5. Yellow fever vaccine
  6. BCG vaccine
  7. Oral poliovirus vaccine(OPV)

Vaccines in HIV-infected children

- Despite suboptimal immune responses, routine inactivated immunizations are recommended. Live attenuated vaccines are generally not recommended with the exception of measles, mumps, rubella vaccine and varicella vaccines which can still be given to children who are not severely immunocompromised (CD4 lymphocytes >15%).
- A theoretical concern is enhanced HIV virus replication due to immune activation following immunization, but this is predicted to be greater following infection so the consensus has been to immunize. HIV viral replication may be enhanced transiently without increased progression of HIV disease.
- Additional data are pending on rotavirus and human papillomavirus vaccine in HIV.

Specific Vaccines

1. **Rotavirus vaccine:** may be administered to infants exposed to or infected with HIV, irrespective of CD4+ T-lymphocyte percentage or count, according to the schedule for uninfected infants.

2. **BCG vaccine**
   - Recent data have demonstrated, that children who are HIV infected when immunized with BCG at birth, and who later progress to AIDS, are at increased risk of developing disseminated BCG disease later in life.
   - WHO recommended that BCG vaccine not be given to any child known to be HIV infected (symptomatic or asymptomatic). So, infant of HIV positive mother should not be vaccinated with BCG vaccine except after complete exclusion of HIV.

3. **Pneumococcal vaccine (Pneumococcal Conjugate Vaccine [PCV]; Pneumococcal Polysaccharide Vaccine [PPSV])**
   - Invasive pneumococcal disease remains a source of significant morbidity and mortality among HIV-infected individuals. Although the availability of ART has decreased the rates of pneumococcal bacteremia, incidence remains 35-fold higher than in age-matched HIV-uninfected persons in the United States. Therefore, pneumococcal vaccination is recommended in HIV infection to help reduce invasive pneumococcal disease.
   - HIV-infected children who have already received a dose or doses of PPSV23 should receive a dose of PCV13 a minimum of 8 weeks after the dose of PPSV23. A second dose of PPSV23 is recommended 5 years later.
   - PCV: 0.5ml, IM, 4 doses, at 2,4,6,15 mo. with routine vaccinations
     - If started > 6mo. 2 doses , 2 mo apart + booster at 15 mo
     - If started > 1y , 2 doses, 2 mo apart
     - If started > 2y , one dose in case of special cases (before splenectomy,----------)
     - After 5 yrs not recommended except in immunocompromised

4. **Hepatitis B (HepB) vaccine**
   - ► HBV vaccination for all individuals with HIV infection, as is recommend by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC).
   - ► Standard vaccination series are given at 0 (Birth dose), 2, 4 and 6 months.
   - ► When Mother is HBsAg-negative: 1 dose within 24 hours of birth for all medically stable infants ≥2,000 grams. Infants ≤2,000 grams: administer 1 dose at chronological age 1 month or hospital discharge.
     - ■ When Mother is HBsAg-positive:
       Administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) (at separate anatomic sites) within 12 hours of birth, regardless of birth weight. For infants ≤2,000 grams, administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
     - ■ Post-Vaccination:
       - ▪ Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose using a method that allows determination of a protective level of anti-HBs (≥10 mIU/mL).
       - ▪ Children with anti-HBs < 10 mIU/mL after the primary schedule should receive revaccination (a second series), followed by anti-HBs testing 1 to 2 months after the third dose, which usually is more practical than serologic testing after one or more doses of vaccine and booster doses when anti-HBs levels decline to <10 mIU/mL should be considered in individuals with ongoing risk of exposure.
   - ► Mother's HBsAg status is unknown:
     - ■ Administer HepB vaccine within 12 hours of birth, regardless of birth weight.
     - ■ For infants ≤2,000 grams, administer 0.5 mL of HBIG in addition to HepB vaccine within 12 hours of birth. Administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
     - ■ Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, administer 0.5 mL of HBIG to infants ≥2,000 grams as soon as possible, but no later than 7 days of age.

5. **Hepatitis A (HepA) Vaccine**
   - ► Minimum age: 12 months
   - ► Administer to all children aged 12 months through 23 months.
   - ► The 2 doses in the series should be administered at least 6 months apart.
   - ► Harivix 1440 (1ml) for adults , Harivix 720 (0.5ml) for pediatrics.
   - ► Given IM, 2 doses, given > 1yr, 6-18 months interval.

6. **Haemophilus influenza vaccine**
   - ► Vaccination is recommended for HIV-infected children, as for HIV-uninfected children.
   - ► Patients with HIV should not receive the live attenuated, cold-adapted vaccine, which is given intranasally. The inactivated vaccine should be the only vaccine used for HIV-infected patients. It should be administered in the autumn and repeated annually because of the vaccine's low immunogenicity and changes in the type of influenza causing infection from year to year.

- Influvac, Vaxigrib:
  - IM.
  - 6months-3years: 0.25ml, 2 doses with one-month interval at 1st time then once per year.
  - 3-9 years: 0.5ml, 2 doses with one-month interval at 1st time then once per year.
  - More than 9 years: 0.5ml per year.

7. **Polio vaccine (OPV,IPV)**
   - The live-attenuated oral polio vaccine (OPV) should be avoided because of an increased risk of paralytic polio in immunocompromised vaccine recipients. If a patient requires polio vaccination, clinicians should use the inactivated vaccine to avoid the risks of a live vaccine.
   - Inactivated Polio Vaccine (IPV).
   - Minimum age: 6 weeks
   - If 4 or more doses are administered prior to age 4 years, an additional dose should be administered at ages 4 through 6 years.
   - The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

8. **Diphtheria, Pertussis, and Tetanus**
   Inactivated vaccines are used for diphtheria, pertussis, and tetanus and thus are unlikely to pose significant risk

9. **Measles, Mumps, Rubella**
   - The CDC recommends MMR vaccination for all HIV-infected adults with CD4 counts of >200 cells/μL who lack evidence of measles immunity.It is contraindicated when CD4% <15% and total CD4 cell count of<200/mm3.
   - For persons in whom it is deemed appropriate to give both MMR and varicella vaccines, they can be given simultaneously. If they are not given on the same day, the varicella vaccine should be given at least 28 days after MMR, based on data in children showing that failure rates are higher if given <28 days after MMR vaccination.

10. **Haemophilus influenza type B vaccine (Hib vaccine):**
    - Overall, children with HIV have about 6 fold increased risk of Hib invasive disease compared to children who are not been infected with HIV. Therefore, WHO recommend the inclusion of conjugate Hib vaccines in all infant immunization programmes.
    - Hib vaccine is recommended routinely for all children through age 59 months. One dose of Hib vaccine should be administered to unvaccinated or partially vaccinated individuals aged 5 years or older who have leukemia, malgnant neoplasms, anatomic or functional asplenia (including sickle cell disease), who are HIV-infected, or who have other immunocompromising conditions.
    - 0.5ml, IM, 4 doses, at 2,4,6,15 mo. with routine vaccinations
    - If started > 6mo. 2 doses , 2 mo apart + booster at 15 mo
    - If started > 1y , 2 doses, 2 mo apart
    - If started > 2y , one dose
    - After 5 yrs not recommended except in immunocompromised

11. Varicella and Herpes Zoster

- The varicella vaccine is now recommended as a 2-dose series, with a minimum 3-month interval between the doses. Children with HIV infection are at increased risk of complications from varicella and herpes zoster compared with HIV-uninfected children.
- ACIP currently recommends primary varicella vaccination for HIV-infected children with CD4 percentages of ≥15%. It is contraindicated when CD4% <15% and total CD4 cell count of<200/mm3.

Recommended Child and Adolescent Immunization Schedule by HIV infection derived from United States Immunization Schedule, 2019

VACCINE	CD4% <15% and total CD4 cell count of <200/mm3	CD4% ≥15% and total CD4 cell count of ≥200/mm3
Hepatitis B	Routine schedule	
Rotavirus (it is not in Egyptian schedule)	Precaution might be indicated if vaccine benefit of protection outweighs risk of adverse reaction	
Diphtheria, tetanus, & acellular pertussis (DTaP)	Routine schedule	
Haemophilus influenza type b	Recommended, and additional doses may be necessary	
Pneumococcal conjugate (it is not in Egyptian schedule)	Recommended, and additional doses may be necessary	
Inactivated poliovirus	Routine schedule	
Influenza (IIV) (it is not in Egyptian schedule)	Recommended	
Influenza (LAIV) (it is not in Egyptian schedule)	Contraindicated	
Measles, mumps, rubella	Contraindicated	routine schedule
Varicella (it is not in Egyptian schedule)	Contraindicated	routine schedule

Hepatitis A (it is not in Egyptian schedule)	Recommended
Meningococcal ACWY	recommended, and additional doses may be necessary
Tetanus, diphtheria, & acellular pertussis (Tdap)	routine schedule
Human papillomavirus (it is not in Egyptian schedule)	recommended, and additional doses may be necessary
Meningococcal B	Recommended for persons with an additional risk factor for which the vaccine would be indicated
Pneumococcal Polysaccharide (it is not in Egyptian schedule)	recommended, and additional doses may be necessary

8. HIV and Opportunistic infections

Definition

Opportunistic Infection is an infection by a microorganism that normally does not cause disease but becomes pathogenic when the body's immune system is impaired and unable to fight off infection, as in AIDS, neutropenia, and congenital or iatrogenic host defense defects .

Opportunistic infections can adversely affect the natural history of HIV infection by causing reversible increase in circulating viral load that could accelerate HIV progression and increase transmission of HIV .

There are several fungal, parasitic, viral, and bacterial opportunistic infections, and opportunistic malignancies most common to HIV-infected patients at GHTM.

Primary prophylaxis or preventive treatment is used to prevent opportunistic infections in individuals with HIV/AIDS.

Secondary prophylaxis is used to prevent relapse of OI's in individuals already infected with an infection

CDC definition of an HIV positive person as having AIDS :

Has had at least one of over 21 AIDS defining opportunistic infections . And / or

Has had a CD4 cell count of 200 or less .

Opportunistic Infection & CD4

CD4 count	Respiratory disease
Any CD4 count	• URI • Bacterial pneumonia • TB • Lymphoma • Non-specific interstitial pneumonias.
CD4 count <200/mm^3	• PCP , TB but often disseminated , Cryptococcus pneumonia , Bacterial pneumonia often with bacteraemia or sepsis.
CD4 count <100/mm^3	Bacterial pneumonia due to Pseudomonas aeruginosa , Toxoplasmosis , Kaposi
CD4 <50/mm^3	MAC , CMV , Fungal infections

When to Start Antiretroviral Therapy (ART) in Patients with Opportunistic Infections (OIs)

Opportunistic Infection	When to Start ART
► Cryptosporidiosis ► Microsporidiosis ► Progressive multifocal ► leukoencephalopathy	As part of initial therapy for the OI
► Pneumocystis pneumonia ► Mycobacterium avium-complex	As part of initial therapy for the OI
► Toxoplasmosis	Within ~2 weeks of initiating OI treatment
► Tuberculosis (TB)	After 3 weeks
► Tuberculosis (TB)	► CD4 cell count < 50/mm3 – within 2 wks after starting TB therapy ► CD4 cell count >50/mm3 – within 8 weeks after starting TB therapy ► After 8 weeks for TB meningitis
► Cryptococcal Meningitis	4-6 weeks from the initiation of antifungal therapy according to induction and consolidation therapy (4 weeks for Amphotericin B-containing regimen and 4-6 weeks for fluconazole) containing regimen.

Are OIs common in people with HIV?

HIV medicines reduce the risk of OIs . By preventing HIV from damaging the immune system,

Some people with HIV get OIs for the following reasons:

- About 20% of people who have HIV don't know that they are infected.
- An OI may be the first sign that they have HIV.
- Some people who know they have HIV aren't getting treatment with HIV medicines. Without HIV treatment, they are more likely to get an OI.
- Some people may be taking HIV medicines, but the medicines aren't controlling their HIV.

WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV

Clinical stage 1

Asymptomatic

Persistent generalized lymphadenopathy .

Clinical stage 2 :

Moderate unexplained weight loss (<10 % of presumed or measured body weight)

- Recurrent respiratory tract infections (sinusitis, tonsilitis, otitis media , and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections

Clinical stage 3 :

- Unexplained weight loss (>10% of presumed or measured body weight).
- Unexplained chronic diarrhea for longer than one month.
- Unexplained persistant fever (intermittent or constant for longer than one month.
- Persistent oral candidiasis.
- Oral hairy leukoplakia.
- Pulmonary tuberculosis (current) .
- Severe bacterial infections (such as pneumonia ,empyema ,pyomyositis , bone or joint infection , meningitis or bacteremia) .
- Acute nectroizing ulcerative stomatitis , gingivitis or periodontitis.
- Unexplained anemia (<8 gm/dl) neutropenia (<500) , or thrombocytopenia (<50,000)

Clinical stage 4

- HIV wasting syndrome
- Pneumocystis pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month duration or visceral at any site) .
- Recurrent severe bacterial pneumonia
- Oesophageal candidiasis (or candidiasis of trachea bronchi or lungs) .
- Extrapulmonary tuberculosois
- Kaposi's sarcoma
- Cytomegalo virus infection (retinitis or infection of other organs)
- CNS toxoplasmosis
- HIV encephalopathy
- Extra pulmonary cryptococcosis including meningitis
- Disseminated non tuberculous mycobacterial infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis (with diarrhea)
- Dissiminated mycosis (coccidiomycosis or histoplasmosis)
- Recurrent non typhoidal salmonella bacteremia
- Lymphoma (cerebral or B-cell non Hodgkin) or other solid HIV associated tumours
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV associated nephropathy or cardiomyopathy .

Management of OI of the Respiratory System

The common respiratory diseases among people living with HIV are opportunistic infections, which occur across the spectrum of clinical HIV infection: infection by Streptococcus pneumoniae, Mycobacterium tuberculosis and Pneumocystis. jiroveci. Upper respiratory tract and lower respiratory tract infections are common but lower respiratory tract infections are life-threatening.
Upper respiratory tract diseases include pharyngitis, tonsillitis, rhinitis, sinusitis and otitis media. They occur relatively early, before advanced immune deficiency develops and thus constitute WHO stage II clinical conditions. The common organisms are Streptococcus pneumoniae, Staph aureus or H. influenza. Candida albicans is also a recognized cause of pharyngitis indicative of clinical stage III

Treatment:

The preferred regimen for bacterial URI is amoxicillin/clavulanic acid 625mg BID for seven to ten days. An altenrative regimen is ampicillin or amoxicillin preferably extending the course of treatment to fourteen days. If penicillin allergy is a problem
Give paracetamol for pain. It is necessary to document resolution of clinical findings after treatment and if not resolved refer to the next health facility. Oral and pharyngeal thrush are treated with oral miconazole gel 2% applied twice daily; patients should not eat/drink for two hours after applying the gel. If this does not work or is unavailable, use fluconazole 100mg daily for 14 days. This regimen is also effective for oro-pharyngeal candidiasis.
Common diseases of lower respiratory tract infections: include TB, bacterial pneumonia and PCP. The principal symptoms of respiratory diseases include cough, sputum production, chest pain, dyspnea, wheezing and haemoptysis but it is difficult to differentiate these by history and physical examination alone. In any case, the history should indicate whether onset of illness is acute or chronic and also record symptoms related to upper respiratory tract diseases like nasal discharge, sneezing, facial pain, stridor and tracheal pain. Some of these symptoms may be primarily due to illnesses outside the lungs, like congestive heart failure resulting from valve, myocardial and pericardial diseases.

Physical Examination:

Assess vital signs, recording blood pressure, respiratory rate , temperature. And decrease oxygen saturation • Observe for evidence of distress, such as inability to talk, facial sweating, nasal flaring, use of accessory muscles, presence of central cyanosis and altered mental function.
It is useful to consider the following during patient assessment

- Evidence of advanced immune deficiency state e.g. oral thrush
- Evidence for extra pulmonary involvement like meningitis, arthritis, hepatitis and pericarditis. Presence of these conditions usually warrants inpatient management.
- Evidence for poor prognosis, like age over 60, severe distress manifested by tachypnea (RR>30/minute), cyanosis, grunting, retractions, multiple lobe involvement and systolic blood pressure below 80mmHg. These conditions necessitate inpatient management.

Recurrent pneumonia is an AIDS defining condition

Bacterial pneumonia can occur at any stage and at any CD4 count
The frequency of Pseudomonas aeruginosa and staphylococcus aureus is higher in HIV infected persons.
MRSA is a potential etiology for pneumonia.
Bacterial pneumonia is associated with increased mortality.

Clinical manifestations

Acute onset of fever, chills, rigors, dyspnea, chest pain or pleurisy, cough productive of purulent sputum
Tachypnea and desaturation indicate moderate to severe pneumonia
Signs of focal consolidation.

Treatment

Outpatient antibiotic regimens

Amoxicillin 1 g three times daily OR
Doxycycline 100 mg twice daily OR
A macrolide (azithromycin 500 mg on day one then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin extended release 1,000 mg daily) .
In outpatients adults with CAP who have comorbidities , the following antibiotic regimens are recommended

Combination therapy :

Amoxicillin /clavulanate 500 mg/125 mg (625) three times daily OR
Amoxicillin /clavulanate 875 mg/125 mg (1g) twice daily OR
or cefuroxime 500 mg twice daily) PLUS
A macrolide (azithromycin 500 mg on day one then 250 mg daily , clarithromycin (500 mg twice daily or extended release 1,000 mg once daily) or doxycline 100 mg twice daily OR
Monotherapy : Respiratory fluroquinolone (Levofloxacine 750 mg daily , moxifloxacine 400 mg daily , or gemifloxacin 320 mg daily)

Adults with severe CAP without risk factors for MRSA or pseudomonas aeruginosa :

dual therapy e.g beta lactam e.g. ceftriaxone 1-2 g daily or , cefotaxime 1-2 g every 8 hours or cefatrolin 600 mg every 12 hours) or ampicilline-sulbactam 1.5 – 3 g) every 8 hours plus a macrolide (azithromycin500 mg daily or clarithromycin 500 mg twice daily) or monotherapy with iv respiratory fluroquinolone (moxifloxacine 400 mg or levofloxacine 750mg/day)
Routine addition of anaerobic coverage for suspected aspiration pneumonia is not recommended except when lung abscess or empyema is suspected .

Empiric anti staphylococcal treatment

Vancomycin (15 mg /kg every 12 hours) or linezolid 600 mg every 12 hours
Empiric pseudomnas aeruginosa treatment
Treatment options for pseudomonas aeruginosa incude : piperacillin tazobactam (4.5 gm every 6 hours , ceftazime (2 g every 8 hours) , aztreonam (2 g every 8 hours) , meropenem (1g every 8 hours) plus either ciprofloxacin or levofloxacin

Routine corticosteroid treatment is not recommended in adults with CAP(regadless of severity) or severe influenza pneumonia except patients who have refractory septic shock .

Treatment duration

The duration of antibiotics should be guided by clinical stability , continuous treatment until stability is achieved for at least 5 days.

Pneumocystitis Pneumonia

Pneumocystitis pneumonia is caused by pneumocystis jirovecii (a widespread fungus)
The disease probably occurs by new acquisition of infection (possible airborne route) or by reactivation of latent infection .

Risk factors

CD4<200
High plasma HIV RNA level
Increasing evidence suggest that aerosolization of the fungus can occur from infected patients and may play a role in nosocomial transmission .

Clinical manifestations :

Progressive dyspnea , fever ,non productive cough and chest discomfort that worsens within days to weeks
Oral thrush is a common co-infection .
Fever is apparent in most cases and may be the predominant symptom in some patients .
Hypoxemia is the most characteristic laboratory abnormality
Elevated LDH to more than 500 mg/dl is common but non specific
The radiography typically demonstrates diffuse bilateral , symmetrical ground glass interstitial infiltrates
May be normal in early disease
Spontaneous pneumothorax in a patient with HIV infection should raise suspicion of PCP.
Normal CT chest has a high negative predictive value
CT demonstrates a ground glass attenuation even in mild to moderates cases or with normal chest radiograph.

Diagnosis

Blood tests and chest radiographs are not pathogonomonic for PCP .
Histopathologic or cytopathologic demonestration of the organism in tissue , bronchoalveolar(BAL) fluid is required for a definitive diagnosis .
Spontaneously expectorated sputum has low senstivity .
PCR is an alternative method for diagnosing PCP .
PCR is highly senstive and specific for diagnosis .

Treatment

TMP-SMX is the treatment of choice (15-20 mg / kg per day (trimethoprim) and 75-100 mg/kg/day (sulphamethoxazole) divided into four daily doses po for a minimum of 21 days .
Patients with documented or suspected PCP and moderate to severe disease should receive corticosteroids as early as possible (within 72 hours after starting PCP therapy) .
The corticosteroid treatment should be started as early as possible but within 72 hours after starting the PCP specific therapy , the following 21 day oral regimen with prednisone has been recommended , 40 mg orally twice daily followed by a steroid taper over several weeks .

Intravenous methylprednisolone can be used

Altrnative therapy include

Second line agents include primaquine 30 mg/day with clindamycin 600 mg TID or atovaquone 750 mg BID or iv pentamidine 4 mg/kg/day or 600 mg aerosol daily
Prognosis is poor in patients who have severe hypoxemia
Preventive measures as (e.g. smoking cessation and chemoprophylaxis) can play an important role in disease management .

PCP Prophylaxis

Indications for Initiating Primary Prophylaxis:

CD4 cell count <200/mm3
Oropharyngeal candidiasis
CD4 cell percentage <14%
History of AIDS-defining illness

Preferred Prophylaxis Therapy:

- TMP-SMX, 1 DS PO daily
- TMP-SMX, 2 SS PO daily
- Dose may be reduced to 1 SS PO daily in case of anemia

Selected Alternative Therapies:

- TMP-SMX 1 DS PO three times a week, in case of haematological adverse events
- Dapsone 100 mg PO daily
- Atovaquone 1500 mg PO daily with food

Indication for Discontinuing Primary Prophylaxis:

- CD4 cell count increased from <200/mm3 to ≥200/mm3 for at least 6 months in response to ART

Tuberculosis

TB is the most common opportunistic disease in people living with HIV and is a frequent first indication of HIV infection in developing countries.

- The virus breaks the immune system down, making people living with HIV highly susceptible to TB.
- TB in turn accelerates the progression of HIV to AIDS and shortens survival of patients with HIV infection.
- Immuno-suppressed persons may reactivate an old tuberculosis infection or may become infected de novo with Mycobacterium tuberculosis.

Types of TB

- Pulmonary tuberculosis
- Extrapulmonary tuberculosis

Symptoms of Pulmonary TB

- Chronic cough o Loss of weight o Mild fever o Sweating at night
- Pain in chest or upper back o
- Loss of appetite

Symptoms of Extra Pulmonary TB

- Lymph nodes swelling and fever o
- Intestines : -pain in the abdomen, diarrhoea and fever o
- Liver - jaundice and fever o
- Brain - meningitis with alteration in the conscious level .

Diagnosis

- Chest x-ray
- Sputum smear and culture in symptomatic patient (sputum smear negative is common among HIV patients (3 sputum specimens)
- Lymph nodes aspirate for histopathology smear and culture .
- Samples from pleural fluid, pericardial fluid , ascites and CSF if involved for acid fast bacilli smear, culture , nucleic acid amplification Gene X pert MTB/RIF assay.
- Lipoarabinomannan (LAM) : is an M.tuberculosis cell wall polysaccharide that can be detected in the urine of TB patients LAMt has higher senstivity with worse prognosis .

Immune based tests :

- Tuberculin skin test
- IGRA (interferon gamma release assay)
- Both tests are not diagnostic of active TB and negative tests should not rule out TB disease .

Treatment of Newly Diagnosed Cases

Intensive phase: 2(HRZE)3, i.e., isoniazid, rifampicin, pyrazinamide, and ethambutol in a blister pack, administered 3 times a week for 2 months. The medication must be taken by the patient under the direct observation of the health staff.

When the patient has completed the initial intensive phase of 2 months and the sputum smear is negative for AFB, the continuation phase will start. If the sputum smear is positive at 2 months, the intensive phase of 4 drugs is continued for another month, after which the continuation phase is started, regardless of the results of sputum smear examinations.

The contents of the blister pack are:

Isoniazid ,Rimfampicin ,Pyrazinamide , mg Ethambutol Continuation phase: In this phase, 4(HR)3, i.e. isoniazid and rifampicin are given 3 times a week for 4 months. For patients with tuberculosis meningitis, disseminated TB or spinal disease with neurological complications, isoniazid and rifampicin should be given for 6 to 7months (i.e., a total of 8 to 9 months of therapy).

The weekly blister pack for self-administration contains the following drugs to be taken 3 times a week with vitamins in the remaining days of the week:

- Isoniazid 300 mg Rifampicin 450 mg
- Retreatment Regimen
- Intensive phase: 2(HRZES)3/1HRZE)3, i.e., rifampicin combined with isoniazid, pyrazinamide, and ethambutol, supplemented with streptomycin for the first 2 months, followed by the same drugs without streptomycin for 1 month given 3 times a week.

The initial intensive phased should be given for 3 months. The tablets are given in the same type of blister pack as for the new smear-positive cases. If the sputum is smear-negative for AFB at 3 months, the continuation phase is started. If the sputum smear is positive at 3 months, the 4 oral drugs are continued for another month. If the sputum is still smear positive at the end of the fourth month and facilities for culture are available, the sputum should be sent for culture and sensitivity after stoppage of the drugs for 3 days. Regardless of the availability of culture facilities, the patient should start the continuation phase after the fourth month.

1. Mycobacterium tuberculosis Infection and Disease:

The 3HP regimen (weekly isoniazid plus rifapentine for 3 months) for the treatment of latent tuberculosis infection (LTBI) is now recommended as an alternative regimen when provided as self-administered therapy or directly observed therapy.

Four months of daily rifampicin monotherapy is now recommended for the treatment of LTBI in patients who cannot receive isoniazid.

When dolutegravir is given with concurrent rifampin, it is recommended that the dose be increased to 50 mg twice daily.

Bictegravir is not recommended to be given with rifamycin-containing TB treatment.
Prednisone is no longer recommended for the treatment of TB pericarditis.
Isoniazid-monoresistant TB should be treated with 6 months of rifampin, pyrazinamide, ethambutol, and either levofloxacin or moxifloxacin.
prednisone may be used as adjunctive therapy to reduce the risk of TB-associated IRIS.

Respiratory fluoroquinolones such as levofloxacin or moxifloxacin are also active against Mycobacterium tuberculosis. In patients with undiagnosed TB, fluoroquinolones may alter response to therapy, delay TB diagnosis, and increase the risk of drug resistance. These drugs should be used with caution in patients in whom TB is suspected but who are not receiving a standard 4-drug TB regimen.

Disseminated Mycobacterium avium complex disease
MAC disease typically occurs in patients with CD4 cell count less than 50 cells /mm3
The mode of transmission through inhalation , ingestion , or inoculation through the respiratory or GIT .

Clinical manifestations
In patients with AIDS who are not on ART
MAC typically is disseminated , multi organ infection .
Anemia ,hepatomegaly ,splenomegaly , or lymphadenopathy .
Elevated liver alkaline phosphatase .

In patients on ART :
localized manifestations : cervical or mesenteric lymphadenitis , pneumonitis, pericarditis , osteomyelitis , skin or soft tissue abscesses , genital ulcers , or CNS infection

Diagnosis
Isolation of MAC from cultures of blood , lymph node, bone marrow or other normally sterile tissue .

Treatment

- 2 or more antimycobacterial drugs to prevent or delay the emergence of resistance .
- Clarithromycin is the preferred first agent .
- Ethambutol is recommended second drug .
- Rifabutin can be added as a third drug .

New update :

Primary prophylaxis for MAC in people living with HIV who immediately initiate antiretroviral therapy is no longer recommended, regardless of CD4 cell count

Dermatologic clues to opportunistic infections in HIV patients

- Nearly every patient with human immuno-deficiency virus (HIV) has some cutaneous manifestations during the course of the disease .
- In some cases HIV may be first diagnosed by certain dermatological manifestations that reflect early signs of HIV infections .
- Dermatologic manifestations of HIV can present as infections , malignancies , exacerbations of existing skin ailment or side effects of anti retro viral therapy
- An HIV test should be ordered in a patient less than 50 years-old with herpes zoster (shingles)
- Suspicion for HIV infection should be raised when a patient presents with multiple skin diseases. For example, a patient with psoriasis and thrush.

Seborrhoeic Dermatitis

Common presenting feature in persons with HIV infection
Probably caused by a fungus known as Pityrosporum ovale (also known as Malasezia furfur)

Symptoms:

Erythematous, scaly rash, which may be extensive, persistent, and recurrent
Dandruff is seborrhoeic dermatitis of the scalp
Seen over scalp, face, anterior chest, back, and axillae.

Diagnosis:

- The diagnosis is made on clinical grounds and may be confirmed by finding fungal elements on microscopic examination of skin scrapes.
- Differential diagnosis: Psoariasis and T.capitis.

Treatment:

- Frequent skin washing to remove scales is advised, and shampooing with selenium sulphide shampoo is effective.
- Zinc pyrithione or Ketoconazole shampoos also can be used.
- Topical application of 1% hydrocortisone is probably the most effective.
- Another steroid preparation used is Triamcinolone 0.1%.
- Ketoconazole 2% cream has also been shown to be effective.

Some diseases are so characteristic of the immunosuppression of HIV-infection:

Kaposi sarcoma

- Kaposi sarcoma is a vascular neoplastic condition linked to the infection with human herpesvirus 8 (HHV-8).
- The human herpes virus type 8, also known as HHV8 or Kaposi sarcoma herpes virus
- (KSHV) has been shown to be the cause of Kaposi sarcoma.
- Kaposi sarcoma (KS) is a skin malignancy.
- This cancer of the lymphatic system leads to generalized lymphadenopathy and lymphoedema of affected areas.
- Kaposi sarcoma is the most common AIDS-related malignancy •
- In HIV-infected persons, the cancer (epidemic Kaposi sarcoma) is generalized and rapidly progressive, and it often affects the viscera.
- KS that is associated with HIV/AIDS can present in two forms: mucocutaneous form and lymphadenopathic form.
- Cutaneous lesions can be flat, raised, or nodular, and usually have a purple or brown color. Scattered red or brown purple-violaceous macules, plaques, and nodules of varying sizes and shapes, mainly found on the truck and face
- They can occur anywhere on the body, including the palms of the hands and inside the mouth.
- The most effective treatment for KS is antiretroviral therapy.
- Prognosis for KS seems to be related to the patient's overall immune status and the organ systems that are involved.

leukoplakia

white or greyish patches that can not be rubbed off as would be the case in pseudomembraneous candidiasis (oral thrush) .

Epstein Barr virus is thought to be the cause of oral hairy leukoplakia .

It presents as raised, white, corrugated lesions of the oral mucosa, especially on the lateral aspect of the tongue.

- It is a nonmalignant lesion of epithelial cells.
- It can be diagnosed from a biopsy and electron microscopy.
- Oral hairy leukoplakia can be treated with Acyclovir 800mg, five times a day for three weeks However, most cases are not treated and are usually relapse after treatment.(Source: John Hopkins 2004 Medical Management of HIV Infection Bartlet and Gallant).

It may be one of the first signs of HIV infection , its appearance on patients on antiretroviral therapy may be an indication that antiretroviral therapy is failing .

Hairy leukoplakia is not painful

Molluscum Contagiosum

Molluscum contagiosum is a superficial skin infection caused by the molluscum contagiosum virus (MCV).

• The virus invades the skin causing the appearance of firm, flesh-coloured papules

containing a white sebaceous material that can occur anywhere on the body and often remain unchanged for many months, after which they disappear.

Lesions are spread through direct skin to skin and sexual contact

Firm multiple papules taking color of the skin with central umbilication
Lesions commonly found on the face and genital areas
Many HIV-related mucocutaneous changes occur in the mouth

Treatment:

- The lesions are thoroughly opened with a needle or scalpel.
- The contents expressed and the inner wall treated with phenol solution, or tincture iodine, or 2.5% trichloro acetic acid or ferric subsulphate.
- The lesions can be subjected to:
  1. Gentle cryotherapy (liquid nitrogen can be used).
  2. Electro dessication.
  3. Electrosurgery for larger lesions.
  4. The lesions also respond to antiretroviral therapy.

Prevention:

• Do not pick or shave the lesion because they tend to auto inoculate the virus and the virus will spread.

Cytomegalovirus infection (other than liver ,spleen or lymph node

Symptoms include fever from CMV colitis ,dyspnea from CMV pneumonitis and blindness from CMV retinitis .

Clinical diagnosis

Retinitis only : typical eye lesions on fundoscopic examination .
Definitive diagnosis : compatible histology or cytomegalovirus demonestrated in CSF by PCR , or culture .

Treatment

Oral valganciclovir ,intravenous (IV) ganciclovir ,IV ganciclovir followed by oral valganciclovir ,IV foscarnet ,and IV cidofovir are all effective treatments for CMV retinitis.
They have high toxicity and limited efficacy .
treatment with systemic anti-CMV therapy, such as oral valganciclovir for the first 3 to 6 months until ART has induced immune recovery .
Systemic therapy is given twice daily for the first 14 to 21 days (induction) followed by once daily dosing (maintenance) until immune reconstitution occurs

When To Stop Maintenance Therapy

Maintenance therapy can be discontinued safely in adults and adolescents with CMV retinitis whose lesions have been treated for at least 3 to 6 months and are inactive and who have sustained increase in CD4 cell counts to >100 cells/mm3 in response to ART

Herpes simplex virus disease

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common

Clinical Manifestations

Orolabial herpes (e.g., cold sores, fever blisters) is the most common manifestation of HSV-1 infection
Lesions recur 1 to 12 times per year and can be triggered by sunlight or physiologic stress
Genital herpes is the most common manifestation of HSV-2 infection

Diagnosis

HSV DNA polymerase chain reaction (PCR), and viral culture are preferred methods for diagnosis.
PCR is the most sensitive method.
Patients with orolabial lesions or genital HSV can be treated with oral acyclovir, valacyclovir, or famciclovir for 5 to 10 days .
Severe mucocutaneous HSV lesions respond best to initial treatment with intravenous (IV) acyclovir Patients can be switched to oral antiviral therapy after their lesions have begun to regress .

Varicella-Zoster Virus Diseases

Virus that causes chickenpox and shingles in children
and adults; spread by aerosolized viral particles

- Contagious period is 24 to 48 hours before rash is observed and until all lesions are crusted over
- In immune suppressed persons, zoster is often multidermatomal and multi-segmental in distribution, persistent and extensive, may be bilateral and associated with severe pain and debility .

Skin changes begin with an erythematous maculopapular rash , followed by the appearance of clear vesicles and accompanied by pain (which may be severe)
herpes zoster-related complications in HIV-seropositive patients, including disseminated herpes zoster, occur in patients with CD4 counts of less than 200 cells/ul
Related neurologic syndromes occur in HIV-infected patients, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, and aseptic meningitis.

Treatment

valacyclovir (1 g PO 3 times daily), or famciclovir (500 mg PO 3 times daily) for 5 to 7 days
Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg 5 times daily) can be an alternative
Intravenous (IV) acyclovir for 7 to 10 days is the recommended initial treatment for HIV-infected patients with severe varicella

Varicella-Zoster Virus Disease:

Guidance on the use of two available vaccines (recombinant zoster vaccine [RZV, Shingrix] and zoster vaccine live [ZVL, Zostavax]) to prevent herpes zoster (shingles) in persons with HIV aged 50 years and older is provided.

RZV (Shingrix) is recommended to prevent herpes zoster using a two-dose schedule (intramuscular injection at Month 0 and Month 2) for adults with HIV aged 50 years and older.

RZV is preferred over ZVL (Zostavax) for prevention of herpes zoster.

If RZV is not available or cannot be given because of allergy or intolerance, ZVL can be given as a single subcutaneous dose among adults with CD4 counts ≥200 cells/mm.
ZVL is contraindicated for persons with CD4 counts <200 cells/mm^3.

Scabies :

Caused by the mite Sarcoptes scabei

- Female mite burrows into the skin and the burrows appear as raised lines up to several centimeters long
- The mite deposits eggs in the burrows and then migrates to other sites of the body
- The eggs hatch out and develop into adult mites which mate and more eggs are deposited in new burrows

Symptoms

First Infestation: Usually little evidence for first month (range 2 to 6 weeks)
Subsequent infestations: People usually become sensitized to mites with, symptoms generally occurring within 1 to 4 days
Mites burrowing under the skin cause a rash most frequently found on the hands, particularly the web spaces between the fingers
Also found on folds of wrist, elbow or knee, ulna margins of forearms, penis, the breast, and shoulder blades
Intense pruritis (most intense by night) Superficial burrows

Treatment

- Treatment of choice is the topical use of 1% gammabenzene hexachloride
- Permethrin or lindane application are also useful
- Ivermectin in a single oral dose of 200 mg is an alternative drug that is effective for crusted scabies in immunocompromised persons

Household precautions:

- All clothes, bedding, and towels should be washed in hot water, and dried and ironed
- All members of the household should also be treated

Candidiasis

2 main types :

Localized disease (of the mouth ,throat and of the vagina)

Systemic disease (of the oesophagus and disseminated disease)

Oropharyngeal candidiasis causes oral pain and makes swallowing difficult .

Oesophageal candidiasis causes pain in the chest that increases with swallowing .

Disseminated candidiasis causes fever and symptoms in the organs affected by the disease (for example blindness when it affects the eyes)

Diagnosis

Clinically based on the characteristic appearance of the lesions .

Treatment

Localized disease is treated first with topical drugs such as nystatin , miconazole ,or clotrimazole .

Systemic antifungals are given only when topical therapy fails .

Systemic antifungal agents such as ketokonazole , itraconazole ,fluconazole or amphotericin B

Oral fluconazole at 100mg once a day is considered the drug of choice to treat oropharyngeal candidiasis except during pregnancy

One to two weeks of therapy is recommended for oropharyngeal candidiasis

Two to three weeks of therapy is recommended for esophageal candidiasis .

Cryptococcosis

Cryptococcosis is presumed to be a primary infection with Cryptococcus neoformans rather than reactivation of previously acquired disease.

The organism is encapsulated yeast like fungus that is an important cause of infection and mortality in HIV/AIDS patients.

Cryptococcosis most often appears as meningitis and occasionally as pulmonary or disseminated disease .

Cryptococcal meningitis is the most frequent systemic fungal infection in HIV infected persons

The most common symptom patients present with is headache.

The second most common is diplopia or double vision, and the third, indolent fever.

Clinically

Fever with increasing severe headache ,meningism , confusion,behavioural changes .

Diagnosis

India ink staining of CSF

Isolation of cryptococcus neoformans from extrapulmonary site or positive cryptococcal antigen test on CSF or blood

Treatment

The theraptic goal is to control the acute infection followed by lifelong suppression of C neoformans
Amphotericin B with or without flucytosine , amphotersin B at 0.7-1 mg/kg /day for 2 weeks with or without 2 weeks of flucytosine at 100 mg/kg /day in 4 divided doses , followed by fluconazole at 400 mg/day for minimum of 8 -10 weeks
Addition of dexamethasone is not advised as it causes slower clearance of Cryptococcus from the spinal fluid.

Cerebral toxoplasmosis

It is an AIDS related infection and one of the causes of CNS mass lesions in AIDS .
It can present with a rapidly fatal form of diffuse encephalitis .
it is caused by the parasite toxoplasma gondii
The patient presents clinically with headache , altered mental status and fever and common focal neurological signs .

Diagnosis :

positive serology for toxoplasma IgG and absolute CD4 count less than 2oocells /mm3.
CSF : protein elevation ,mild pleocytic mononuclear predominence
The cranial imaging features on CT or MRI are not pathognomonic but their distribution or appearance may have a predictive value
lesions are mainly located in the periventricular region as well as at the grey -white matter junction and showed enhancement in the periphery as well as tiny nodular enhancement in the center .
Occasionally a peripheral enhancing lesion associated with an eccenteric nodular area of enhancement the so called eccentric target sign is typical of toxoplasmosis

Differential diagnosis :

CNS lymphoma differeniated by :
CNS toxoplasmosis are being more than 3 lesions , subcortical in location , absence of ependymal or leptomeningeal involvement , marked perilesional edema

Treatment

Preferred regimen
Standard therapy consists of pyrimethamine , sulphadiazine ,and folinic acid in combination , trimethoprim – sulphamethoxazole can be used as an alternative regimen

Suggested dosing

Sulfadiazine : 1000 mg 4 times daily among patients <60kg or 1500 mg four times a day among patients >60 kg .
Pyrimethamine : 200 mg loading dose followed by 50 mg daily among patients >60 kg .
Leucovorine should be administered to prevent pyrimethamine induced hematologic toxicity . Dose : 10-25 mg daily
Primary therapy is given for 6 weeks followed by long term suppressive therapy at reduced doses .
The long term suppressive therapy can be discontinued in patients with persistent elevation of CD4 counts greater than 200 cells /ul and resolution of lesions in MRI

Chronic Diarrhea

- Cryptosporidiosis
- Diarrhoeal disease caused by Cryptosporidium parvum
- Can live in the intestine of humans and animals
- Passed in the stool of an infected person or animal
- Symptoms | Diarrhoea | Abdominal pain with mild fever
- A common cause of chronic diarrhea in AIDS patients in developing countries .
- If the biliary system is involved (gallbladder and biliary ducts), there may also be nauseous and right upper quadrant abdominal pain.

Clinical manifestations

- Watery diarrhea may be accompanied by nausea ,vomiting and lower abdominal cramping (cholera like diarrhea)

Diagnosis

- Microscopic identification of oocysts in stool or tissue with acid fast staining or direct immunofluorescence examination .
- Antigen detection by ELISA .
- PCR
- from small section of intestinal biopsy

Treatment

- In severe immune suppression restoration to a CD4 count >100 cells /ul usually leads to resolution of clinical cryptospordiosis
- Symptomatic treatment of diarrhea with anti-motility agent
- Rehydration and repletion of electrolytes
- Nitazoxanide 500-1000mg twice daily for 14 days

Bacterial Enteric Infections

Epidemiology

The risk of bacterial diarrhea varies according to CD4 T lymphocyte (CD4) count and is greatest in individuals with clinical AIDS or <200 CD4 cells/mm

the probable source for most enteric infections in HIV-infected patients is ingestion of contaminated food or water.

Sexual activity with the potential for direct or indirect fecal-oral exposure also increases risk of infections, especially with Shigella and Campylobacter

HIV-associated alterations in mucosal immunity or intestinal integrity and treatment with acid-suppressive agents may increase risk of enteric bacterial infections.

Clinical Manifestations

The three major clinical syndromes of infection with Gram-negative enteric bacteria among HIV-infected patients are
-Self-limited gastroenteritis;
- More severe and prolonged diarrheal disease :
potentially associated with fever, bloody diarrhea, and weight loss; and
-Bacteremia associated with extra-intestinal involvement
Empiric Therapy
Decisions on therapy are based on an assessment of diarrhea severity and hydration status.
oral or intravenous (IV) rehydration, if indicated
consuming a bland diet and avoiding fat, dairy, and complex carbohydrates also are likely to be useful .
Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including CDI .
After obtaining stool samples for diagnostic evaluation, initiation and duration of empiric antimicrobial therapy depend upon the patient's CD4 count and clinical appearance.
If stool samples are obtained, antibiotic susceptibility testing should be performed to confirm and inform antibiotic choice.
no treatment other than oral rehydration may be required, for example, in patients with CD4 counts >500 cells/mm who have had 1 to 2 days of loose stools without fever or blood.
a short course of antibiotics may be indicated in HIV-infected patients with CD4 counts of 200 to 500 cells/mm who have diarrhea severe enough to compromise quality of life or ability to work.
Patients with advanced HIV disease (i.e., CD4 counts <200 cells/mm3 or concomitant AIDS-defining illness) and clinically severe diarrhea (i.e., ≥6 liquid stools per day or bloody stools or a lower number of liquid stools per day but accompanied by fever or chills concerning for invasive bacterial disease) should undergo diagnostic evaluation to determine the etiology of the diarrheal illness and receive antimicrobial treatment.
Empiric therapy with ciprofloxacin is reasonable
IV ceftriaxone or IV cefotaxime are reasonable alternatives
Therapy should be adjusted subsequently based on the results of the diagnostic work-up.
Diarrhea that is persistent (i.e., lasting >14 days) in the absence of other clinical signs of severity, such as bloody stool or dehydration, should be evaluated and directed therapy should be started once a diagnosis is confirmed.

Pathogen-Specific Therapy
Salmonella spp.
HIV infection increases the risk of Salmonella bacteremia 20- to 100-fold and mortality as much as 7-fold compared with that in patients who are not HIV-infected
The initial treatment of choice for Salmonella infection is a fluoroquinolone
Ciprofloxacin is the preferred agent .
Depending on antibiotic susceptibility, alternatives to the fluoroquinolones might include TMP-SMX or expanded-spectrum cephalosporins such as ceftriaxone or cefotaxime .
The optimal duration of therapy for HIV-related Salmonella infection has not been defined.
For patients with CD4 counts ≥200 cells/mm who have mild gastroenteritis without bacteremia, 7 to 14 days of treatment is reasonable.

For the same patients with bacteremia, 14 days is appropriate, provided clearance of bacteremia is documented.
Longer treatment is suggested if bacteremia persists or if the infection is complicated, that is, if metastatic foci are present .
For patients with advanced HIV disease (CD4 count <200 cells/mm3), 2 to 6 weeks of antibiotics is often recommended .
Some patients with Salmonella bacteremia may remain febrile for 5 to 7 days despite effective therapy.
HIV-infected patients with Salmonella bacteremia, which typically occurs in those with advanced HIV disease, should be monitored clinically for recurrence after treatment .
Recurrence may present as bacteremia or as an anatomically localized infection, including intra-abdominal, endothelial, urinary tract, soft tissue, bone and joint, lung, or meningeal foci.
Secondary prophylaxis should be considered for patients with recurrent Salmonella bacteremia and it might also be considered for patients with recurrent gastroenteritis (with or without bacteremia) and in those with CD4 counts <200 cell/mm with severe diarrhea .
The value of this secondary prophylaxis has not been established and must be weighed against the risks of long-term antibiotic exposure.
Recurrent Salmonella bacteremia constitutes an AIDS-defining illness and suppression of HIV replication with ART appears to decrease the risk of recurrent illnesses.
In patients whose Salmonella infection is resolved and who have responded to ART with sustained viral suppression and CD4 counts >200 cells/mm3, secondary prophylaxis for salmonellosis can probably be stopped .
Recurrence may represent development of antimicrobial resistance during therapy.
Shigella spp.
Therapy for Shigella infections is recommended both to shorten the duration of illness and to possibly prevent spread of the infection to others .
The recommended treatment for shigellosis is with a fluoroquinolone, preferably ciprofloxacin, for 7 to 10 days
Depending on antibiotic susceptibilities, alternative agents might include TMP-SMX (7–10 days) or azithromycin (5 days) .
Treatment for patients with Shigella bacteremia is less well defined, but extending treatment to at least 14 days is reasonable
. Azithromycin is not recommended for treatment of Shigella spp. bacteremia .
Chronic suppressive or maintenance therapy is not recommended for first-time Shigella infections .
Recurrent infections can occur, particularly in individuals with CD4 counts <200 cells/mm3, in which case extending antimicrobial therapy for up to 6 weeks is reasonable .
As with Salmonella infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent shigellosis.

Campylobacter spp.
The optimal treatment of Campylobacteriosis in HIV-infected patients is poorly defined.
Culture and testing for the antibiotic susceptibility of Campylobacter isolates is recommended .
For mild-to-moderate Campylobacteriosis, initiating therapy with a fluoroquinolone such as ciprofloxacin for 7 to 10 days (if the organism is sensitive) or azithromycin for 5 days is a reasonable approach.
Patients with Campylobacter bacteremia should be treated for at least 14 days using a fluoroquinolone if the isolate is sensitive .

Azithromycin is not recommended for treatment of Campylobacter bacteremia .
Adding a second active agent, such as an aminoglycoside, may be prudent in these patients to limit the emergence of antibiotic resistance .
Antibiotic choice should be guided by antibiotic susceptibility tests.
Chronic suppressive or maintenance therapy is not recommended for first-time Campylobacter infections in HIV-infected patients .
Recurrent infections can occur, particularly in patients with CD4 counts <200 cells/mm.
In recurrent disease, extending the length of antimicrobial therapy for 2 to 6 weeks is reasonable .
As with Salmonella infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent Campylobacter spp. infections.

Clostridium difficile-associated infection (CDI)

CDI is common in HIV-infected patients
Health care providers should also consider CDI in the evaluation of outpatient diarrheal illnesses in HIV-infected individuals.

Diagnosis

Assessment of patients with diarrhea should include a complete exposure history ; a medication review, because diarrhea is a common side effect of some ART and antibiotics .
Quantification of the diarrheal illness by stool frequency, volume, duration, and presence of blood; and associated signs and symptoms, such as presence and duration of fever.

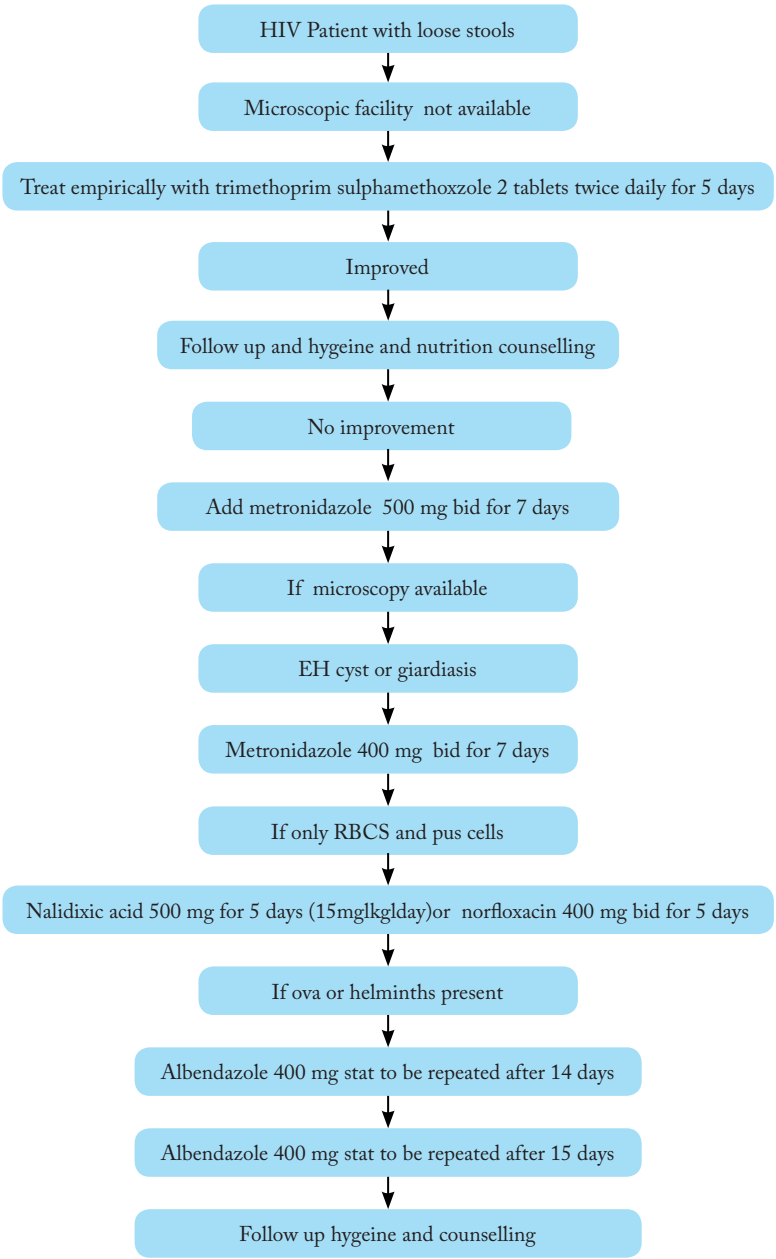
Physical examination

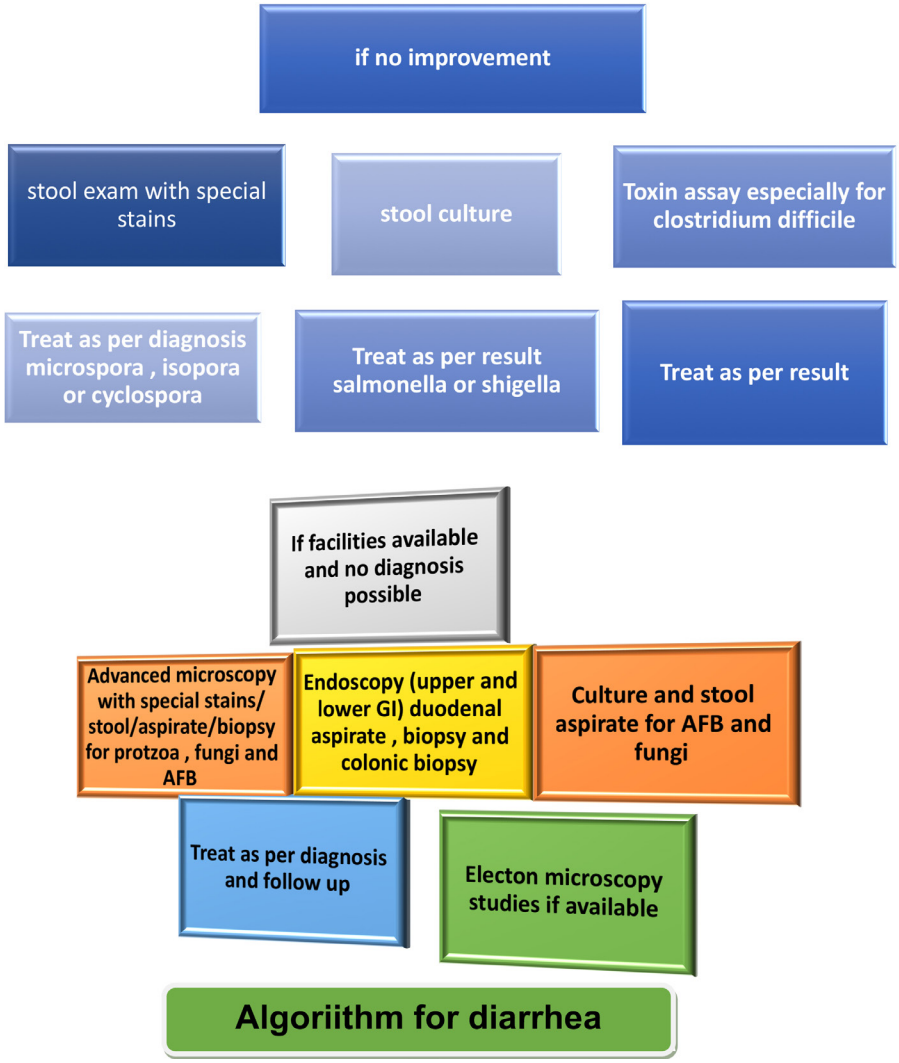
Measurement of temperature and assessment of volume and nutritional status.
Because incidence of bacteremia associated with Salmonella gastroenteritis is high in HIV-infected individuals, particularly those with advanced disease .
blood cultures should be obtained from any patient with diarrhea and fever.
For shigellosis, blood cultures may be helpful but are less likely to be positive than in salmonellosis.

A stool sample for C. difficile toxin or polymerase chain reaction (PCR) assay should be routinely performed :

- For patients with diarrhea who have recently received or are currently receiving antibiotics (including antimicrobial prophylaxis) or cancer chemotherapy,
- Those who have been hospitalized in the past 4 to 6 weeks (or are currently hospitalized),
- Those who reside in a long-term care facility,
- Those with CD4 counts <200 cells/mm3,
- Those taking acid-suppressive medications,
- Those with moderate-to-severe community-acquired diarrhea.

Endoscopy should generally be reserved for patients in whom stool culture, microscopy, C. difficile toxin assay, and blood culture fail to reveal an etiology or in whom treatment for an established diagnosis fails.


HIV Patient with loose stools
Microscopic facility not available
Treat empirically with trimethoprim sulphamethoxzole 2 tablets twice daily for 5 days
Improved
Follow up and hygeine and nutrition counselling
No improvement
Add metronidazole 500 mg bid for 7 days
If microscopy available
EH cyst or giardiasis
Metronidazole 400 mg bid for 7 days
If only RBCS and pus cells
Nalidixic acid 500 mg for 5 days (15mglkglday)or norfloxacin 400 mg bid for 5 days
If ova or helminths present
Albendazole 400 mg stat to be repeated after 14 days
Albendazole 400 mg stat to be repeated after 15 days
Follow up hygeine and counselling


if no improvement
stool exam with special stains
stool culture
Toxin assay especially for clostridium difficile
Treat as per diagnosis microspora , isopora or cyclospora
Treat as per result salmonella or shigella
Treat as per result
If facilities available and no diagnosis possible
Advanced microscopy with special stains/ stool/aspirate/biopsy for protzoa , fungi and AFB
Endoscopy (upper and lower GI) duodenal aspirate , biopsy and colonic biopsy
Culture and stool aspirate for AFB and fungi
Treat as per diagnosis and follow up
Electon microscopy studies if available
Algoriithm for diarrhea

What can people with HIV do to prevent getting an OI?

- The best protection against OIs is to take HIV medicines every day.
- People living with HIV can also take the following steps to reduce their risk of getting an OI.
- Avoid contact with the germs that can cause OIs
- Be careful about what you eat and drink.
- With regard to preventing enteric infection, soap and water are preferred over alcohol-based cleansers, which do not kill C. difficile spores and are only partially active against norovirus and Cryptosporidium
- Some vaccines can prevent HIV-related OIs. For example, people with HIV can get vaccinated to prevent pneumonia

Vaccine-Preventable Opportunistic Infections

Vaccines contraindicated during pregnancy

Live attenuated influenza vaccine
Measles ,Mumps and Rubella (MMR) Vaccine
Varicella vaccine (VAR)
Zoster live vaccine (ZVL)

Vaccines should be delayed until after pregnancy if vaccine is indicated:

Human papiloma virus (HPV) (female).
Zoster recombinant vaccine .
Pneumococcal vaccine can be administered during pregnancy .
Inactivated influenza vaccine also can be administered during pregnancy,and the vaccine is recommended for all pregnant women during influenza season .
Administration of vaccines can be associated with a transient rise in plasma HIV RNA levels,
Vaccination of pregnant women is recommended after ART has been initiated to minimize increases in plasma HIV RNA levels that might increase the risk of perinatal transmission of HIV.

Human Papillomavirus

Infection with oncogenic high-risk human papillomavirus (HPV) types is the major risk factor for the development of cervical cancer in women and anal cancer in both men and women.

HPV Vaccine

Currently there are two HPV vaccines , the bivalent vaccine protects against HPV 16 and 18; the quadrivalent vaccine protects against HPV 16 and 18 and the non-oncogenic HPV 6 and 11 (the most common causes of genital warts).
The CDC Advisory Committee on Immunization Practices (ACIP) recommends:

- For females, either the bivalent or quadrivalent HPV vaccine at age 11 or 12 years and for those aged 13–26 years if not previously vaccinated
- For males, quadrivalent HPV vaccine at age 11 or 12 years and for those aged 13–21 years if not previously vaccinated. Males aged 22 through 26 years may be vaccinated.
- The quadrivalent HPV vaccine is safe and immunogenic in HIV-infected women and men.

9. HIV and Viral Hepatitis

Initial assessment of all people living with HIV should include:

- anti-HCV (HCV Ab)
- HBsAg
- Anti-HBc IgG
- HCV RNA for patients with profound immunosuppression (CD4 count <100 cells/mm3) in the presence of any of the following criteria:
  - liver tests (albumin, bilirubin, INR) abnormalities, or
  - Clinical suspicion of liver disease.

Patients at high risk of HCV and/or HBV co-infection (PWID, FSW or MSM) should be screened for anti-HCV and HBsAg every 6 months.

A.HIV-HCV coinfection

1. Evaluation of HCV disease severity should include all the following:

- ALT
- AST
- Serum bilirubin
- Serum albumin
- Prothrombin time and concentration, INR
- CBC
- Creatinine
- AFP
- Abdominal ultrasonography
- Calculation of the following scores:
  - Child-Pugh
  - FIB-4

- Treatment decision ART should be initiated in all patients with HCV/HIV coinfection, regardless of CD4 cell count.
- HCV treatment should be a priority for persons with HCV/HIV coinfection.

2. Exclusion criteria for anti-HCV treatment

- Patients <18 years.
- Child-Pugh class C cirrhosis.
- Clinically manifest liver decompensation: ascites, encephalopathy.
- Platelet count <50,000/mm3.
- HCC, except 6 months after concluding intervention aiming at cure with no evidence of activity by dynamic CT or MRI.
- Extrahepatic malignancy except after two years of disease-free interval. In lymphomas and chronic lymphatic leukemia, treatment can be initiated immediately after remission based on the treating oncologist's report.
- Pregnancy or inability to use effective contraception.

3. Precautions before starting treatment

- Ladies in the childbearing period should have a recent negative pregnancy test.
- A male receiving ribavirin should have two methods of contraception applied with his wife during, and for 6 months after, treatment.
- Drug-drug interactions should be checked for medications received by the patient especially cardiovascular disease therapy (e.g. amiodarone), anti-psychotic therapy and statins.

4. Persons already on ART and eligible for anti-HCV DAAs

- Before starting DAAs, patients should have:
  - CD4 >200 cells/mm3, and
  - HIV RNA below detection limit by PCR.

5. Persons not taking ART and eligible for anti-HCV DAAs

- Check CD4 count:
  - If CD4 >500 cells/mm3: complete HCV treatment, then start ART.
  - If CD4 <200 cells/mm3: ART for 3-6 months till HIV controlled (CD4 >200cells/mm3 and HIV RNA below detection limit by PCR), then start DAAs.
- If CD4 200-500 cells/mm3: Start ART first, then DAAs after 4-6 weeks.

6. Recommended regimens in HCV treatment-naïve patients

- Easy to treat HCV: ALL of the following fulfilled:
  - Total bilirubin ≤1.5 mg/dl
  - Serum albumin ≥3.2 g/dl
  - INR ≤1.5
  - Platelet count ≥100.000/mm3

HCV	HIV
Sofosbuvir 400 mg + daclatasvir 60 mg for 12 weeks	DTG 50 mg + TDF 300 mg + FTC 200 mg
Sofosbuvir 400 mg + daclatasvir 90 mg for 12 weeks	EFV 600 mg + TDF 300 mg + FTC 200 mg EFV 600 mg + AZT 300 mg + 3TC 150 mg

- Difficult to treat HCV: Presence of ANY of the following:
  - IFN and/or sofosbuvir-experienced.
  - Total serum bilirubin >1.5 mg/dl.
  - Serum albumin <3.2 g/dl.
  - INR >1.5.
  - Platelet count <100,000/mm3.

HCV	HIV
Sofosbuvir 400 mg + daclatasvir 60 mg + ribavirin 800 mg for 12 weeks*	Daily DTG 50 mg + TDF 300 mg + FTC 200 mg
Sofosbuvir 400 mg + daclatasvir 90 mg + ribavirin 800 mg/day for 12 weeks*	Daily EFV 600 mg + TDF 300 mg + FTC 200 mg

*For 24 weeks without ribavirin if ribavirin ineligible (e.g. hemoglobin <10 g/dl or cardiac dysfunction) or intolerant. A drop of hemoglobin of 2 g, or less than 10 g/dl, from baseline necessitates ribavirin dose reduction with possible use of erythropoietin or ribavirin discontinuation.

7. Recommended regimens in HCV treatment-experienced patients

HCV			HIV
Previous Regimen	**Child-Pugh class A**	**Child-Pugh class B**	
► IFN + RBV ► INF+ SOF + RBV ► SOF + RBV ► SOF + SIM ± RBV ► OBV/ PTV/r + RBV	SOF + DCV + RBV for 24 weeks		DTG 50 mg + TDF* 300 mg + FTC 200 mg
SOF + DCV for 12 weeks	SOF/VEL/VOX for 12 weeks	SOF/VEL + RBV (initial dose 600 mg daily) for 24 weeks (Treatment in special centers)	
► OBV/ PTV/r + SOF ± RBV for 12/24 weeks ► SOF + SIM +DCV ± RBV for 12 weeks	SOF/VEL/VOX for 12 weeks		
SOF/VEL/VOX for 12 weeks	SOF/VEL/VOX + RBV for 24 weeks		

*Should be monitored for adverse events when received concomitantly with SOF/VEL/VOX.
DCV, daclatasvir; DTG, dolutegravir; FTC, emtricitabine; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; TDF, tenofovir; VEL, velpatasvir; VOX, voxilaprevir.

8. Recommended regimens in HCV patients with chronic kidney diseases

- As described above for HCV treatment-naïve and experienced patients.
- Sofosbuvir-containing regimens could be used without dose adjustment in patients with renal disease, including those with an eGFR ≤30 ml/min and those on dialysis.
- RBV dose adjusted according to eGFR and hemoglobin level:
  - eGFR > 50: 600-1,200 mg daily as tolerated.
  - eGFR 30-50: 400 mg alternating with 200 mg.
  - eGFR < 30, not on dialysis: 200 mg daily to be reduced if not tolerated to 200 mg, 3 times weekly.
  - eGFR <30, on dialysis: 200 mg, every other day given on dialysis day, 4 hours before dialysis.
  - Should be discontinued if hemoglobin level declines by more than 2 g/dl despite the use of erythropoietin.

Dose adjustment of ARTs as described above (section).

9. Precautions after the end of treatment

- Confirmatory PCR test for the sustained virologic response should be performed 12 weeks after the end of treatment.
- Patients with advanced liver fibrosis (FIB4 ≥ 3.25) should be enrolled in the HCC surveillance program using AFP and abdominal ultrasonography every 4 months.
- HBV vaccination should be initiated if not already received.

B.HIV-HBV coinfection

Initial assessment of patients with chronic HBV infection

- ALT
- AST
- CBC
- Random blood sugar
- Serum total bilirubin
- Serum albumin
- PT and INR
- Serum phosphorus
- Serum creatinine, and eGFR calculated by the CKD-EPI equation
- HBeAg
- Quantitative HBV DNA serum level
- AFP
- Abdominal ultrasound
- Transient elastography (TE)

Recommended therapy (first line regimens)

- EFV 600 mg + TDF 300 mg + FTC 200 mg (or 3TC).
- DTG 50 mg + TDF 300 mg + FTC 200 mg (or 3TC).

Alternative regimen

- If TDF cannot be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen which does not contain 3TC or FTC.
- Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC.

Follow-up after 3 months

- PCR for HIV RNA
- CD4 count
- Quantitative PCR for HBV DNA
- ALT
- AST

According to the response to treatment:

1. If both HIV and HBV are responding: continue on the same regimen.
2. If HIV virologic failure but adequate HBV suppression:
   - ART drugs active against HBV (TDF/FTC or 3TC) should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression
   - Ritonavir boosted PI is used combined with 2 NRTIs in this preferential order:
     - LPV/r
     - ATV/r
     - DRV/r
3. HIV is responding but HBV is not responding: Entecavir in addition to a fully suppressive ART regimen which does not contain 3TC or FTC.

Need to discontinue ART medications active against HBV

The use of entecavir to prevent flares can be considered, especially in patients with marginal hepatic reserve such as those with compensated or decompensated cirrhosis.
These alternative HBV regimens should only be used in addition to a fully suppressive ART regimen.

C. HIV/HCV/HBV triple infection

- Persons with HCV/HIV coinfection and active HBV infection (determined by a positive HBsAg test) should receive ART that includes two agents with anti-HBV activity prior to initiating HCV therapy.
- Start DAAs 12 weeks after ART for those who achieved undetectable HIV and HBV viral loads.
  - HIV-infected individuals with active HBV infection (HBsAg positive) should receive NRTIs with anti-HBV activity: (TAF or TDF) plus (3TC or FTC).
  - Initiate ART prior to DAAs to minimize the risk of HBV reactivation with DAAs

10. HIV Drug Formulary

HIV Drug Formulary

1. Abacavir (ABC)

Dosage form/strengths	Tablet : 300 mg Solution : 20mg/ml
Route of administration	Oral
Pharmacological action	Nucleoside reverse transcriptase inhibitor. which interferes with HIV viral RNA-dependent DNA polymerase resulting in inhibition of viral replication.
Indication	Used for Treatment of HIV-1 infection for children in the following situations : ► First line regimen in combination with lamivudine and dolutegravir ► alternative first line regimen in combination with lamivudine and lopinavir/ritonavir ► alternative first line regimen in combination with lamivudine and raltegravir ► second line regimen in combination with lamivudine and dolutegravir

Dosage Regimen	**HIV-1 infection, treatment: Infants ≥3 months, Children, and Adolescents: Oral:** **Twice daily dose regimen** ► **If body weight ≤ 14 kg** Oral solution: 8 mg/kg/dose twice daily; maximum dose: 300 mg/dose. Note: Weight-band dosing may be used in certain patients weighing at least 14 kg; especially rapid growing younger children . ► **If body weight ≥14 kg** Tablets (scored 300 mg tablets), oral solution: 14 to <20 kg: 150 mg twice daily. 20 to <25 kg: 150 mg in the morning and 300 mg in the evening. ≥25 kg: 300 mg twice daily. **Once daily dose regimen** In clinically stable patients with undetectable viral load for more than 6 months (24 weeks) on the liquid formulation of abacavir twice daily, the daily dose can be changed from twice daily to once daily with liquid or tablet formulations. Initiation with once-daily dosing is recommended for children who can be treated with tablet formulation ► **If body weight ≤ 14 kg** Oral solution: 16 mg/kg/dose once daily; maximum dose: 600 mg/dose ► **If body weight ≥14 kg** Tablets (scored 300 mg tablets), oral solution: 14 to <20 kg: 300 mg once daily. 20 to <25 kg: 450 mg once daily. ≥25 kg: 600 mg once daily. **Adult** HIV-1 infection, treatment: Oral: 300 mg twice daily or 600 mg once daily in combination with other antiretroviral agents.
Administration	May be administered without regard to food
Dosing: Renal Impairment	There are no dosage adjustments
Dosing: Hepatic Impairment	► Mild impairment: Dosing adjustment is required; however, pediatric-specific recommendations are not available ► Moderate to severe hepatic impairment (Child-Pugh class B or C): Use is contraindicated.

Contra-indications	► Hypersensitivity to abacavir or any component of the formulation ► moderate to severe hepatic impairment ► patients who are positive for the HLA-B*5701 allele
Major Adverse Drug Reactions	► **Central nervous system:** Headache (adults: ≤13%; infants, children, & adolescents: 1%), fatigue (≤12%), malaise (≤12%) ► **Gastrointestinal:** Nausea, vomiting and diarrhea (7% to 10%) ► **Dermatologic:** Skin rash (5% to 7%) ► **Endocrine & metabolic:** Hypertriglyceridemia (2% to 6%) ► **Hematologic & oncologic:** Neutropenia (2% to 5%), thrombocytopenia (1%) ► **Hepatic:** Increased serum alanine aminotransferase (6%), increased serum aspartate aminotransferase (6%) ► Drug-induced hypersensitivity (9%) ► **Respiratory:** ENT infection (5%), viral respiratory tract infection (5%), bronchitis (4%), pneumonia (infants, children, & adolescents: 4%) ► **Neuromuscular & skeletal:** Increased creatine phosphokinase (7% to 8%), musculoskeletal pain (5% to 6%). ► **Miscellaneous:** Fever (≤9%)
Monitoring Parameters	CBC with differential, CD4 count, HIV RNA plasma levels, serum transaminases, fasting lipid panel; serum creatine kinase, serum amylase (as clinically indicated); HLA-B*5701 genotype status prior to initiation of therapy and prior to reinitiation of therapy in patients of unknown HLA-B*5701 status; signs and symptoms of hypersensitivity.
Common harmful Drug Interactions	► **Cladribine:** abacavir may diminish the therapeutic effect of Cladribine. Risk X: Avoid combination. ► **Orlistat :** Risk C: Monitor therapy.
pregnancy & lactation	► **Pregnancy** Short-term data on the use of abacavir in pregnancy do not suggest major concerns about fetal safety Abacavir is a preferred NRTI for use in pregnancy in the United States. ► **Lactation** Abacavir was detected in the serum of an infant following exposure via breast milk.

Warnings/Precautions	**adverse effects:** ► **Hypersensitivity reactions:** [US Boxed Warning]: Serious and sometimes fatal hypersensitivity reactions have occurred. Patients who carry the HLA-B*5701 allele are at a higher risk for a hypersensitivity reaction to abacavir. Abacavir should be permanently discontinued if hypersensitivity cannot be ruled out ► **Immune reconstitution syndrome:** Inflammatory response to an preexisting indolent or residual opportunistic infection during initial HIV treatment or activation of autoimmune disorders (eg, Graves disease, polymyositis, Guillain-Barré syndrome) later in therapy; further evaluation and treatment may be required. ► **Lactic acidosis/hepatomegaly** **Disease-related concerns:** ► **Coronary heart disease:** Use has been associated with an increased risk of MI in some cohort studies. Consider using with caution in patients with risks for coronary heart disease and minimizing modifiable risk factors (eg, hypertension, hyperlipidemia, diabetes mellitus, and smoking) prior to use. ► **Hepatic impairment:** Use with caution and adjust dosage in patients with mild hepatic impairment (contraindicated in moderate to severe impairment). ► May cause mild hyperglycemia; more common in pediatric patients.
Storage	Store at 20°C to 25°C , Oral solution may be refrigerated; do not freeze.

2. Atazanavir(ATV)

Dosage form/strengths	Capsules: 100 mg, 150 mg, 200 mg. Packet:50mg.
Route of administration	Oral
Pharmacological action	Antiretroviral protease inhibitor: prevents cleavage of the viral polyprotein precursors and thus; prevents the formation of the proteins necessary for the virus to be infective.
Indication	Treatment of HIV-1 infections in combination with other antiviral drugs
Dosage Regimen	**Adults :** 300 mg of atazanavir + 100 mg of ritonavir or atazanavir 400 mg once daily in patients unable to tolerate ritonavir in antiretroviral-naïve patients. **Pediatrics:** (Boosted regimen (preferred regimen) **Oral powder: Infants ≥3 months, Children, and Adolescents:** Oral: 5 to <15 kg: Atazanavir 200 mg once daily plus ritonavir 80 mg once daily. In antiretroviral-naive patients weighing 5 to <10 kg unable to tolerate this dose, may use atazanavir 150 mg once daily plus ritonavir 80 mg once daily with close HIV viral load monitoring. 15 to <25 kg: Atazanavir 250 mg once daily plus ritonavir 80 mg once daily. ≥25 kg (who cannot swallow a capsule): Atazanavir 300 mg oncedaily plus ritonavir 100 mgonce daily. Oral capsule: Children ≥6 years weighing ≥15 kg and Adolescents <18 years: Oral: 15 kg to <35 kg: Atazanavir 200 mg once daily plus ritonavir 100 mg once daily. ≥35 kg: Atazanavir 300 mg once daily plus ritonavir 100 mg once daily **Adolescents ≥18 years:** Oral: Atazanavir 300 mg once daily plus ritonavir 100mg once daily
Dosing: Renal Impairment	**No change in patients with mild to severe impairment.** **End-stage renal disease:** atazanavir is not appreciably removed during hemodialysis Antiretroviral-naive patients: Atazanavir 300 mg plus ritonavir 100 mg once daily **Antiretroviral-experienced patients:** Not recommended.

Dosing: Hepatic Impairment	**Adult:Atazanavir without ritonavir in antiretroviral-naïvepatients:** Mild impairment (Child-Pugh A): 400 mg daily. Moderate impairment (Child-Pugh B): 300 mg daily. Severe impairment(Child-Pugh C): not recommended. Atazanavir with ritonavir is not recommended for hepatic patients (has not been studied). **Pediatric :**Boosted regimens (with ritonavir): Infants, Children, and Adolescents: Mild to severe impairment: Use is not recommended
Administration	Administer with food. Administer atazanavir 2 hours before or 1 hour after antacids. Administer atazanavir (with ritonavir) simultaneously with, or at least 10hours after, H2-receptor antagonists, 12 hours after proton pump inhibitor
Contra-indications	Hypersensitivity to atazanavir or other components of the formulation.
Major Adverse Drug Reactions	Skin rash – elevated serum cholesterol – elevated amylase – elevated serum bilirubin – jaundice – cough – fever – elevated creatine phosphokinase.
Monitoring Parameters	Lipid profile – AST – ALT – Billirubin - Virologic response
Common Drug Interactions	Atazanavir/ritonavir should not be combined with drugs metabolized by CYP3A4 as ritonavir is a potent CYP3A4 inhibitor. list of interactions should be checked before administration.
Pregnancy	Atazanavir crosses placental barrier in low amounts. The use of atazanavir in pregnancy without a booster is not recommended.
Warnings/Precautions	Elevated bilirubin - Fat redistribution - Hypersensitivity reactions - Immune reconstitution syndrome - Nephrolithiasis/cholelithiasis Caution in patients with diabetes, Hemophilia A or B, or patients with hepatic or renal diseases.
Storage	Store between 15°C and 30°C.

3-Dolutegravir (DTG)

Dosage form/strengths	Film Coated Tablets: 50 mg.
Route of administration	Oral
Pharmacological action	Antiretroviral integrase strand transfer inhibitor (INSTI): prevents integration of the viral DNA into the host DNA.
Indication	Treatment of HIV-1 infection in combination with other antiretroviral agents for treatment naïve or experienced adult or pediatric patients.
Dosage Regimen	**Adults :** ► **INSTI naïve:** 50 mg daily. ► **INSTI-naive when coadministered with carbamazepine, efavirenz, or rifampin:** 50 mg twice daily ► **INSTI experienced with suspected resistance:** 50 mg twice daily. ► **Virologically suppressed patients switching to dolutegravir plus rilpivirine:** 50 mg daily. Pediatrics : ► Treatment-naive or treatment-experienced and integrase strand transfer inhibitor (INSTI)-naive: ■ Infants and Children weighing 3 to <14 kg: Oral: Soluble tablets for oral suspension : 3 to <6 kg: 5 mg once daily. 6 to <10 kg: 15 mg once daily. 10 to <14 kg: 20 mg once daily. ■ Infants, Children, and Adolescents weighing ≥14 kg: Oral: Soluble tablets for oral suspension : Preferred in patients <20 kg: 14 to <20 kg: 25 mg once daily. ≥20 kg: 30 mg once daily. Tablets : 14 to <20 kg: 40 mg once daily. ≥20 kg: 50 mg once daily. ► INSTI-experienced with any INSTI-associated resistance mutation or clinically suspected . ► **INSTI resistance:** Children and Adolescents weighing ≥40 kg: Oral: Tablets : 50 mg twice daily.

Dosing: Renal Impairment	**Treatment-naive or treatment-experienced INSTI-naive: Mild, moderate, or severe impairment: No dosage adjustment necessary.** **INSTI experienced with suspected resistance and creatinie clearance less than 30 ml/min:** it should be used with caution taking into consideration that decreasing dolutegravir doses may lead to loss of therapeutic effect and the development of resistance. **End-stage renal disease:** No dosage adjustments provided in the manufacturer labeling (has not been studied).
Dosing: Hepatic Impairment	**Severe impairment (Child-Pugh C):** not recommended Hepatoxicity during therapy (in pediatrics) : If asymptomatic hepatitis, consider discontinuation of therapy for ALT or AST >5 times ULN; if symptomatic hepatitis, discontinue therapy
Administration	Administer without regard to meals. Administer 2 hours before or 6 hours after cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium.
Contra-indications	Hypersensitivity to dolutegravir or any other component in the formulation.
Major Adverse Drug Reactions	Gastrointestinal: Increased serum lipase , Hyperglycemia, Elevated ALT,AST
Monitoring Parameters	ALT – Blood Glucose – Viral load - CD4 count – Monitor signs of hypersensitivity

Common Drug Interactions	► **Risk X: Consider therapy modification** **Oxcarbazepine:** decrease serum concentration of dolutegravir by CYP450 induction. Risk X: Avoid combination. **Phenobarbital, phenytoin :** May decrease the serum concentration of Dolutegravir. Avoid combination. ► **Risk D: Consider therapy modification** **Aluminum Hydroxide, Calcium Salts, Iron preparations, Zinc Salts, Selenium:** May decrease the serum concentration of Dolutegravir. Management: Administer dolutegravir at least 2 hours before or 6 hours after oral Aluminum Hydroxide, Calcium Salts, Iron preparations, Zinc Salts, Selenium. **Carbamazepine:** May decrease the serum concentration of Dolutegravir. **Management:** Increase dolutegravir to 50 mg twice/day in adults. Increase weight based dose to twice daily in pediatric patients. **Efavirenz:** May decrease the serum concentration of Dolutegravir. **Management:** Increase dolutegravir to 50 mg twice/day in adults. Increase weight based dose to twice daily in pediatric patients. **MetFORMIN:** Dolutegravir may increase the serum concentration of MetFORMIN. Management: Consider alternatives to this combination or use of lower metformin doses. Carefully weigh the risk of metformin toxicities (including lactic acidosis) against the benefit of combining dolutegravir with metformin. **RifAMPin:** May decrease the serum concentration of Dolutegravir. **Management:** Increase dolutegravir to 50 mg twice/day in adults. Increase weight based dose to twice daily in pediatric patients.
Pregnancy	A small but significant increase in neural tube defects (NTDs) was observed following maternal use of dolutegravir in a study conducted in Botswana. The risk of NTDs was increased in women who became pregnant while taking dolutegravir, but not in women who started dolutegravir during pregnancy.
Warnings/Precautions	Hepatotoxicity, Hypersensitivity reactions, Immune reconstitution syndrome.
Storage	Store at 15°C to 30°C ,protect from moisture.

4-Darunavir/ritonavir(DRV/r)

Dosage form/strengths	Suspension, Oral: 100 mg/mL (200 mL) Tablet, Oral: 75 mg, 150 mg ,600 mg ,800 mg
Pharmacological action	Antiretroviral, Protease Inhibitor (Anti-HIV) .Binds to the site of HIV-1 protease activity. This results in the formation of immature, noninfectious viral particles.
Indication	► Treatment of HIV-1 infection, coadministered with ritonavir and other antiretroviral agents, in adults and pediatric patients 3 years and older. ► Alternative second-line regimen in Adults , adolescents, Children and infants in combination with zidovudine and lamivudine . ► HIV-1 infection, nonoccupational postexposure prophylaxisin combination with other antiretroviral agents.
Dosage Regimen	**Dosing: Adult** ► **Treatment naïve or experienced patients With no darunavir resistance-associated substitutions :** Oral: 800 mg once daily; coadministrated with ritonavir 100 mg ► **Treatment experiencedWith ≥1 darunavir resistance-associated substitution or If genotypic testing is not possible:** 600 mg twice daily; coadministrated with ritonavir 100 mg twice daily. ► **Pregnant patients:** Oral: 600 mg twice daily, coadministered with ritonavir 100 mg twice daily. ► **HIV-1 infection, nonoccupational postexposure prophylaxis:** Oral: 800 mg plus ritonavir 100 mg once daily (in combination with other antiretroviral agents); initiate therapy within 72 hours of exposure and continue for 28 days. **Dosing: Pediatric** **Children 3 to 11 years weighing ≥10 kg:** Treatment-naive patients or treatment-experienced patients without or with darunavir resistance-testing results that demonstrate at least one mutation associated with resistance Fixed-dosing: Tablets, Oral solution (darunavir: 100 mg/mL): 10 kg to <11 kg: Darunavir 200 mg (2 mL) twice daily **plus** ritonavir 32 mg twice daily.

	12 kg to <13 kg: Darunavir 240 mg (2.4 mL) twice daily **plus** ritonavir 40 mg twice daily. 13 kg to <14 kg: Darunavir 260 mg (2.6 mL) twice daily **plus** ritonavir 40 mg twice daily. 14 kg to <15 kg: Darunavir 280 mg (2.8 mL) twice daily **plus** ritonavir 48 mg twice daily. 15 kg to <30 kg: Darunavir 375 mg (tablets or 3.8 mL) twice daily **plus** ritonavir 48 mg twice daily. 30 kg to <40 kg: Darunavir 450 mg (tablets or 4.6 mL) twice daily **plus** ritonavir 100 mg twice daily. ≥40 kg: Darunavir 600 mg (tablet or 6 mL) twice daily **plus** ritonavir 100 mg twice daily. **Children ≥12 years and Adolescents weighing 30 to <40 kg:** Treatment-naive patients or treatment-experienced patients without or with mutations associated with darunavir resistance: Twice-daily regimen: Darunavir 450 mg twice daily plus ritonavir 100 mg twice daily. Once-daily regimen: Darunavir 675 mg (combination of tablets) once daily plus ritonavir 100 mg once daily; **Children ≥12 years and Adolescents weighing ≥40 kg:** refere to adult dosing.
Dosing: Renal Impairment	No dose adjustment in case of renal impairment
Dosing: Hepatic Impairment	► Mild to moderate impairment (Child-Pugh class A or B): No dosage adjustments necessary ► Severe impairment (Child-Pugh class C): Use not recommended.
Dosing: Adjustment for Toxicity: Adult	► Severe rash: Discontinue treatment. ► New or worsening liver dysfunction: Consider interrupting or discontinuing treatment.

Administration	► Administer with food. ► Shake suspension prior to each dose; use provided oral dosing syringe to measure dose. **Missed doses** ► In patients taking darunavir once daily, if a dose is missed by >12 hours, the next dose should be taken at the regularly scheduled time. If a dose is missed by <12 hours, the dose should be taken immediately and then the next dose should be taken at the regularly scheduled time. **In patients taking darunavir twice daily,** if a dose is missed by >6 hours, the next dose should be taken at the regularly scheduled time. If a dose is missed by <6 hours, the dose should be taken immediately and then the next dose should be taken at the regularly scheduled time.
Contra-indications	► Hypersensitivity to darunavir or any component of the formulation ► severe (Child-Pugh class C) hepatic impairment ► coadministration with amiodarone, apixaban, lidocaine (systemic), rivaroxaban or drugs that are highly dependent on CYP3A for clearance and drugs for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index).
Major Adverse Drug Reactions	**Dermatologic:** Skin rash **Endocrine & metabolic:** Increased serum cholesterol, increased LDL cholesterol), increased serum glucose (≤11%) **Gastrointestinal:** Vomiting, nausea, diarrhea (children & adolescents: 11% to 24%; adults: 9% to 14%)
Monitoring Parameters	► Viral load, CD4, baseline genotypic and/or phenotypic testing in treatment-experienced patients (if possible); serum glucose; transaminase levels prior to and during therapy (increase monitoring in patients at risk for liver impairment), cholesterol, triglycerides, glucose

Common Drug Interactions	**Long list of interactions should be checked before administration, includes:** ► **Calcium Channel Blockers (Nondihydropyridine)** eg verapamil & diltiazem : darunavir /ritonavir may decrease the metabolism of these drugs . Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. Management: Avoid concurrent use when possible. If used, monitor for CCB toxicity. Risk D: Consider therapy modification ► **Colchicine:** ritonavir may increase the serum concentration of Colchicine. Management: Colchicine is contraindicated in patients with impaired renal or hepatic function who are also receiving darunavir/ritonavir . In those with normal renal and hepatic function, reduce colchicine dose. Risk D: Consider therapy modification ► **Domperidone:** darunavir /ritonavir may increase the serum concentration of Domperidone. Management: Drugs listed as exceptions to this monograph are discussed in further detail in separate drug interaction monographs. Risk X: Avoid combination ► **Dronedarone:** ritonavir may increase the serum concentration of Dronedarone. Management: Risk X: Avoid combination ► **Efavirenz:** ritonavir may increase the serum concentration of Efavirenz. Efavirenz may decrease the serum concentration of Darunavir. Management: Monitor for decreased concentrations and effects of darunavir and/or increased concentrations and effects of efavirenz Risk D: Consider therapy modification ► **Eplerenone or ivabradine or lovastatin:** ritonavir may increase the serum concentration of Eplerenone. Risk X: Avoid combination ► **Estrogen Derivatives (Contraceptive):** Protease Inhibitors may decrease the serum concentration of Estrogen Derivatives (Contraceptive). Management: Use of an alternative, non-hormonal contraceptive is recommended with other protease inhibitors. Risk D: Consider therapy modification ► **Fluticasone (Nasal):** ritonavir may increase the serum concentration of Fluticasone (Nasal). Risk X: Avoid combination ► **RifAMPin or rifapentine:** May decrease the serum concentration of Darunavir. Risk X: Avoid combination ► **Sildenafil:** ritonavir may increase the serum concentration of Sildenafil. Management: Erectile dysfunction: sildenafil max = 25 mg/48 hrs with ritonavir, Contraindicated if sildenafil being used for pulmonary arterial hypertension. Risk D: Consider therapy modification

	► **Simvastatin ,lovastatin:** Protease Inhibitors may increase the serum concentration of Simvastatin. Risk X: Avoid combination ► **Tacrolimus (Systemic):** ritonavir may increase the serum concentration of Tacrolimus (Systemic). Tacrolimus dose reductions or prolongation of dosing interval will likely be required. Risk D: Consider therapy modification
pregnancy	► No increased risk of overall birth defects has been observed following first trimester exposure according to data collected by the antiretroviral pregnancy registry. ► The Health and Human Services (HHS) perinatal HIV guidelines consider darunavir (when combined with low-dose ritonavir boosting) a preferred protease inhibitor for pregnant females living with HIV.
Warnings/Precautions	► Fat redistribution , Hepatotoxicity , Hypersensitivity reactions , Sulfonamide allergy Immune reconstitution syndrome, Diabetes , Hemophilia A or B
Storage	Store between 15°C and 30°C. Do not refrigerate or freeze oral suspension.

5.Efavirenz(EFV)

Dosage form/strengths	Tablets , capsules 200mg , 600 mg
Pharmacological action	Non-nucleoside reverse transcriptase inhibitor, efavirenz has activity against HIV-1 by binding to reverse transcriptase. It consequently blocks the RNA-dependent and DNA-dependent DNA polymerase activities including HIV-1 replication.
Indication	HIV-1 infection: Treatment of HIV-1 infection in combination with other antiretroviral agents in adults and pediatric patients at least 3 months old and weighing at least 3.5 kg. Alternative first-line regimen in adults and adolescents in combination to tenofovir and lamivudine

Dosage Regimen	**Dosing: Adult** **HIV-1 infection, treatment:** Oral: 600 mg once daily, in combination with other appropriate agents; 400 mg once daily may be used in combination with tenofovir and lamivudine. **Dosing: Pediatric** **HIV-1 infection, treatment:** Use in combination with other antiretroviral agents: Infants <3 months or <3 kg: Not recommended for use. Infants ≥3 months weighing ≥3 kg and Children <3 years: Oral: BSA-directed dosing: Oral: 367 mg/m2/dose once daily, maximum dose: 600 mg/dose; recommended by some experts
Dosage adjustment in Renal impairment:	- No dosage adjustment necessary
Dosage adjustment in hepatic impairment	Mild impairment (Child-Pugh class A): No dosage adjustment necessary; use with caution. Moderate-to-severe impairment (Child-Pugh class B or C): Use is not recommended.
Administration	Administer on an empty stomach. Dosing at bedtime is recommended to limit central nervous system effects.
Contra-indications	Hypersensitivity (eg, Stevens-Johnson syndrome) to efavirenz or any component of the formulation
Major Adverse Drug Reactions	Dermatologic: Skin rash (5% to 32%) Endocrine & metabolic: Increased serum cholesterol (20% to 40%), increased HDL cholesterol (25% to 35%), increased serum triglycerides (≥751 mg/dL: 6% to 11%) Gastrointestinal: Diarrhea (3% to 14%) Nervous system: Central nervous system toxicity (53%), dizziness (2% to 28%), depression (3% to 19%), insomnia (7% to 16%), anxiety (2% to 13%), pain (1% to 13%)
Monitoring Parameters	Serum transaminases; cholesterol and triglycerides (prior to therapy and periodically during); signs and symptoms of infection; psychiatric effects

Common Drug Interactions	**Atazanavir:** Efavirenz may decrease the serum concentration of Atazanavir. Management: the adult atazanavir dose should be 400 mg daily, boosted with ritonavir 100 mg daily for treatment-naive patients only; treatment-experienced patients should not use atazanavir with efavirenz. Risk D: Consider therapy modification **Bromperidol:** May enhance the CNS depressant effect of CNS Depressants. Risk X: Avoid combination **CarBAMazepine:** May decrease the serum concentration of Efavirenz. Efavirenz may decrease the serum concentration of CarBAMazepine. Risk X: Avoid combination **Caspofungin:** efavirenz may decrease the serum concentration of Caspofungin. **Management:** Consider using an increased caspofungin dose of 70 mg daily in adults (or 70 mg/m2, up to a maximum of 70 mg, daily in pediatric patients) Risk D: Consider therapy modification **Clarithromycin:** Efavirenz may enhance the QTc-prolonging effect of Clarithromycin & may decrease the serum concentration of Clarithromycin **Management:** Consider using an alternative antibiotic in patients taking efavirenz or monitor for decreased therapeutic effect of clarithromycin and for QT interval prolongation. Risk D: Consider therapy modification **Darunavir:** May increase the serum concentration of Efavirenz. Efavirenz may decrease the serum concentration of Darunavir. Management: Monitor for decreased concentrations and effects of darunavir and/or increased concentrations and effects of efavirenz Risk D: Consider therapy modification **Itraconazole:** Efavirenz may decrease the serum concentration of Itraconazole. Risk X: Avoid combination **Maraviroc:** Efavirenz may decrease the serum concentration of Maraviroc.

	Management: Increase maraviroc adult dose to 600mg twice/day, but only in the absence of a concurrent strong CYP3A4 inhibitor. Not recommended for pediatric patients not also receiving a strong CYP3A4 inhibitor. Do not use in patients with CrCl less than 30 mL/min. Risk D: Consider therapy modification. **Nevirapine:** May enhance the adverse/toxic effect of Efavirenz. Efavirenz may enhance the adverse/toxic effect of Nevirapine. Nevirapine may decrease the serum concentration of Efavirenz. Risk X: Avoid combination **Orphenadrine:** CNS Depressants may enhance the CNS depressant effect of Orphenadrine. Risk X: Avoid combination **Progestins (Contraceptive):** Efavirenz may decrease the serum concentration of Progestins (Contraceptive). Management: Use an alternative or additional method of contraception Injected depot medroxyprogesterone acetate does not appear to participate in this interaction. Risk D: Consider therapy modification. **Simeprevir:** CYP3A4 Inducers (Moderate) may decrease the serum concentration of Simeprevir. Risk X: Avoid combination **Voriconazole**: Efavirenz may decrease the serum concentration of Voriconazole. Voriconazole may increase the serum concentration of Efavirenz. Management: The voriconazole oral maintenance dose should be increased to 400 mg every 12 hours, and the efavirenz dose should be reduced to 300 mg daily. Risk D: Consider therapy modification
Pegnancy	The Health and Human Services (HHS) perinatal HIV guidelines consider efavirenz an alternative ART for pregnant females living with HIV who are antiretroviral-naive, who have had ART therapy in the past but are restarting, or who require a new ART regimen (due to poor tolerance or poor virologic response of current regimen). Females who become pregnant while taking efavirenz may continue if viral suppression is effective and the regimen is well tolerated. Efavirenz is present in breast milk.

Warnings/Precautions	► May cause CNS effects (eg, abnormal dreams, insomnia, impaired concentration, hallucinations, dizziness, drowsiness); symptoms usually begin within 1 to 2 days after starting efavirenz, and generally resolve within 2 to 4 weeks of continued therapy; dosing at bedtime may improve tolerability ► Fat redistribution: May cause redistribution/accumulation of fat ► Hepatotoxicity: Hepatitis, including fulminant hepatitis progressing to hepatic failure (sometimes fatal or requiring transplantation), has been reported, including patients with no preexisting hepatic disease or other identifiable risk factors. ► Hypercholesterolemia ► Serious psychiatric side effects have been associated with use ► QT prolongation ► Use with caution in patients with a history of seizure disorder; dementia or hepatic toxicity.
Storage	15°C to 30°C

6. Emtricitabine (FTC)

Dosage form/strengths	capsules 200mg oral solution 10mg/ml
Pharmacological action	Nucleoside reverse transcriptase inhibitor which interferes with HIV viral RNA dependent DNA polymerase resulting in inhibition of viral replication.
Indication	Treatment of HIV-1 infection in combination with other antiretroviral agents. HIV-1 nonoccupational& occupational postexposure prophylaxis

Dosage Regimen	**Dosing: Adult** **HIV-1 infection, treatment:** Capsule: 200 mg once daily Solution: 240 mg once daily **HIV-1 nonoccupational & occupational postexposure prophylaxis** Capsule: 200 mg once daily; initiate therapy within 72 hours of exposure and continue for 28 days in combination with other antiretrovirals (3-drug regimen) . The fixed-dose emtricitabine and tenofovir disoproxil fumarate combination product is recommended for these components of the 3-drug regimen **Dosing: Pediatric** **HIV-1 infection, treatment:** Use in combination with other ARV agents **Infants 1 to <3 months:** Oral solution: 3 mg/kg/dose once daily. Infants ≥3 months, Children, and Adolescents ≤17 years: Oral solution: 6 mg/kg/dose once daily; maximum daily dose: 240 mg/day. **Capsules:** Patient weight >33 kg: 200 mg once daily. **Adolescents ≥18 years:** adult doses **HIV-1 nonoccupational postexposure Note:** Initiate therapy within 72 hours of exposure and continue for 28 days in combination with other ARV agents. The same doses as in HIV-1 infection, treatment
Dosage adjustment in Renal impairment:	► **Renal Impairment: Adult** CrCl ≥50 mL/minute: No dosage adjustment necessary. CrCl 30 to 49 mL/minute: Capsule: 200 mg every 48 hours; solution: 120 mg every 24 hours. CrCl 15 to 29 mL/minute: Capsule: 200 mg every 72 hours; solution: 80 mg every 24 hours. CrCl <15 mL/minute: Capsule: 200 mg every 96 hours; solution: 60 mg every 24 hours. Hemodialysis: Capsule: 200 mg every 24 hours; solution: 240 mg every 24 hours; administer after hemodialysis on dialysis days. ► **Renal Impairment: Pediatric** Monitor clinical response and renal function closely. Dialysis: 30% of the dose is removed by hemodialysis (over 3 hours). Infants, Children, and Adolescents <18 years: There are no specific dosage adjustments however, may consider a reduction in the dose and/or an increase in the dosing interval similar to dosage adjustments for adults. Adolescents ≥18 years: as adults Hemodialysis: as adults
Dosage adjustment in hepatic impairment	There are no dosage adjustments in adults & pediatrics.

Administration	Administer with or without food.
Contra-indications	Hypersensitivity to emtricitabine or any component of the formulation.
Major Adverse Drug Reactions	**Central nervous system:** Dizziness , headache, insomnia , abnormal dreams **Dermatologic:** Hyperpigmentation skin rash **Gastrointestinal:** Diarrhea , vomiting , nausea , abdominal pain, gastro-enteritis **Infection:** (children: 44%) **Neuromuscular & skeletal:** Weakness , increased creatine phosphokinase **Otic:** Otitis media (children: 23%) **Respiratory:** Cough , rhinitis, pneumonia **Miscellaneous:** Fever (children: 18%) **Endocrine & metabolic:** Increased serum triglycerides ,amylase ,hyper-glycemia **Hematologic & oncologic:** Anemia , neutropenia **Hepatic:** Increased serum transaminases,serum alkaline phosphatase (>550 units/L: 1%), increased serum bilirubin .
Monitoring Parameters	Viral load, CD4, liver function tests; serum creatinine; hepatitis B testing is recommended prior to or when initiating therapy.
Common Drug Interactions	**Cladribine:** emtricitabine may diminish the therapeutic effect of Cladribine. Risk X: Avoid combination. **LamiVUDine:** May enhance the adverse/toxic effect of Emtricitabine. Risk X: Avoid combination.
pregnancy	No increased risk of overall birth defects has been observed according to data collected by the antiretroviral pregnancy registry. The HHS perinatal HIV guidelines consider emtricitabine with tenofovir disoproxil fumarate to be a preferred NRTI backbone for initial therapy in antiretroviral-naive pregnant females.
Warnings/Precautions	► Immune reconstitution syndrome ► Lactic acidosis/hepatomegaly ► Severe acute exacerbations of hepatitis B (HBV) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued emtricitabine. ► Hyperpigmentation may occur at a higher frequency in pediatric patients compared to adults (children: 32%; adults: 2% to 6%).
Storage	Capsules: Store at 15°C to 30°C , Dispense in original container. Oral solution: Store at 2°C to 8°C , Use within 3 months if stored at 15°C to 30°C .

7. Lamivudine (3TC)

Dosage form/strengths	Oral Film Coated Tablet: 150 - 300 mg Oral Solution: 10 mg/mL , 5 mg/mL
Pharmacological action	Inhibition of HIV reverse transcription via viral DNA chain termination
Indication	Treatment of HIV-1 infection in combination with other antiretroviral agents. HIV-1 nonoccupational l postexposure prophylaxis Prevention of perinatal HIV transmission ► Lamivudine is not recommended for use as monotherapy
Dosage Regimen	**HIV-1 infection, treatment: Adult, adolescents and children (weighing at least 25 kg):** Oral: 150 mg twice daily or 300 mg once daily **HIV-1 infection, treatment: Infants <3 months:** ► Weight-directed dosing: Oral: Oral solution: 4 mg/kg/dose twice daily ► Fixed weight-band dosing (HHS [pediatric 2020]): Oral: Oral solution: 3 to <6 kg: 30 mg twice daily. 6 to <10 kg: 40 mg twice daily. 10 to <14 kg: 60 mg twice daily. **HIV-1 infection, treatment: Infants ≥3 months to Children <: 3 years** ► Weight-directed dosing: Oral: Oral solution: 5 mg/kg/dose twice daily; maximum dose: 150 mg/dose ► Fixed weight-band dosing: Oral: Oral solution: 3 to <6 kg: 30 mg twice daily. 6 to <10 kg: 40 mg twice daily. 10 to <14 kg: 60 mg twice daily. **HIV-1 infection, treatment: Children : ≥3 years and Adolescents Twice daily** ► Weight-directed dosing: Oral: Oral solution: 5 mg/kg/dose twice daily; maximum dose: 150 mg/dose ► Fixed weight-band dosing: Oral: Oral solution: 3 to <6 kg: 30 mg twice daily. 6 to <10 kg: 40 mg twice daily. 10 to <14 kg: 60 mg twice daily.

- Oral tablet: Weight-band dosing for patients weighing ≥14 kg who are able to swallow tablets (using scored 150 mg tablets):
  14 to <20 kg: 75 mg (1/2 tablet) twice daily.
  20 to <25 kg: 75 mg (1/2 tablet) in the morning and 150 mg (1 tablet) in the evening.
  ≥25 kg: 150 mg (1 tablet) twice daily.

Once daily

- Oral solution: 10 mg/kg/dose once daily; maximum dose: 300 mg/dose.
- Fixed weight-band dosing: Oral: Oral tablet: for children patients ≥14 kg <25 kg
  14 to <20 kg: 150 mg (1 tablet) once daily.
  20 to <25 kg: 225 mg (1 + 1/2 tablet) once daily.
  ≥25 kg: 300 mg (2 tablets) once daily.

Once daily dosing in Pediatric patients can be used after the patient being stable on twice-daily treatment for ≥36 weeks with an undetectable viral load and stable CD4 count .

HIV-1 nonoccupational postexposure prophylaxis (nPEP): Initiate therapy within 72 hours of exposure and continue for 28 days in combination with other retroviral agents.

Infants, Children, and Adolescents <16 years:

- Weight-directed dosing: Oral solution: 4 mg/kg (maximum dose: 150 mg/dose) twice daily has been recommended (HHS [nPEP] 2016); however, a higher dose of 5 mg/kg/dose twice daily has been recommended for HIV treatment in patients ≥3 months of age

- Weight-band dosing: Oral tablet: For patients ≥14 kg who are able to swallow tablets (scored 150 mg tablets):
  14 to <20 kg: 75 mg (1/2 tablet) twice daily.
  20 to <25 kg: 75 mg (1/2 tablet) in the morning and 150 mg (1 tablet) in the evening.
  ≥25 kg: 150 mg (1 tablet) twice daily.

Adolescents ≥16 years: Oral solution or tablet:
<50 kg: 4 mg/kg twice daily; maximum dose: 150 mg/dose.
≥50 kg: 150 mg twice daily or 300 mg once daily

Dosage adjustment in Renal impairment:	► **Renal Impairment: Adult** CrCl ≥50 mL/minute: No dosage adjustment necessary. CrCl 30 to 49 mL/minute: Administer 150 mg once daily. CrCl 15 to 29 mL/minute: Administer 150 mg first dose, then 100 mg once daily. CrCl 5 to 14 mL/minute: Administer 150 mg first dose, then 50 mg once daily. CrCl <5 mL/minute: Administer 50 mg first dose, then 25 mg once daily. ► **Hemodialysis or Peritoneal dialysis:** Administer 50 mg first dose, then 25 mg once daily , dosing after hemodialysis is recommended , Supplemental dosing not needed after Peritoneal dialysis. ► **Renal Impairment: Pediatric** **Infants, Children, and Adolescents <25 kg:** There are no dosages adjustments consider reducing the dose or increasing the dosing interval; use with caution; monitor closely. ► **Children and Adolescents ≥25 kg:** the same as in adult
Dosage adjustment in hepatic impairment	There are no dosage adjustments in adults & pediatrics However, has not been studied in the setting of decompensated liver disease.
Administration	May be administered with or without meals May be crushed and added to a small amount of liquid and should be consumed immediately. Whenever possible in children, lamivudine as tablet formulation should preferably be used than oral solution.
Contra-indications	Hypersensitivity to lamivudine or any component of the formulation.

Major Adverse Drug Reactions	**Central nervous system:** Headache (35%), fatigue (≤27%), malaise (≤27%), neuropathy (12%), insomnia (≤11%), sleep disorder (≤11%). **Dermatologic:** Skin rash (9% to 12%), Angioedema. **Gastrointestinal:** Nausea (≤33%), diarrhea , Pancreatitis , sore throat (13%), vomiting . **Hematologic & oncologic:** Neutropenia (7% to 15%), anaemia, thrombocytopenia. **Hepatic:** Increased serum alanine aminotransferase (adults: 4% to 27%, children: 1%), hepatomegaly (children: 11%, adults: <1%), Hepatitis. **Infection:** infection (25%; includes ear, nose, and throat). **Neuromuscular & skeletal:** Musculoskeletal pain (12%). **Respiratory:** Nasal signs and symptoms (8% to 20%), cough (15% to 18%) **Miscellaneous:** Fever (children: 25%, adults: ≤10%), weight and levels of blood lipids and glucose may increase.
Monitoring Parameters	► Hepatic function, signs/symptoms of lactic acidosis; signs/symptoms of pancreatitis. ► HIV patients: Coinfection with HBV (prior to therapy); HIV viral load and CD4 count; immune reconstitution syndrome
Common Drug Interactions	**Cladribine:** emtricitabine may diminish the therapeutic effect of Cladribine. Risk X: Avoid combination. **LamiVUDine:** May enhance the adverse/toxic effect of Emtricitabine. Risk X: Avoid combination.
pregnancy	The risk of spontaneous abortions, induced abortions, and preterm birth is less in lamivudine-containing regimens compared with regimens without lamivudine. The HHS perinatal HIV guidelines consider lamivudine in combination with either abacavir or tenofovir disoproxil fumarate to be a preferred NRTI backbone for initial therapy in antiretroviral-naive pregnant females.
Warnings/Precautions	► Immune reconstitution syndrome ► Lactic acidosis/hepatomegaly ► Pancreatitis. ► Coinfection with hepatitis B.
Storage	Oral solution: 20°C to 25°C tightly closed. Tablet: Store between 15°C and 30°C

8. Lopinavir/Ritonavir

Dosage form/strengths	Solution, oral: Lopinavir 80 mg and ritonavir 20 mg per 1 mL Tablet: Lopinavir 200 mg and ritonavir 50 mg
Pharmacological action	The lopinavir component binds to the site of HIV-1 protease activity, results in the formation of immature, noninfectious viral particles. The ritonavir component inhibits the CYP3A metabolism of lopinavir, allowing increased plasma levels of lopinavir.
Indication	Treatment of HIV-1 infection in adults and pediatric patients 14 days and older in combination with other antiretroviral agents. Not recommended as a component of initial therapy for the treatment of HIV.

Dosage Regimen	**HIV-1 infection, treatment (as a component of combination therapy): Oral, Adults:** ► **Patients receiving concomitant antiretroviral therapy without efavirenz, nelfinavir, or nevirapine:** Twice-daily dosing: Lopinavir 400 mg/ritonavir 100 mg twice daily. Once-daily dosing: Therapy-naive or experienced patients with <3 lopinavir Resistance-associated substitutions: Lopinavir 800 mg/ ritonavir 200 mg once daily. ► **Dosage adjustment for combination therapy with efavirenz, nelfinavir, or nevirapine:** Oral: Solution: Lopinavir 520 mg/ritonavir 130 mg (6.5 mL) twice daily. Tablet: Lopinavir 500 mg/ritonavir 125 mg twice daily ► **Pregnant women:** tablet, oral: Lopinavir 400 mg/ritonavir 100 mg twice,may increasedose of lopinavir 600 mg/ritonavir 150 mg twice daily, or lopinavir 500 mg/ritonavir 125 mg twice daily, during the second and third trimesters of pregnancy avoid use once daily or solution form. **HIV-1 infection, treatment (as a component of combination therapy): Oral , Pediatrics:** Use of tablets in patients <15 kg or <0.6 m2 is not recommended; oral solution preferable. Once-daily dosing is not recommended in children <18 years of age. ► **(Infants (≥42 weeks PMA):** Patients not receiving concomitant efavirenz, nelfinavir, or nevirapine: Lopinavir 16mg/kg/dose or 300mg/ m2/dose, Twice daily. Patients with concomitant efavirenz, nelfinavir, or nevirapine: lopinavir/ ritonavir is not recommended in infants who are receiving these agents. ► **Children and Adolescents:** Patients not receiving concomitant efavirenz, nelfinavir, or nevirapine: <15 kg: Lopinavir 12 mg/kg/dose twice daily. 15 to 40 kg: Lopinavir 10 mg/kg/dose twice daily. >40 kg: Lopinavir 400 mg twice daily. Patients with concomitant efavirenz, nelfinavir, or nevirapine): <15 kg: Lopinavir 13 mg/kg/dose twice daily. ≥15 to 45 kg: Lopinavir 11 mg/kg/dose twice daily. >45 kg: Adult dose

	HIV-1 nonoccupational postexposure prophylaxis (nPEP): Initiate therapy within 72 hours of exposure and continue for 28 days; use in combination with other antiretroviral agents. Oral: the same dose of HIV-1infection treatment in pediratric.
Dosage adjustment in Renal impairment:	No dosage adjustments provided. Hemodialysis: Avoid once-daily dosing.
Dosage adjustment in hepatic impairment	► Mild to moderate impairment: There are no dosages adjustments use with caution. ► Severe impairment: There are no dosage adjustments (has not been studied); use with caution.
Administration	**Solution:** Must be administered with food **Tablet:** May be taken with or without food. Swallow whole, do not break, crush, or chew.
Contra-indications	Hypersensitivity (eg, toxic epidermal necrolysis, Stevens-Johnson syndrome,) to lopinavir, ritonavir, or any component of the formulation.
Major Adverse Drug Reactions	**Dermatologic:** Skin rash (children 12%; adults ≤5%) **Endocrine & metabolic:** Hypercholesterolemia (3% to 39%), increased serum triglycerides (3% to 36%),hyrglycemia **Gastrointestinal:** Diarrhea (greater with once-daily dosing), dysgeusia , vomiting **Hepatic:** Increased serum ALT (grade 3/4: 1% to 11%) **Respiratory:** Upper respiratory tract infection (14%) **Cardiovascular:** Vasodilation (≤3%) **Hematologic & oncologic:** Thrombocytopenia (4% children), neutropenia (1% to 5%)
Monitoring Parameters	► Prior to therapy, consider genotypic or phenotypic testing for lopinavir resistance-associated substitutions. ► Triglycerides and cholesterol (prior to initiation then periodically thereafter), LFTs, electrolytes, glucose.
Common Drug Interactions	**Amiodarone:** Lopinavir may enhance the QTc-prolonging effect of Amiodarone. Lopinavir may increase the serum concentration of Amiodarone. Management: If this combination cannot be avoided, monitor for increased amiodarone serum concentrations and effects as well as for evidence of QT interval prolongation. Risk X: Avoid combination **Aprepitant:**ritonavir may increase the serum concentration of it Risk X: Avoid combination.

Apixaban: ritonavir may increase the serum concentration of Apixaban. **Management:** US labeling recommends a 50% apixaban dose reduction in patients who would otherwise receive 5 or 10 mg twice daily, and avoiding in patients who would otherwise receive 2.5 mg twice daily. Risk D: Consider therapy modification

Bromocriptine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Bromocriptine. Risk X: Avoid combination

Clarithromycin: May enhance the QTc-prolonging effect of Lopinavir-Risk X: Avoid combination.

ARIPiprazole: CYP3A4 Inhibitors (Strong) may increase the serum concentration of ARIPiprazole. Management: Aripiprazole dose reductions are required for indications other than major depressive disorder. Dose reductions vary based on formulation, CYP2D6 genotype, and use of CYP2D6 inhibitors. See full interaction monograph for details. Risk D: Consider therapy modification.

Fluticasone (Nasal): may increase the serum concentration of Fluticasone (Nasal). Risk X: Avoid combination.

Ivabradine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ivabradine. Risk X: Avoid combination

Lovastatin: Protease Inhibitors may increase the serum concentration of Lovastatin. Risk X: Avoid combination

MetroNIDAZOLE (Systemic): Ritonavir may enhance the adverse/toxic effect of MetroNIDAZOLE (Systemic) and metronidazole may result in a disulfiram-like reaction. Risk X: Avoid combination.

Midazolam: Protease Inhibitors may increase the serum concentration of Midazolam. Management: close monitoring, and consideration of lower IV midazolam doses with concurrent use.

NiMODipine: may increase the serum concentration of NiMODipine. Risk X: Avoid combination.

Propafenone: Ritonavir may increase the serum concentration of Propafenone. Risk X: Avoid combination

RifAMPin: May enhance the adverse/toxic effect of Lopinavir. Specifically, the risk of hepatocellular toxicity may be increased.

RifAMPin may decrease the serum concentration of Lopinavir. Risk X: Avoid combination

Salmeterol: may increase the serum concentration of Salmeterol. Risk X: Avoid combination.

Simeprevir: may increase the serum concentration of Simeprevir. Risk X: Avoid combination.

Simvastatin: Risk X: Avoid combination

	Tamsulosin: may increase the serum concentration of Tamsulosin. Risk X: Avoid combination. **Ticagrelor:** CYP3A4 Inhibitors (Strong) may decrease serum concentrations of the active metabolite(s) of Ticagrelor. CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ticagrelor. Risk X: Avoid combination. **VinCRIStine (Liposomal):** CYP3A4 Inhibitors (Strong) may increase the serum concentration of VinCRIStine (Liposomal). Risk X: Avoid combination. **Voriconazole:** Lopinavir may decrease the serum concentration of Voriconazole. Risk X: Avoid combination.
pregnancy	Lopinavir has a low level of transfer across the human placenta; fetal exposure is increased with ritonavir, Based on information collected by the Antiretroviral Pregnancy Registry, an increased risk of teratogenic effects has not been observed in humans.
Warnings/Precautions	1. Cardiovascular concerns: Possible higher risk of myocardial infarction associated with the cumulative use of lopinavir/ritonavir; consider avoiding lopinavir/ritonavir-based regimens in patients with high cardiac risk. 2. May alter cardiac conduction and prolong the QTc and/or PR interval. 3. Fat redistribution. 4. Hepatotoxicity, use with caution in patients with Hepatitis B or C and cirrhosis. 5. Immune reconstitution syndrome. 6. Increased cholesterol. 7. Changes in glucose tolerance, hyperglycemia, exacerbation of diabetes, DKA, 8. Use with caution in patients with hemophilia A or B 9. Hepatic impairment: Use with caution; lopinavir concentrations may be increased. 10. Pancreatitis: Use with caution in patients with increased triglycerides
Storage	Oral solution: Store at 2°C to 8°C, Avoid exposure to excessive heat. If stored at 25°C use within 2 months. Tablet: Store at 15°C to 30°C. Exposure to high humidity outside of the original container >2 weeks is not recommended.

9. Nevirapine

Dosage form/strengths	Suspension, Oral:10 mg/ mL , dispersable tab : 50mg Tablet, Oral:200 mg
Pharmacological action	Non-nucleoside reverse transcriptase inhibitor ,It consequently blocks the RNA-dependent and DNA-dependent DNA polymerase activities including HIV-1 replication.
Indication	Treatment of HIV-1, in combination therapy with other antiretroviral agents, in adults and pediatric patients ≥15 days of age (immediate release) and ≥6 years of age with a BSA of ≥1.17 m2. Not recommended as a component of initial therapy for the treatment of HIV, unless the benefit outweighs the risk, in adult females with CD4+ cell counts >250 cells/mm3 or adult males with CD4+ cell counts >400 cells/ mm3.

Dosage Regimen	**HIV-1 infection, treatment: Oral, Adults:** Initial: Immediate release: 200 mg once daily for 14 days Maintenance:Immediate release: 200 mg twice daily (in combination with additional antiretroviral agents) if there is no rash or untoward effects during initial dosing period. **HIV-1 infection, treatment: Oral,Pediatrics:** ► Infants and Children <8 years: **With lead-in dosing:** Initial: 200 mg/m2/dose once daily (maximum dose: 200 mg/dose) for the first 14 days of therapy; increase to 200 mg/m2/dose twice daily (maximum dose: 200 mg/dose) **Without lead-in dosing:** Infants and Children <2 years: 200 mg/m2/dose twice daily (maximum dose: 200 mg/dose). ► Children ≥8 years: **Initial (lead-in dosing):** 120 to 150 mg/m2/dose once daily (maximum dose: 200 mg/dose) for the first 14 days of therapy; increase to 120 to 150 mg/m2/dose twice daily (maximum dose: 200 mg/dose) if no rash or other adverse effects occur. ► Adolescents: **Initial:** 200 mg once daily for the first 14 days; increase to 200 mg every 12 hours if no rash or other adverse effects occur; if patient able to swallow tablets whole, may convert maintenance dose to the extended release formulation (400 mg once daily). If nevirapine therapy is interrupted for ≤14 days (infants/children) or <7 days (adolescents), restart at the full-dose due to mechanisms of nevirapine resistance.
Dosage adjustment in Renal impairment:	► **CrCl <20 mL/minute:** There are no dosage adjustments (has not been studied). ► **Hemodialysis:** An additional 200 mg immediate release dose is recommended following dialysis
Dosage adjustment in hepatic impairment	Permanently discontinue if symptomatic hepatic events occur. Mild impairment (Child-Pugh class A): There are no dosage adjustments; use with caution. Moderate to severe impairment (Child-Pugh class B or C): Use is contra-indicated.
Administration	May be administered with or without food. May be administered with an antacid

Contra-indications	Moderate to severe hepatic impairment (Child-Pugh class B or C); use in occupational or nonoccupational postexposure prophylaxis (PEP) regimens hypersensitivity to nevirapine or any component of the formulation.
Major Adverse Drug Reactions	**Endocrine & metabolic:** Increased serum cholesterol (3% to 19%), increased LDL cholesterol **Hematologic & oncologic:** Decreased serum phosphate (≤38%), neutropenia (1% to 13%) **Hepatic:** Increased serum alanine aminotransferase (2% to 14%)
Monitoring Parameters	► Monitor CBC and viral load. ► Intensive monitoring is required during the initial 18 weeks of therapy to detect potentially life-threatening hepatic, dermatologic, and hypersensitivity reactions. ► Baseline and repeat liver function tests. ► Assess/evaluate AST/ALT immediately in any patients with a rash.
Common Drug Interactions	**Atazanavir:** May increase the serum concentration of Nevirapine. Risk X: Avoid combination. **CarBAMazepine:** May decrease the serum concentration of Nevirapine. Risk X: Avoid combination. **Caspofungin:** may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70 mg daily in adults (or 70 mg/m2, up to a maximum of 70 mg, daily in pediatric patients) Risk D: Consider therapy modification. **Dolutegravir:** Nevirapine may decrease the serum concentration of Dolutegravir. Risk X: Avoid combination. **Efavirenz:** Nevirapine may enhance the adverse/toxic effect of Efavirenz- Risk X: Avoid combination **Itraconazole:** Nevirapine may decrease the serum concentration of Itraconazole. Risk X: Avoid combination.
	Lopinavir: Nevirapine may decrease the serum concentration of Lopinavir. Management: Avoid once daily use of lopinavir/ritonavir with nevirapine. Avoid use of this combination in patients less than 6 months of age. Risk D: Consider therapy modification. **RifAMPin:** May decrease the serum concentration of Nevirapine. Management: Avoid whenever possible. When this combination is necessary, use immediate-release nevirapine (avoid extended-release nevirapine) at a dose of 200 mg twice daily with no lead-in (per adult/adolescent HIV guidelines). Monitor nevirapine response closely. Risk D: Consider therapy modification.

pregnancy	The Health and Human Services (HHS) perinatal HIV guidelines do not recommend nevirapine as an initial non-nucleoside reverse transcriptase inhibitor for use in antiretroviral-naive pregnant patients because of the potential for adverse events, complex dosing, and low barrier to resistance. Use is not recommended (except in special circumstances) .
Warnings/Precautions	► Fat redistribution, hepatotoxicity, skin reactions, Immune reconstitution syndrome, Rhabdomyolysis.
Storage	Store at 15°C to 30°C.

10. Raltegravir

Dosage form/strengths	Tablet, Oral:100 mg ,400mg, 600 mg Sachets, chewable tablets : 25 mg
Pharmacological action	Inhibits the catalytic activity of integrase, thus preventing integration of the proviral gene into human DNA.
Indication	Treatment of HIV-1 infection in combination with other antiretroviral agents HIV-1 nonoccupational& occupational postexposure prophylaxis
Dosage Regimen	**HIV-1 infection, treatment: Adults, Oral:** ► Treatment-naive patients: 400 mg twice daily or 1,200 mg once daily ► Treatment-experienced patients: 400 mg twice daily. **HIV-1 nonoccupational & occupational postexposure prophylaxis: Adult, Oral:** 400 mg twice daily for 28 days in combination with other antiretroviral agents. Initiate therapy within 72 hours of exposure **Dosage Modifications,** Treatment-naïve or treatment-experienced when co-administered with rifampin 800 mg (two 400-mg tabs) PO BID.
	HIV-1 infection, treatment: Pediatrics: ► Oral Chewable tablets: Children weighing ≥11 kg: Weight-directed dosing: 6 mg/kg/dose twice daily; maximum dose: 300 mg/dose. ► Oral solution: Infants and Children <20 kg: Weight-directed dosing: 6 mg/kg/dose twice daily; maximum dose: 100 mg/dose. ► Oral Film Coated Tablets: Children and Adolescents ≥25 kg to 40 kg: 400 mg twice daily. ► Oral Film Coated Tablet: Children and Adolescents ≥40 kg: 1,200 mg once daily.

Dosage adjustment in Renal impairment:	**Mild, moderate, and severe impairment:** No dosage adjustment necessary. **End-stage renal disease (ESRD) on intermittent hemodialysis (IHD):** Dose after dialysis on dialysis days.
Dosage adjustment in hepatic impairment	**Mild-to-moderate impairment:** No dosage adjustment necessary. **Severe impairment:** There are no dosage adjustments (has not been studied). **Film-coated tablet (600 mg formulation):** Use is not recommended in mild, moderate and severe (has not been studied).
Administration	May be administered without regard to meals. Oral suspension:, pour packet contents into water at a concentration of 10 mg/mLand swirl in a circular motion for 45 seconds; do not shake. Do not turn the mixing cup upside down. Administer within 30 minutes of mixing with water. Discard any remaining suspension in the trash. Film-coated tablets and chewable tablets or oral suspension are not bio-equivalent and are not substitutable on a mg/mg basis.
Contra-indications	Hypersensitivity to raltegravir or any other component of the formulation.
Major Adverse Drug Reactions	**Hepatic:** Increased serum ALT, hyperbilirubinemia, increased serum alkaline phosphatase (≤2%), hepatitis (<2%) **Central nervous system:** Headache (≤4%), insomnia (≤4%), abnormal dreams (≥2%), suicidal ideation (<2%), **Endocrine & metabolic:** Increased serum glucose (126 to 250 mg/dL: 7% to 10%; 251 to 500 mg/dL: 2% to 3%) **Gastrointestinal:** Increased serum lipase (≤5%), increased serum amylase (≤4%), **Hematologic & oncologic:** Decrease in absolute neutrophil count (1% to 4%), thrombocytopenia (≤3%), decreased hemoglobin (≤1%)
Monitoring Parameters	Viral load, CD4 count, signs of skin rash, signs/symptoms of depression and suicidal ideation.
Common Drug Interactions	**Aluminum Hydroxide:** May decrease the serum concentration of Raltegravir. Management: Avoid the use of oral / enteral aluminum hydroxide. Risk X: Avoid combination **Calcium Carbonate:** May decrease the serum concentration of Raltegravir. Management: Use of once-daily raltegravir with calcium carbonate is not recommended; Risk D: Consider therapy modification. **Magnesium Salts:** May decrease the serum concentration of Raltegravir.. Risk X: Avoid combination. **RifAMPin:** May decrease the serum concentration of Raltegravir. Management: Increase raltegravir dose to 800 mg twice daily (adult dose). Concurrent use of rifampin with once-daily raltegravir is not recommended. Risk D: Consider therapy modification.

pregnancy	No increased risk of overall birth defects has been observed following first trimester exposure according to data collected by the antiretroviral pregnancy registry. The Health and Human Services (HHS) Perinatal HIV Guidelines consider raltegravir a preferred integrase strand transfer inhibitor (INSTI) for pregnant females living with HIV Once daily dosing is not recommended for use during pregnancy,
Warnings/Precautions	► Immune reconstitution syndrome, Myopathy, Skin and hypersensitivity reactions. ► At birth, the enzyme responsible for the metabolism of raltegravir (UGT1A1) is low and ► Raltegravir elimination in neonates may be prolonged. The activity of UGT1A1 increasee ► Rapidly over the first 4 to 6 weeks of life. ► Do not use in combination with darunavir and ritonavir in patients with HIV RNA >100,000 copies/mL and/or CD4 count <200 cells/mm3, or in combination with abacavir and lamivudine in patients with HIV RNA >100,000 copies/mL).
Storage	Store at 15°C to 30°C.

11. Tenofovir Disoproxil Fumarate (TDF)

Dosage form/strengths	Oral Tablet 300 mg
Pharmacological action	A nucleotide reverse transcriptase inhibitor; it interferes with the HIV viral RNA dependent DNA polymerase resulting in inhibition of viral replication.
Indication	Treatment of HIV-1 infection in combination with other antiretroviral agents HIV-1 nonoccupational& occupational postexposure prophylaxis

Dosage Regimen	**HIV-1 infection, treatment, Adults: Oral** 300 mg once daily (in combination with other antiretrovirals). **HIV-1 nonoccupational& occupational postexposure prophylaxis (nPEP), Adults: Oral** 300 mg once daily for 28 days (in combination with other antiretroviral agents). Initiate Therapy within 72 hours of exposure. The fixed dose emtricitabine and Tenofovir Disoproxil Fumarate combination is recommended for these components of the 3-drug regimen. **HIV-1 infection, treatment, Pediatrics:** ► **Weight-directed dosing:** Children ≥2 years weighing ≥10 kg and Adolescents: Oral: 8 mg/kg/dose once daily; maximum daily dose: 300 mg/day ► **Fixed weight-band dosing: Children ≥2 years weighing ≥17 kg and Adolescents:** Oral: 17 to <22 kg: 150 mg once daily 22 to <28 kg: 200 mg once daily 28 to <35 kg: 250 mg once daily ≥35 kg: 300 mg once daily
Dosage adjustment in Renal impairment:	**Adult :** ► CrCl ≥50 mL/minute: No dosage adjustment necessary. ► CrCl 30 to 49 mL/minute: 300 mg every 48 hours ► CrCl 10 to 29 mL/minute: 300 mg every 72 to 96 hours ► CrCl <10 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
	Hemodialysis: 300 mg following dialysis every 7 days or after a total of ~12 hours of dialysis (usually once weekly assuming 3 dialysis sessions lasting about 4 hours each). Alternate recommendations (IDSA [Lucas 2014]): CrCl <50 mL/minute (and not on hemodialysis) or GFR <60 mL/minute/1.73 m2: Avoid use. Peritoneal dialysis: Use with caution; dose reduction recommended (no specific adjustment provided) **Pediatric :** Children ≥2 years and Adolescents: There is no dosage adjustments provided in manufacturer's labeling. Dosage should be decreased in patients with CrCl <50 mL/minute (HHS [pediatric] 2018).

Dosage adjustment in hepatic impairment	No dosage adjustment necessary
Administration	Tablets may be administered without regard to meals, but fatty meals may increase the bioavailability of tenofovir.
Contra-indications	Hypersensitivity to tenofovir or any component of the formulation
Major Adverse Drug Reactions	**Central nervous system:** Insomnia (3% to 18%), headache (5% to 14%), pain (12% to 13%), dizziness (8% to 13%), depression (4% to 11%) **Dermatologic:** Skin rash **Endocrine & metabolic:** Hypercholesterolemia (19% to 22%), increased serum triglycerides (1% to 4%), hyperglycemia, lipodystrophy **Gastrointestinal:** Abdominal pain (4% to 22%), nausea (8% to 20%), diarrhea (9% to 16%), vomiting (2% to 13%) **Neuromuscular & skeletal:** Decreased bone mineral density Fever (4% to 11%) **Cardiovascular:** Chest pain (3%) **Hepatic:** Increased serum ALT (2% to 10%), increased serum AST (3% to 5%), increased serum transaminases (2% to 5%), increased serum alkaline phosphatase (1%) **Renal:** Increased serum creatinine (9%), renal failure (7%) Infections.
Monitoring Parameters	► CBC with differential, reticulocyte count, creatine kinase, CD4 count, HIV RNA plasma levels, serum phosphorus (baseline and as clinically indicated in patients with chronic kidney disease). ► Serum creatinine, urine glucose, urine protein (baseline and as clinically indicated during therapy). ► Hepatic function tests; bone density (patients with a history of bone fracture or have risk factors for bone loss); testing for HBV is recommended prior to the initiation of antiretroviral therapy; weight (children).
Common Drug Interactions	**Atazanavir:** TDF may decrease the serum concentration of Atazanavir. **Management:** Use boosted atazanavir in adults; give combo (atazanavir/ritonavir with tenofovir) as a single daily dose with food.. Risk D: Consider therapy modification **Cladribine:** TDF may diminish the therapeutic effect of Cladribine. Risk X: Avoid combination **Diclofenac (Systemic):** May enhance the nephrotoxic effect of Tenofovir **Products. Management:** Seek alternatives to this combination whenever possible. Avoid use of tenofovir with multiple NSAIDs or any NSAID given at a high dose. Risk D: Consider therapy modification.

pregnancy	The HHS perinatal HIV guidelines consider TDF in combination with emtricitabine or lamivudine to be preferred dual NRTI backbone for initial therapy in antiretroviral-naive pregnant females. The guidelines also consider tenofovirdisoproxil fumarate plus emtricitabine or lamivudine as recommended dual NRTI backbone for HIV/hepatitis B virus coinfected pregnant females. Hepatitis B flare may occur if TDF is discontinued. TDF is also a preferred component of a regimen when acute HIV infection is detected during pregnancy.
Warnings/Precautions	Decreased bone mineral density , Immune reconstitution syndrome Lactic acidosis/hepatomegaly, Osteomalacia and renal dysfunction Renal toxicity: May cause renal toxicity (acute renal failure and/or Fanconi syndrome); avoid use with concurrent or recent nephrotoxic therapy (including high dose or multiple NSAID use).
Storage	Store at 15°C to 30°C.

12. Zidovudine

Dosage form/strengths	Capsule 100 mg , 300 tablet
Pharmacological action	A nucleotide reverse transcriptase inhibitor; it interferes with the HIV viral RNA dependent DNA polymerase resulting in inhibition of viral replication.
Indication	► Treatment of HIV-1 infection in combination with other antiretroviral agents ► Perinatal HIV-1 transmission, prevention

Dosage Regimen	**Adults:** **HIV-1 infection, treatment** Oral: 300 mg twice daily **Pediatrics:** **HIV-1 infection, treatment:** Infants (postconceptional age [PCA] ≥35 weeks and PNA ≥4 weeks), Children, and Adolescents: ► Weight-directed dosing: Oral: <9 kg: 12 mg/kg/dose twice daily. 9 to <30 kg: 9 mg/kg/dose twice daily. ≥30 kg: 300 mg twice daily. ► BSA-directed dosing: Oral: 240 mg/m2/dose every 12 hours, ► Range: 180 to 240mg/ m2/ dose every 12 hours (maximum dose: 300 mg/dose). **Dosing adjustment for hematologic toxicity:** interruption of therapy for significant anemia (Hgb <7.5 g/dL or >25% decrease from baseline) and/or significant neutropenia (ANC <750 cells/mm3 or >50% decrease from baseline) until evidence of bone marrow recovery occurs; once bone marrow recovers, dose may be resumed using appropriate adjunctive therapy
Dosage adjustment in Renal impairment:	► **Adult :** CrCl ≥15 mL/minute: No dosage adjustment necessary. CrCl <15 mL/minute: Oral: 100 mg 3 times daily or 300 mg once daily . ► **End-stage renal disease on intermittent hemodialysis** (administer dose after dialysis on dialysis days): 100 mg 3 times daily or 300 mg once daily . ► **Peritoneal dialysis: Oral:** 100 mg every 6 to 8 hours.
Dosage adjustment in hepatic impairment	There are no specific dosage adjustments provided in the manufacturer's labeling (has not been studied). However, adjustment may be necessary due to extensive hepatic metabolism.
Administration	May be administered without regard to meals

Contra-indications	Potentially life-threatening hypersensitivity to zidovudine or any component of the formulation.
Major Adverse Drug Reactions	**Central nervous system:** Headache (63%), malaise (53%) **Dermatologic:** Skin rash **Gastrointestinal:** Nausea ,anorexia (20%), vomiting **Hematologic & oncologic:** Macrocytosis (infants, children, & adolescents: >50%), anemia (neonates: 22%; infants, children, & adolescents: 4%; adults, grades 3/4: 1%), Lymphadenopathy, neutropenia, splenomegaly, thrombocytopenia **Hepatic:** Hepatomegaly , increased ALT , AST **Respiratory:** Cough (infants, children, & adolescents: 15%) Fever (infants, children, & adolescents: 25%) **Cardiovascular:** Cardiac failure (<6%), ECG abnormality, edema Weight loss
Monitoring Parameters	► CBC with differential; LFTs; serum creatinine; HIV viral load and CD4 count.
Common Drug Interactions	**Cladribine:** TDF may diminish the therapeutic effect of Cladribine. Risk X: Avoid combination. **Clarithromycin:** May enhance the myelosuppressive effect of Zidovudine. Management: Monitor response to zidovudine closelyRisk D: Consider therapy modification **Ribavirin (Systemic):** Zidovudine may enhance the adverse/toxic effect of Ribavirin (Systemic). Consider even closer monitoring for anemia than routinely recommended for ribavirin. Alternative therapies should be considered when clinically possible, particularly for patients with other risk factors. Risk D: Consider therapy modification.
pregnancy	The Health and Human Services (HHS) perinatal HIV guidelines consider zidovudine an alternative NRTI for pregnant females living with HIV who are antiretroviral-naive, who have had ART therapy in the past but are restarting, or who require a new ART regimen (due to poor tolerance or poor virologic response of current regimen). In addition, females who become pregnant while taking zidovudine may continue if viral suppression is effective and the regimen is well tolerated. The pharmacokinetics of zidovudine are not significantly altered in pregnancy and dosing adjustment is not needed.
Warnings/Precautions	**Warning box:** Hematologic toxicity (neutropenia and severe anemia), Immune reconstitution syndrome, Lactic acidosis/hepatomegaly, lipoatrophy , myopathy
Storage	Store at 15°C to 25°C Protect capsules from moisture.

References:

- WHO Policy Brief Update of Recommendations on First and Second Line Antiretroviral Regimens – July 2019
- WHO Consolidated Guidelines on HIV Testing Services – December 2019
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- WHO POLICY BRIEF —CONSIDERATIONS FOR INTRODUCING NEW ANTIRETROVI¬RAL DRUG FORMULATIONS FOR CHILDREN - JULY 2020
- NATIONAL GUIDELINES ON CLINICAL CARE AND ANTIRETROVI-RAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION 2014
- AASLD/IDSA guidelines
- Lexicomp-Clinical Drug Information, Last update August 2020,available at: http://online.lexi.com
- Update – Clinical drug Information – Last update August 2020,available at : http://www.uptodate.com.login.