Fourth Edition

# A guide to Anti retroviral treatment

Ministry of Health
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Programme

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National STD / AIDS Control Programme

# A Guide to Antiretroviral Treatment

4th Edition

National STD and AIDS Control Programme

Ministry of Health Sri Lanka

National STD/AIDS Control Programme, Sri Lanka

# A Guide to Antiretroviral Treatment

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# Contents

# Abbreviations

| | |
|---|---|
| 3TC | lamivudine |
| ABC | abacavir |
| ART | antiretroviral treatment |
| ARV | antiretroviral (drugs) |
| ATT | anti tuberculosis treatment |
| ATV | atazanavir |
| AZT | zidovudine |
| BB | beach boys |
| BMI | body mass index |
| CMV | cytomegalo virus |
| COCP | combined oral contraceptive pill |
| Cu-IUD | copper intra uterine device |
| CXR | chest X ray |
| DTG | dolutegravir |
| DRV | darunavir |
| DU | drug users |
| EFV | efavirenz |
| FBC | full blood count |
| FSW | female sex worker |
| FTC | emtricitabine |
| Hb | haemoglobin |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HEP B | hepatitis B |
| HEP C | hepatitis C |
| HIV | human immunodeficiency virus |
| IDU | injecting drug user |
| IDV | indinavir |
| INSTI | integrase strand transfer inhibitors |
| LFT | liver function tests |
| LNG-IUS | levonorgestrel intra uterine system |
| PEP | post exposure prophylaxis |
| PEPSE | post exposure prophylaxis following sexual exposure |
| POEC | progesterone only emergency contraception |
| POP | progesterone only pill |
| LPV | lopinavir |
| MSM | men having sex with men |
| NGO | non governmental organization |
| NNRTI | non nucleoside reverse transcriptase inhibitor |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NSACP | National STD AIDS Control Programme |
| NVF | nelfinavir |
| NVP | nevirapine |
| OI | opportunistic infections |
| PCR | polymerase chain reaction |
| PI | protease inhibitor |
| RAL | raltegravir |
| /r | ritonavir |
| RT | ritonavir |
| SQV | saquinavir |
| STI | sexually transmitted infections |
| TB | tuberculosis |
| TDF | tenofovir |
| TMP | trimethoprim |
| TOXO | toxoplasmosis |
| UD | undetectable |
| UFR | urine full report |
| WHO | World Health Organization |

# HIV comprehensive care services

1

# 1.1 Introduction

Dr. A. Karawita, Dr. C. Hathurusinghe

## Introduction

HIV treatment and care unit of the National STD/AIDS Control Programme (NSACP) of Sri Lanka, in partnership with an expert panel of HIV clinicians in the country, prepared this antiretroviral guideline for the fellow practitioners to provide the best treatment services for beneficiaries. This national guideline is based on the systematic guidelines developed by the WHO and evidence-informed local recommendations and adaptations.

### Goal of the ART guideline

The goal of this guideline is to optimize HIV treatment and care in the country to minimize the morbidity and mortality related to HIV and to improve the quality of life of people living with HIV.

### i. Objectives

The objectives of these guidelines are:

To educate clinicians and supporting staff on updated, evidence-informed, clinical recommendations in HIV medicine in order to provide best quality prevention, treatment and care services

To encourage decisions makers, policy planners, actors and beneficiaries to advocate and lobby to implement best quality ART service in the country.

To provide guidance on monitoring and evaluation of HIV treatment and care programmes.

### ii. Target audience

This guideline is primarily intended for those who practice HIV medicine and managers of ministry of health and national HIV programme. Furthermore, this guideline also target all involved in the planning of policy, law, programme, projects, and final service delivery for the beneficiaries such as people living with HIV, community-based organizations, community service organizations, national and provincial AIDS committees, subcommittees, national TB programme managers, managers of national laboratory services and international and bilateral agencies and organizations that provide financial and technical support to HIV programmes in the country.

### iii. Guiding principles

Implementation of this antiretroviral guideline need to be accompanied by efforts to promote and protect the human rights of people who need HIV services, including ensuring informed consent, preventing stigma and discrimination and promoting gender equity. Furthermore, implementation of the recommendations should be in line with the local context, including HIV epidemiology and prevalence of other comorbidities, availability of resources and capacity of the health system.

## Goals of Antiretroviral Therapy

Currently available ARV drugs cannot eradicate HIV from the human body. This is because a pool of latently infected CD4 cells is established during the earliest stages of acute HIV infection and persists within the organs/cells and fluids (eg: liver and lymphoid tissue) even with prolonged suppression of plasma viraemia to <50 copies/ml by antiretroviral therapy.

The goals of therapy are given below:

| Goals of ARV therapy | |
|---|---|
| Clinical goals | Prolongation of life and improvement in quality of life |
| Virological goals | Greatest possible sustained reduction in viral load |
| Immunological goals | Immune reconstitution that is both quantitative and qualitative |
| Therapeutic goals | Rational sequencing of drugs in a manner that achieves clinical, virological and immunological goals while maintaining future treatment options, limiting drug toxicity and facilitating adherence |
| Prevention goals | Reduction of HIV transmission through viral suppression |

These goals are achieved by completely suppressing viral replication for as long as possible using well-tolerated and sustainable treatment. With prolonged viral suppression, the CD4 lymphocyte count usually increases, which is accompanied by partial restoration of pathogen-specific immune function. For most patients, this results in a dramatic reduction in the risk of HIV-associated morbidity and mortality.

The Programmatic goals of ART are:

To provide lifelong ART to all eligible patients,

To monitor and report treatment outcomes on a quarterly basis,

To attain individual drug adherence rates of 95% or more

To ensure retention in care and provide necessary care and support services

## 1.2 Comprehensive care services for PLHIV

Dr. S. Somawardhana

Individuals living with undiagnosed HIV infection need to be identified, offered testing and commenced on antiretroviral therapy, to eliminate the risk of further transmission.

HIV treatment guidelines universally acknowledge the benefits of initiating immediate antiretroviral treatment regardless of CD4 cell count for an individual's own health as well as prevention benefits to the community by reducing onward transmission of HIV infection.

General HIV care includes the following:

Counseling

Management of acute infections

Screening for opportunistic infections and co infections

Management of infections, malignancies etc.

Prophylaxis to prevent infections (Cotrimoxazole, INAH)

Anti-retroviral treatment

Monitoring of immunological, virological and biochemical parameters

Family planning services and Pap smear screening among females

Prevention services for mother to child transmission of HIV

Vaccination

Psychological and psychiatric referral

Maintain satisfactory nutritional status

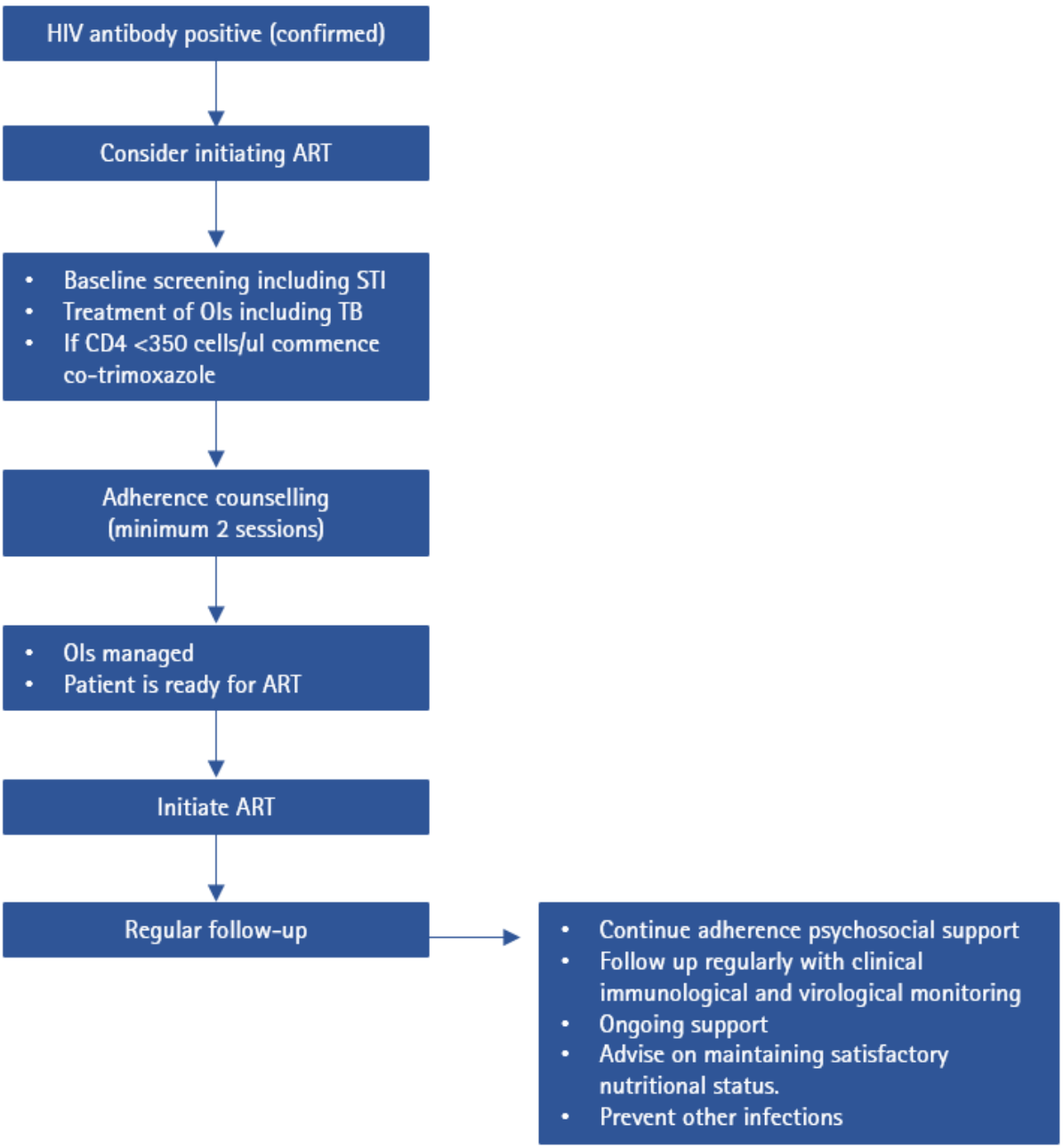
Sexual health services for prevention of sexually transmitted infections

Monitoring and counselling on the lifestyle modifications for prevention of non- communicable diseases and related morbidities

Positive prevention

Link to NGO/CBO s and positive support groups for social support

Figure 1-Flow chart -ART eligibility for adults and adolescents



## 1.3 Baseline assessments prior to ART

Dr. N. Jayasuriya

Before any person is started on ART, he/she should undergo a baseline assessment that addresses the following questions:

What is the clinical status?

What is the immunological, virological, hematological, biochemical and microbiological status?

What is the family/social support available to initiate and continue treatment?

Should OI treatment and/or prophylaxis be provided?

Is the person interested in and motivated to take ART?

Should other support services be provided? (eg. Linking to positive support groups)

Are there any comorbidities including non-communicable diseases and psychiatric illnesses?

- Annexures 1-Depression screening questionnaire
- Annexure 2-FRAX fracture risk
- Annexure 3-Framingham risk score

Clinical assessment and laboratory tests play a key role in assessing individuals before ART is initiated.

Table 1.1- Laboratory monitoring before initiating ART

| Phase of HIV management | Recommended | Desirable (if feasible) |
|---|---|---|
| HIV diagnosis | • Screening for sexually transmitted infections<br>• Pap smear<br>• Pregnancy test<br>• CD4 cell count<br>• Viral load test<br>• Full blood count<br>• ESR<br>• UFR<br>• Liver function tests<br>• Renal function tests (e-GFR)<br>• Fasting blood sugar<br>• Lipid profile<br>• TB screening<br>• Eye referral if CD4 <100 cells/µl<br>• Hep B surface antigen<br>• HCV antibody<br>• Cytomegalovirus antibodies<br>• Toxoplasma antibodies<br>• *Cryptococcus* antigen if CD4 count <100 cells/mm3 | • HLA- B * 5701 testing if planning to start ABC<br>• ECG if planning to start ATV<br>• Hepatitis A antibodies<br>• Pre ART resistance test |

Availability of these test reports should not delay ART initiation. WHO recommends rapid ART initiation within 7 days maximum or even same day ART if patient understands the illness and need of ART and has understood adherence/ side effect issues. Test samples can be taken and ART can be initiated after counselling the patient, awaiting reports.

## 1.4 Important topics in counselling

Dr. H. Perera

Consider these topics in counselling based on the patient's needs. Counselling is an ongoing issue and these issues can be focused in subsequent visits after initial understanding of the patient regarding basic facts on HIV/AIDS and ART. Introduce these topics gradually over continuing counselling sessions during follow up visits as the needs vary from patient to patient.

1. Explain the natural history of HIV
    - about HIV/AIDS
    - progression of the disease
    - mode of transmission and non-transmission
    - myths about the disease
2. Discuss the importance of early diagnosis
3. Early initiation of ART can lead to reduction of transmission
4. Sexuality – importance of responsible sexual life, disclosure to the partner
5. Advise for healthy lifestyle measure
    - diet and nutrition
    - regular physical exercises
    - abstinence of alcohol, smoking, recreational drugs
    - positive living
6. Female patients – Reproductive issues: pregnancy, family planning, annual PAP screening
7. Law and Policy in the country with regard to HIV
8. Prevention of STIs and reinfection with resistant strains of HIV
    - safe sexual practices – abstinence, be faithful
    - correct and consistent condom use
9. PMTCT services
10. Blood and body fluid safety
    - avoid blood and body fluid, organ donations
    - measures to be taken during an injury
11. Prevention of opportunistic infections
    - antibiotic, antiviral and antifungal prophylaxis (Primary /Secondary)
    - good hygienic practices
    - satisfactory nutrition status
    - safe food and water

- vector born infections
- Hepatitis A, B, HPV Vaccination

12. Disclosure related issues - to relevant heath care facility, partner or family member
13. Partner screening and relevant family screening
14. Availability of NGO and positive support groups
15. Counselling prior to initiating ART
    - Explain the benefits of early initiation of ART
    - Objectives of treatment
    - Adherence counselling (Please refer Chapter 1.6)
    - Common side effects and possibility of drug-drug and drug- food interactions
    - ART storage and keeping drug stocks for emergency situations eg: traveling for long distance/ staying overnight outside home
    - Need for regular follow- up (clinical, biochemical, microbiological, immunological and virological)
    - Treatment failure and drug resistance
16. Pre exposure Prophylaxis (PrEP) and Post exposure prophylaxis following sexual exposure (PEPSE)
17. Multidisciplinary approach (psychiatric services, nutritional support etc.)
18. Special supportive services (PLHIV support groups, NGOs, Social service workers)
19. Stigma and discrimination issues
20. Importance of regular screening for STI and PAP smear

## Counselling for special groups

Table 1.2 - Counselling for special groups

| | |
|---|---|
| **Pregnant mothers** | • Importance of early diagnosis and treatment<br>• Shared care (ANC service through the MOH, VOG, HIV clinic)<br>• The methods of maintaining the confidentiality<br>• PMTCT services<br>• Delivery options<br>• Feeding options<br>• Family planning<br>• Infant ART<br>• Infant HIV screening<br>• Infant Vaccination |

| | |
|---|---|
| | • Partner disclosure and screening |
| **Infants and children** | • Growth and development, neuro cognitive and social development<br>• Vaccination<br>• Weight based ART regimen<br>• Schooling<br>• Confidentiality of sero -status<br>• Nutrition<br>• Psychological support |
| **Adolescents & young adults (10-24)** | • Disclosure of HIV status<br>• Risk assessment for on-going transmission<br>• ART adherence<br>• Benefits of maintaining undetectable viral load<br>• PrEP /PEPSE<br>• HIV law /policy in Sri Lanka<br>• Marriage and reproductive issues and options<br>• Partner screening and status disclosure in sero discordant couples<br>• Safe sexual practices<br>• Positive living, self-stigma<br>• Sexual health issues<br>• Issues related to education and occupation<br>• Vaccination – HPV, Hep. B<br>• Contraception<br>• Recreational drug use, alcohol and smoking |

| | |
|---|---|
| **Elderly (over 60y)** | • HIV and risk for other comorbidities (cardiovascular, stroke, osteoporosis, metabolic syndrome, renal disease, malignancies)<br>• Shared confidentiality with other specialities when providing comprehensive care<br>• ART adherence<br>• Sexual dysfunctions and other psychological issues with aging<br>• Positive living<br>• Address the issues on geriatric syndrome<br>• End of life care, palliative care |
| **MSM/ TGW** | • ART adherence<br>• Importance of maintaining undetectable viral level<br>• Safe sexual practices - risk of transmission through unprotected anal sex, condoms and lubricants, reduce number of partners, importance of monogamous relationship<br>• Sexual and gender related issues<br>• Risk of STI facilitating transmission of HIV<br>• PrEP and PEPSE for partners |
| **FSW** | • Safe sexual practices - condoms<br>• Risk of STI facilitating transmission of HIV<br>• Pregnancy<br>• Family planning services<br>• HIV and law<br>• Pap smear – risk of cervical cancer |
| **IVDU/DU** | • Sterile needle practices, avoid sharing needles<br>• High risk of HIV transmission to others<br>• High risk of Hep B and Hep C transmission<br>• Safe sex |
| **Prisoners** | • ART adherence<br>• Regular follow up<br>• Safe sex<br>• Continuity of care when released from prison |

# 1.5 STI Screening

Dr. D. Mallikarachchi

### Sexual health screening for PLHIV

Sexually transmitted infections (STIs) frequently coexist with HIV and can be asymptomatic. While STIs can increase the risk of HIV transmission, HIV can alter the natural history of STIs and PLHIV are more at risk of complications of STIs. Therefore, screening, diagnosis and treatment of sexually transmitted infections should be offered routinely and regularly as part of comprehensive HIV care among adults and adolescents.

PLHIV under care should have following services

- An assessment of sexual health including detailed sexual history at the initial presentations for care and an update on each visit
- Full STI screen should be offered to all HIV-positive individuals at baseline, as per the sexual history.
- Screening for hepatitis B and C at baseline and refer positive patients for appropriate care
- screen for hepatitis B with hepatitis B virus surface antigen (Hep B S Ag)
- screen for hepatitis C antibody status
- all HCV antibody-positive patients require measurement of HCV viral load (at least twice if initially negative)
- Treatment of STIs and partner notification
- Support to maintain sexual health and safe behaviours including condoms use
- Vaccination against hepatitis B (HBV) if not already immune (Annexure 4)
- Annual offer of sexual health screening
- Cervical cytology in all newly diagnosed women aged 25–65 years if it has not been performed within past 12 months or never in the past and annually thereafter

Most STIs in PLHIV can be managed as in people without HIV. Please refer “Sexually Transmitted Infection Management Guidelines” for details.

link-https://www.aidscontrol.gov.lk/images/pdfs/publications/guidelines/Final-Combined-STI-guidelines.pdf

### Cervical cancer screening

Women with HIV infection are more likely to have infection with HPV 16 or 18 compared to women who are HIV negative. Further they have a 4 to 6 times higher risk of CIN than HIV-negative women. At present, annual cervical smears are recommended for women with HIV after the age of 25 while larger studies are awaited to clarify the optimal smear frequency in this group.

### Reference


- British HIV Association, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV infection 2017

# 1.6 Adherence to ART

Dr. G. Samaraweera

Treatment adherence includes linkage to HIV care services, regular attendance for follow up (retention in care) and adherence to antiretroviral therapy (ART).

Adherence to each step in the continuum of care is critical to achieve optimal clinical outcomes.

## Linkage to care

Patients need to be registered for HIV care services soon after diagnosis.

It is important to minimize the time between the diagnosis and linkage to HIV care services as it may lead to loss to follow up. Linkage efforts should include active referral to HIV care services at diagnosis, appointment reminders, and outreach efforts if needed.

## Retention in care

Poor retention in HIV care is associated with higher mortality. Poor retention is more common in persons who are substance users, have serious mental health problems, have socio-economic issues, engage in jobs that have difficulty in getting leave, prison inmates who do not disclose their HIV status and PLHIV who experience stigma. Low trust in providers and a poor patient-provider relationship are also associated with lower retention in care services.

It is the responsibility of the health care providers to deliver services in a nonjudgmental and problem-solving manner when managing patients with poor adherence.

## Adherence to ART

Adherence to ART 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.

Adherence involves a mutual decision-making process between the PLHIV and the health care provider.

The goal of the ART is to achieve maximal and durable viral suppression. To achieve this goal, there should be successful anti-retroviral therapy which requires high-level adherence (>95%).

Suboptimal adherence to ART may ultimately lead to treatment failure due to the development of drug resistance.

Adherence to ART can be influenced by a number of factors

Patient related factors

Behavioural factors: eg: substance abuse

Social factors: low health literacy, low levels of social support, busy or unstructured daily routines, homelessness, poverty, nondisclosure of HIV serostatus, denial and stigma

Clinical conditions: eg: gastrointestinal problems

Psychological barriers: depression and other mental illnesses, neurocognitive impairment

Prescribed regimen: frequency, pill burden (even if not one pill once daily) and side effects

Patient-provider relationship: Good patient provider relationship is essential to improve adherence. Well trained healthcare staff without stigma and discriminatory attitudes towards patients can greatly support patient adherence.

## Consequences of poor adherence

For the individual

Drug resistance

Treatment failure

More complex treatment regimen

Poor quality of life

From a public health perspective

Transmission of resistant virus

From a health economics perspective

Negative impact on the established cost benefit of ART

Increased morbidity and mortality

## Adherence counselling

The main objectives of ART adherence counselling are, to:

a) Support patients in making informed choices on HIV treatment according to individual needs

b) Assist patient in adopting to drug adherence behaviour

Initial drug adherence counselling is done in two stages.

a) General preparation

b) Treatment initiation

### Stage one: general preparation

A trusting and caring relationship between health care provider and patient have to be established in order to achieve mutual understanding of the treatment goal.

Key areas covered at this stage are:

a) Basic information about HIV infection

b) The goals of therapy - achieving and maintaining viral suppression, which will decrease HIV associated complications and prevent transmission

c) The importance of adherence to ART

d) The potential for the development of drug resistance as a consequence of suboptimal adherence.

e) Explore the potential and actual factors in the patient's life that could influence drug adherence

f) Provision of treatment information including different ART regimens available, their potential benefits, drawbacks and side effects.

**Stage two: treatment initiation**

Ensure that the patient understands the benefits of ART and the possible side effects associated with the treatment.

At the end of the counselling session, he/she should be able to make a self-determined choice to start therapy. Counselling shall cover the following issues:

a) Assessment of the patient's readiness to start treatment

b) Assessment of factors that may influence one's adherence

c) Identification of potential facilitators and barriers to drug adherence – eg: treatment supporter

d) Selection of the ART regimen

e) Development of an individualized medication schedule

f) Discussion on the planned regimen: side effects, what need to be done to minimize the side effects, what needs to be done if he/she develops side effects

g) Assessment to check the patient's understanding of the provided information and the importance of adherence.

h) Psychological support.

i) Agreement is reached with patient on the treatment plan

As the current recommendation is for rapid initiation of ART, stage one and two can be done on the same day or two consecutive days rather than going for several adherence counselling sessions before starting ART.

# 1.7 Family planning for women living with HIV

Dr. C. Jayakody

In HIV care services, discussion of family planning should be initiated during pretest and post-test counselling and needs to be continued in follow up visits as well.

Taking a contraceptive history at every visit is important. Since 2016 the country policy is to start ART for all individuals diagnosed with HIV. Therefore, the efficacy of each contraception method with ART should be considered when selecting the suitable choice for each client.

Most available methods of contraception can be considered in Women Living With HIV (WLWH) and are safe and effective, however, special considerations need to be made in women on or about to commence ART due to the potential risk of drug-drug interactions that may impair contraceptive efficacy, and the WHO clinical stage where potential for infection could be high following procedure.

## Condoms

The effectiveness of male condoms in preventing pregnancy is dependent on correct and consistent use. Women using condoms alone should be encouraged to practice additional FP method. They should be given information on emergency contraception in situations such as condom rupture.

## Combined oral contraceptive pill (COC)

Potential drug interactions with ART need to be considered. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Integrase Strand Transfer Inhibitors/Integrase Inhibitors (INSTIs/INI) are not known to reduce the effectiveness of COC. Protease Inhibitors (PIs) has shown potential interactions with COC and given the lack of clinical data of the effectiveness of COC when used with PIs, use of additional contraceptives method is recommended. EFV is known to reduce the effectiveness of COC when used in combination and therefore, co-administration is not recommended.

## Progestogen-only Contraception (POC)

### a) Progestogen-only Pill (POP) - Cerazette, Mini pill

For women on ART a careful review of drug-drug interactions should be undertaken. NRTIs and INSTIs are not known to interact with POPs while PIs have weak interactions with POPs. Therefore, co-administration of POP could be done with NRTIs, INSTIs and PIs without reducing the effectiveness of POP. EFV is known to reduce the concentrations of many POPs and not recommended to be co-administered.

### b) Progestogen-only Injectable Contraception (POIC) - Depot medroxyprogesterone acetate (DMPA)

POICs work primarily by inhibiting ovulation. Progestogen-only injectables are unlikely to be affected by interactions with ARV drugs and could be co-administered safely.

### c) Progestogen-only sub-dermal implants (IMP)

The implant is a long-acting reversible method of contraception.

- Implanon (etonogestrel)- Effective for up to 3 years
- Jadelle (levonorgestrel) - Effective for up to 5 years

Implants containing progestogen, suppress ovulation and prevent sperm penetration by altering the cervical mucus and prevent implantation by thinning the endometrium.

Efavirenz significantly lowers progestogen levels and decreased contraceptive effectiveness has been observed among women using EFV based ART and implant. Concurrent use of efavirenz and IMP is not recommended.

## Intrauterine Contraception (IUC)

### a) Copper Bearing Intrauterine Devices (Cu-IUD)

Cu-IUDs prevent fertilization and inhibiting implantation and are licensed for 5-10 years use. Initiation of Cu-IUD is WHO Medical Eligibility Criteria (MEC) 3 for women with severe or advanced HIV disease (WHO stage 3 or 4) due to potential higher risk of infection post procedure.

### b) Levonorgestrel intrauterine system (LNG-IUS)

LNG-IUS devices contain different doses of levonorgestrel and are licensed for 3-5 years. It acts via direct local effect on the endometrium, preventing implantation. Initiation of LNG-IUS is included in WHO MEC 3 for women with HIV with severe or advanced HIV clinical disease (WHO stage 3 or 4) due to potential higher risk of infection post procedure.

## Male and female sterilization

These are permanent contraceptive methods and can be offered to people living with HIV who are eligible and on any ART regimen.

## Emergency Contraception

Emergency contraception (EC), with Cu-IUD or oral pills, reduces the risk of unintended pregnancy following any unprotected sexual intercourse (UPSI) or when their usual method of contraception has failed.

### a) Cu-IUD

The Cu-IUD is the most effective form of EC. All women presenting between 0 and 120 hours of UPSI or within 5 days of earliest ovulation (e.g. day 19 in a regular 28-day cycle) should be offered a Cu-IUD as EC, if eligible. Use of a Cu-IUD for EC carries the same contraindications as routine Cu-IUD insertion.

### b) Oral Emergency Contraception

Levonorgestrel EC (1.5mg LNG) is licensed up to 72 hours after UPSI or contraceptive failure. Women using liver enzyme inducing drugs (EFV, NVP) should be advised to use a Cu-IUD as EC. If this is not

acceptable the dose of levonorgestral is doubled. These women should be advised to take two 1.5 mg LNG tablets (3 mg) as a single dose as soon as possible and within 72 hours of UPSI.

# ART for adults and adolescents

02

# 2.1 Antiretroviral drugs

Dr. G. Nanayakkara

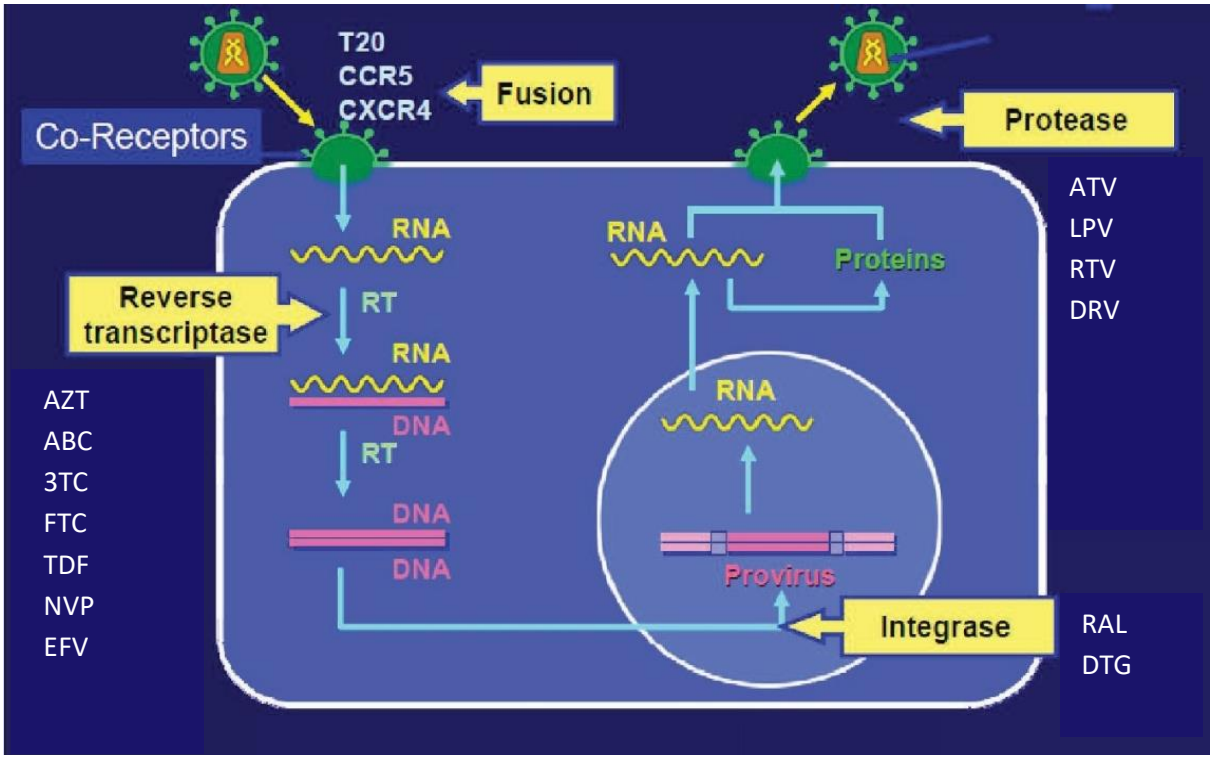
## Classes of Antiretroviral drugs

Depending on the mechanism of action the ARVs are categorized into following classes

1. Nucleoside and nucleotide analogues
    a. Nucleoside reverse transcriptase inhibitors (NRTI)
    b. Nucleotide reverse transcriptase inhibitors (NtRTI)
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)
4. Integrase Strand Transfer Inhibitors (INSTI)
5. Entry Inhibitors
6. Cellular Chemokine Receptor (CCR5) Antagonist
7. Maturation inhibitors

The mechanism of the action of ARV is shown graphically below.

Figure 2 - Targets of antiretroviral drugs



Antiretroviral drugs act on various stages of the HIV life cycle. Hence ARV drugs reduce the destruction of CD4 cells which leads to improvement of the immunity and delay in progression of HIV infection to AIDS.

To understand the mechanism of action of ARV drugs, one needs to understand the basic steps of the viral life cycle. The virus enters into the CD4 (host) cell involving glycoproteins of the viral envelop and receptors of host cells. The process consists of attachment and fusion. ARVs interfering with the viral entry are called entry inhibitors which consist of fusion inhibitors and coreceptor antagonists.

**Entry inhibitors (EI)** act by blocking coreceptors and preventing fusion. It includes drugs like T 20 (Enfuviritide), CCR5 antagonists (Maraviroc) and CXCR4 antagonists. These drugs are not available in Sri Lanka.

After fusion with the host cell membrane, viral particles including the viral RNA and the enzymes (reverse transcriptase, integrase and protease) enter into the cytoplasm of the host cell. The first process inside the host cell is the reverse transcription in which viral DNA is synthesized from viral RNA. The process involves the reverse transcriptase enzyme. The ARVs interfering with this process are called nucleoside and nucleotide reverse transcriptase inhibitors (NRTI/NtRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI).

**Nucleoside/Nucleotide reverse transcriptase inhibitors** inhibit the production of proviral DNA by competing with normal nucleoside/nucleotide. Thus, defective nucleoside/nucleotide analogues are placed in place of normal nucleoside/nucleotide in the DNA fragment thus causing premature viral DNA termination which inhibits viral replication.

Individual ARVs in these groups include Zidovudine (ZDV), Lamivudine(3TC), Tenofovir DF (TDF), Tenofovir AF (TAF) and Abacavir (ABC).

**Non-nucleoside reverse transcriptase inhibitors** act by inhibiting the active site of reverse transcriptase enzyme. Nevirapine (NVP) and Efavirenz (EFV) are some examples of NNRTI.

Viral DNA synthesized in the cytoplasm travels to the nucleus of the host cell, where it integrates with the host DNA to form proviral DNA in the presence of integrase enzyme.

**Integrase inhibitors** are the ARVs that block the process of integration. Some examples of ARV of this class are Raltegravir and Dolutegravir and these two drugs are available in Sri Lanka.

After the integration, the viral DNA transcripts viral RNA. Transcribed RNA is spliced in preparation for translation of viral proteins. Viral proteins are first manufactured as immature polypeptides which are processed into their functional forms by the enzyme protease.

**Protease inhibitors (PI)** inhibit the action of protease enzyme. Examples of protease inhibitors (PI) are Lopinavir, Ritonavir, Atazanavir, Darunavir etc. Boosted PIs (combination of two types of PI) increase the effectiveness, stability of ARV and minimize side effects. Lopinavir boosted with ritonavir (LPV/r), Atazanavir boosted with ritonavir (ATV/r) and Darunavir boosted with ritonavir (Dar/r) are some of the boosted PIs available in Sri Lanka.

**Booster drugs** are used to 'boost' the effects of protease inhibitors. Adding a small dose of a booster drug to an antiretroviral drug, slows down the hepatic metabolism of the primary drug, which maintains the drug concentration in plasma at higher levels for longer period. The

prescribed dose of the primary drug would be ineffective without the boosting agent. Ritonavir and Cobicistat are used as booster drugs and Ritonavir is available in Sri Lanka.

The viral RNA together with immature viral polypeptides are assembled into immature viral particles. These particles eventually leave the infected cell by a process called budding. During budding viral proteins and viral particles are rearranged into mature viruses.

There are some ARV inhibiting the process of maturation and are called **maturation inhibitors**. These ARVs are not available in Sri Lanka.

Table 2.1. Commonly used antiretroviral drugs

| **Classes of ARV Drugs** | | | |
|---|---|---|---|
| **Nucleoside reverse Transcriptase inhibitors (NRTI)** | **Non-nucleoside reverse transcriptase inhibitors (NNRTI)** | **Protease inhibitors (PI)** | **Integrase Inhibitors** |
| Zidovudine (AZT/ZDV)<br>Abacavir (ABC)<br>Lamivudine (3TC)<br>Emtricitabine (FTC) | Nevirapine (NVP)<br>Efavirenz(EFV)<br>*Etravirine<br>*Delveridine | Lopinavir(LPV)<br>Ritonavir (RTV)<br>Atazanavir (ATV)<br>Darunavir (DRV)<br>*Foseamprenavir (FPV)<br>*Amprenavir (APV) | Raltegravir (RAL)<br>Doultagravir (DTG)<br>*Bictegravir |
| **Nucleotide reverse transcriptase inhibitors (NtRTI)** | **Fusion inhibitors (FI)** | **CCR5 Entry Inhibitors** | |
| Tenofovir disoproxil fumarate(TDF)<br>*Tenofovir Alafenamide (TAF) | *Enfuviritide (T-20) | *Maraviroc | |

* currently not available in the country.

The details of individual ARV are given in Annexure 5

# 2.2 First line ART regimen

Dr. J. Ranatunga

### Initiation of ART *

Section revised in 2021 interim update

Rapid ART initiation[a,b] should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment

ART initiation should be offered on the same day to people who are ready to start.

[a] Rapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.
[b] See Table 2.2 for clinical considerations for individuals being evaluated for rapid ART initiation.

Table 2.2. Summary table for the timing of ART initiation among people living with HIV

| Population or clinical status | Timing of ART initiation |
|---|---|
| Adults, adolescents and children living with HIV with no signs and symptoms of TB | Rapid ART initiation on the same day should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment. |
| Adults, adolescents and children living with HIV with suspected TB | Rapid ART initiation should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment and to people living with HIV with signs and symptoms suggesting TB. Except for central nervous system disease (meningitis), initiate ART while rapidly investigating for TB, with close follow-up within seven days to initiate TB treatment if TB is confirmed. |
| Adults, adolescents and children being treated for HIV-associated TB | ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV. |
| Adults, adolescents and children being treated for HIV-associated TB meningitis (either clinically or with a confirmed laboratory test) | ART should be delayed at least four weeks (and initiated within eight weeks) after treatment for TB meningitis is initiated. Corticosteroids should be considered adjuvant treatment for TB meningitis. |
| People living with HIV who are already diagnosed with TB but not receiving ART or treatment for TB | TB treatment should be initiated first, followed by ART as soon as possible within the first two weeks of treatment. |
| People living with HIV with cryptococcal meningitis | Immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred by 4–6 weeks from the initiation of antifungal treatment. Thus, ART should be initiated between 4–6 weeks after undergoing antifungal treatment. |

| | |
|---|---|
| People living with HIV with histoplasmosis infection | ART should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven. |

### First-line ART regimens

Dolutegravir (DTG) in combination with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone is recommended as the preferred first-line regimen for people living with HIV, initiating ART. This recommendation is applicable to adults and adolescents.

Table 2.3. First line ART regimens for adults and adolescents

| Population | Preferred ART | Alternative ART | Special situations |
|---|---|---|---|
| **Adults and adolescents including women in childbearing age not on contraception and/or trying to conceive** | • TDF + 3TC (or FTC) + DTG[a] | • TDF + 3TC (or FTC) + EFV (600mg/400 mg) | • ABC[b] + 3TC + DTG<br>• AZT + 3TC + EFV (600 mg)<br>• TDF + 3TC (or FTC) + LPV/ATV/DRV/r<br>• TDF + 3TC (or FTC) + RAL<br>• TAF[c] + 3TC (or FTC) + DTG |
| **Other combinations (ref)** | | | • DTG + 3TC[d]<br>• ATV/DRV/r + 3TCd |

[a] Effective contraception should be offered to adult women and adolescent girls of child bearing age due to the potential increase in the risk of neural tube defects at conception and until the end of the first trimester. WHO recommends to give informed choice to women of child bearing age group about benefits vs small risk with DTG. If women identify pregnancy after first trimester, DTG should be initiated or continued for the duration of pregnancy.

[b] ABC - Presence of HLA-B 5701 gene indicate higher risk for hypersensitivity. Irrespective of the viral load, ABC can be given in combination with DTG.

[c] TAF may be considered for people with established osteoporosis and/or impaired kidney function.

[d] Dual therapy may be considered in special situations except for individuals with HIV viral load >500,000 copies/ml and HBV coinfection.

**Reference**


- WHO Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017
- WHO Interim guidelines, updated recommendations on first line and second line antiretroviral regimens and post exposure prophylaxis and recommendations on early infant diagnosis of HIV December 2019
- WHO policy brief update of recommendations on first and second line antiretroviral regimens July 2019

- Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection June 2016

# 2.2.1. ART initiation in advanced HIV disease

Dr. A Azran

## Definition of advanced HIV disease

Any adult, adolescent or child over 5 years presenting with either WHO clinical stage 3 or 4 event or CD4 cell count <200cells/µl.

All children younger than 5 years old.

Initiation of ART in advanced HIV disease should be based on following factors.

1. Presence of opportunistic infection (OI) or malignancy especially involving the central nervous system.
2. Concurrent non AIDS related morbidities
3. Factors affecting pharmacodynamics of drugs such as body weight, poor intake, mal-absorption.
4. Drug-drug interactions and toxicities.
5. Risk of IRIS and increased mortality.

## When to start ART in advanced HIV disease

Individuals with AIDS defining infections, and/or with a serious bacterial infection and a CD4 cell count <200 cells/µl, should start ART within 7 days of initiation of specific antimicrobial chemotherapy. However, ART initiation is delayed in certain instances.

Timing of ART in severe cases is upon physician discretion depending on available resources. Following factors may need to be considered prior to starting ART.

1. CD4 cell count at the time of the diagnosis of OI.
2. Involvement of brain and meninges
3. Availability of specific treatment for OIs

### Tuberculosis (TB)*

*Section revised in 2021 interim update

Adults, adolescents and children being treated for HIV-associated TB (including multi drug resistant TB), except TB meningitis should start ART as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count.

For PLHIV with TB meningitis, ART should be delayed at least four weeks (and initiated within eight weeks) after treatment for TB meningitis is initiated. Corticosteroids should be considered adjuvant treatment for TB meningitis.

### Cryptococcal meningitis*

*Section revised in 2021 interim update

Rapid ART initiation is contraindicated in PLHIV with Cryptococcal meningitis. ART initiation should be deferred until evidence of clinical response to antifungal therapy and after 4 weeks of induction and consolidation regime of treatment with amphotericin B+ flucytosine/flucanazole or after 4-6 weeks of treatment with high dose fluconazole induction and consolidation regime.

In an adult with CD count <100 cells/ul, if cryptococcal antigen is negative and no clinical symptoms and signs of cryptococcal meningitis, ART can be initiated

### CMV

ART can be started within 2 weeks after commencing anti-CMV therapy for retinitis or other end organ disease.

### Other OIs

ART can be started 2 weeks after commencing specific therapy for OIs.

## Prophylaxis for Opportunistic Infections

Table 2.4. Prophylaxis for opportunistic infections

| Disease | Indication | Preferred regimen | Alternative regimen |
|---|---|---|---|
| **PJP** | Primary Prophylaxis:<br>CD4 count <350 cells/mm3<br><br>Discontinuing Primary Prophylaxis:<br>• on ART for at least one year, without any new WHO clinical stage 2, 3 or 4 events with CD4 count >350 cells/mm3 and with viral load suppression (ART guide NSACP 2016) | Preferred Therapy:<br>• TMP-SMX, 1 DS PO daily<br>or<br>• TMP-SMX, 2 SS PO daily | • TMP-SMX 1 DS PO three times weekly<br>or<br>• Dapsone 100 mg PO daily or 50 mg PO BID<br>or<br>• Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly<br>or<br>• (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly<br>or<br>• Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month<br>or<br>• Atovaquone 1500 mg PO daily with food |

| | | | |
|---|---|---|---|
| | | | or<br>• (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily with food |
| **Toxoplasmosis** | Primary Prophylaxis:<br>• Toxoplasma IgG positive patients with CD4 count <100 cells/mm3<br>Discontinuing Primary Prophylaxis:<br>• CD4 count >200 cells/mm3 for >3 months in response to ART or<br>• Can consider if CD4 count is 100-200 cells/mm3 and HIV RNA levels remain below limits of detection for at least 3-6 months | Preferred Regimen:<br>• TMP-SMX 1 DS PO daily | Alternative Regimens:<br>• TMP-SMX 1 DS PO three times weekly,<br>or<br>• TMP-SMX SS PO daily, or<br>• Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly<br>or<br>• (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly<br>or<br>• Atovaquone 1500 mg PO daily<br>or<br>• (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily |
| **TB** | Primary Prophylaxis:<br>Suggested by the chest physician | • INAH 300 mg PO daily + pyridoxine 25-50 mg PO daily for 6-9 Months | 3HR (INAH+ RIF for 3 months)<br>or<br>4R (RIF for 4 months) |
| **MAC** | Primary Prophylaxis:<br>• CD4 count <50 cells/mm3 after ruling out disseminated MAC disease<br>Discontinuing Primary Prophylaxis:<br>• CD4 count >100 cells/mm3 for ≥3 months in response to ART | Preferred Therapy:<br>• Azithromycin 1200 mg PO once weekly<br>or<br>• Clarithromycin 500 mg PO BID,<br>or<br>• Azithromycin 600 mg PO twice weekly | • Rifabutin 300 mg PO daily |

| | | | |
|---|---|---|---|
| **Cryptococcosis** | Primary Prophylaxis<br>For localized non-meningeal disease, or in patients with isolated serum CrAg positivity (where cryptococcal meningitis has been excluded) | fluconazole 800 mg/day for two weeks, then<br>400mg/day for 8 weeks, and continued maintenance with fluconazole 200 mg/day for one year. | |

**Reference**


- CDC, 2018
- WHO consolidated guidelines on Tuberculosis 2020
- Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection
- Opportunistic infections guideline NSACP -2017

# 2.3 Specific instructions for prescribing ART

Dr. M. Rajapakshe

## TDF/FTC as NRTI backbone

### How to give TDF + FTC + DTG regimen

Tenofovir (TDF) 300 mg daily

Emtricitabine (FTC) 200mg daily

Dolutegravir 50mg daily

TDF 300mg + FTC 200mg is available in fixed dose formulation and Dolutegravir 50mg available as a single tablet.

Take one tablet of TDF+FTC and 50 mg tablet of DTG once daily at a fixed time with or without food. (in the morning or in the night)

TDF+FTC fixed dose tablet can be crushed. But crushing of Dolutegravir tablet is not recommended.

DTG should not be co-administered with cation Magnesium/Aluminium containing antacids, laxatives and multivitamin or calcium/ iron supplements because of the risk of chelation. If combined, those medications should be administered two hours after or six hours before taking DTG.

For individuals receiving anti TB therapy with rifampicin, DTG dose should be adjusted as 50 mg twice daily for the duration of TB treatment and two weeks post TB therapy with close monitoring. No dose adjustment is required with rifabutin. Drug levels of DTG may be reduced when administered with rifapentin.

### How to give TDF + FTC+ EFV regimen

Tenofovir (TDF) 300 mg daily at night

Emtricitabine (FTC) 200mg daily at night

Efavirenz 600 mg daily at night

Tenofovir (TDF) 300 mg + Emtricitabine (FTC) 200mg + Efavirenz 600 mg is available as a fixed drug combination. One tablet in the night, preferably to be taken on an empty stomach at bedtime. If possible 2-3 hours after dinner.

Crushing or splitting tablet is not recommended.

Avoid administration with a high-fat meal because of potential for efavirenz related side effects due to increased absorption.

### How to give TDF+ FTC + ATV/r regimen

Tenofovir (TDF) 300 mg daily

Emtricitabine (FTC) 200mg daily

Atazanavir (ATV) 300mg with Ritonavir (RTV) 100mg daily

TDF 300mg + FTC 200mg is available in a fixed dose tablet. ATV 300mg is available in capsule form and Ritonavir(r)100mg is available as a separate tablet.

Take one tablet of TDF+FTC, one tablet of Ritonavir 100mg and one capsule of ATV 300mg once daily with food (can take in the morning with breakfast or at night with dinner).

TDF+FTC fixed dose tablet can be crushed, and ATV capsule can be opened and dissolve in water but crushing of Ritonavir tablet is not recommended.

### How to give TDF+ FTC + LPV/r regimen

Tenofovir (TDF) 300 mg once daily

Emtricitabine (FTC) 200mg once daily

Lopinavir (LPV) 400mg twice daily

Ritonavir (RTV) 100mg twice daily

TDF+ FTC (300mg/200mg) is available in fixed dose and Lopinavir/Ritonavir (LPV200mg /r50mg) is available as combined tablet.

Take one tablet of TDF+FTC once a day (in the morning/night) with or without food.

Take 2 tablets of LPV/r(200mg/50mg) twice a day (12 hourly) in the morning and in the night with or without food.

TDF+FTC fixed dose tablet can be crushed but crushing of LPV/r tablet is not recommended.

### How to give TDF+ FTC +DRV/r regimen

Tenofovir (TDF) 300 mg daily

Emtricitabine (FTC) 200mg daily

with

Darunavir 800mg with Ritonavir (RTV) 100mg daily or

Darunavir 600mg with Ritonavir (RTV) 100mg twice daily

TDF+ FTC (300mg/200mg) is available in fixed dose and Darunavir (800mg or 600mg) and Ritonavir(100mg) are available as separate tablets.

Take one tablet of TDF+FTC once daily, 600mg tablet of Darunavir and 100mg tablet of Ritonavir twice daily (12 hourly) with food

**or**

Take one tablet of TDF+FTC and 800mg of DRV (if available) and 100mg of ritonavir with food as once daily regimen

TDF+FTC fixed dose tablet and DRV tablets can be crushed. Crushing of Ritonavir tablet is not recommended

### How to give TDF+ FTC + RAL regimen

Tenofovir (TDF) 300 mg daily

Emtricitabine (FTC) 200mg daily

Raltegravir 400mg twice daily

TDF+ FTC(300mg/200mg) is available in fixed dose tablet and Raltegravir 400mg available as a separate tablet.

Take one tablet of TDF+FTC once daily and 400mg tablet of RAL twice daily (12 hourly) in the morning and in the night with or without food.

TDF+FTC fixed dose tablet can be crushed and but crushing of Raltegravir film coated tablet is not recommended.

Antacids with aluminium/ magnesium are contraindicated to use with RAL.

If necessary, calcium, magnesium and iron containing supplements can be given with a four hours gap with raltegravir dose.

For individuals receiving anti TB therapy with rifampicin, RAL dose should be adjusted as 800 mg twice daily with close monitoring. No dose adjustment is required with rifabutin or rifapentin.

## AZT/3TC as NRTI backbone

### How to give AZT+3TC+EFV regimen

Zidovudine (AZT) 300 mg twice a day

Lamivudine (3TC) 150mg twice a day

Efavirenz (EFV) 600mg daily at night

AZT(300mg )/3TC (150mg) is available in fixed dose and EFV 600mg is available as separate tablet.

In the morning - 1 tablet of AZT + 3TC Fixed drug dose can be taken with or without food

In the night - 1 tablet of AZT + 3TC Fixed drug dose with Efavirenz (EFV) 600mg tablet (better to take on an empty stomach)

AZT+3TC fixed dose tablet can be crushed but crushing of EFV is not recommended.

Avoid administration with a high-fat meal because of potential for increased absorption.

### How to give AZT+3TC+ATV/r regimen

Zidovudine (AZT) 300 mg twice a day

Lamivudine (3TC) 150mg twice a day

Atazanavir (ATZ) 300mg daily

Ritonavir (RTV) 100mg daily

AZT 300mg /3TC 150mg is available in fixed dose tablet and Ritonavir(r)100mg is available as separate tablet+ . ATV 300mg is available in capsule form.

In the morning - 1 tablet of AZT 300mg + 3TC 150mg fixed dose combination, single tablet of 300mg Atazanavir and one tablet of 100mg ritonavir can be taken with or without food

In the night - 1 tablet of AZT 300mg + 3TC 150mg fixed drug dose tablet with or without food.

AZT+3TC fixed dose tablet can be crushed just before taking tablets if there is difficulty in swallowing. ATV capsule can be opened and dissolve in water but crushing of Ritonavir tablet is not recommended.

## ABC/3TC as NRTI backbone

- Test patients for the HLA-B*5701 allele before starting therapy to predict risk of hypersensitivity reaction. Patients positive for the HLA-B*5701 allele should not be given abacavir.
- Warn adult patients and parents of children about risk of serious, potentially fatal hypersensitivity reactions.

### How to give ABC + 3TC + DTG regimen

Abacavir (ABC) 600 mg daily

Lamivudine (3TC) 300mg daily

Dolutegravir (DTG) 50 mg daily

ABC 600mg + 3TC 300mg + DTG 50mg is available in fixed dose combination but currently not available in Sri Lanka. Therefore, separate tablets of ABC, 3TC and DTG need to be taken.

Take ABC 600mg (2 tablets of 300 mg) and 3TC 300 mg (2 tablets of 150 mg) with 1 tablet of DTG 50mg once daily with or without food.

It can also be taken as ABC 300 mg and 3TC 150 mg twice daily (12 hourly) and DTG 50 mg once daily with or without food.

DTG should not be co-administered with cation magnesium/aluminium containing antacids, laxatives and multivitamin or calcium/ iron supplements because of the risk of chelation. If combined, those medications should be administered two hours after or six hours before taking DTG.

For individuals receiving anti TB therapy with rifampicin, DTG dose should be adjusted as 50 mg twice daily for the duration of TB treatment and two weeks post TB therapy with close monitoring. No dose

adjustment is required with rifabutin. Drug levels of DTG may be reduced when administered with rifapentin.

## TAF/3TC or FTC as NRTI backbone

### How to give TAF + FTC/3TC + DTG regimen

Tenofovir AF(TAF) 25 mg daily

Emtricitabine (FTC) 200mg daily or Lamivudine (3TC) 300mg daily

Dolutegravir 50mg daily

TAF 25mg + FTC 200mg and Dolutegravir 50mg available as single tablets.

Take one tablet of TAF 25mg, 200mg of FTC (or 2 tablets of 3TC 150mg) and 50 mg tablet of DTG once daily (in the morning or in the night) with or without food.

DTG should not be co-administered with cation magnesium/aluminium containing antacids, laxatives and multivitamin or calcium/ iron supplements because of the risk of chelation. If combined, those medications should be administered two hours after or six hours before taking DTG.

For individuals receiving anti TB therapy with rifampicin, DTG dose should be adjusted as 50 mg twice daily for the duration of TB treatment and two weeks post TB therapy with close monitoring. No dose adjustment is required with rifabutin. Drug levels of DTG may be reduced when administered with rifapentine.

# 2.4 Monitoring patients on ART

Dr. L. Siriwardena, Dr. N. Jayasekara

This section will consider monitoring of HIV positive individuals following ART initiation, routine monitoring on ART and monitoring in special circumstances.

**CD4 count**

*Section revised in 2022 interim update

- At baseline
- Patient who are not on ART
  - monitor CD4 every 6 monthly if initial CD4 count is < 500 cells/µl
  - annually of CD4 >500 cells/µl
- Patient who are on ART
  - If baseline CD4 count is more than >350 and virally supressed, no further monitoring of CD4 is needed.
  - If baseline CD4 count is < 350 cells/µl, repeat CD4 in 6 months.
  - If 6 months CD4 count is;
    - >350, further CD4 monitoring could be stopped if patient is virally supressed on ART with good adherence.
    - between 200-350 and virally supressed monitor CD4 count annually. If vitally supressed for more than 2 years with good adherence CD4 monitoring could be stopped.
    - < 200 monitor CD4 every 6 monthly
- If patient has poor adherence, symptoms or signs of OI, defaulted from care, CD4 monitoring could be restated as required

**Viral load**

- At baseline
- At 12 weeks (when required)
- At 6 months
- At 12 months
- If virally suppressed, annually thereafter

**Monitoring of older patients:**

All medication history (prescribed and non-prescribed) should be reviewed and documented at each visit.

Fragility fracture risk assessment in all patients over 50 years at baseline and in every 3 years (annexure 2.)

Annual cardiovascular risk assessment in all patients over 40 years (annexure 3)

Table 2.5. Monitoring of patients on ART

| | Baseline | 2 weeks | 4 weeks | 8weeks | 12weeks | 6 monthly | Annually |
|---|---|---|---|---|---|---|---|
| **FBC (Hb & WBC/DC)** | ✓ | ✓ (If on AZT) | ✓ (If on AZT) | | ✓ | ✓ | |
| **Lipid profile** | ✓ | | ✓ | When required | | On PI/ NNRTI +risk | ✓ |
| **FBS** | ✓ | | | | | | ✓ |
| **LFT** | ✓ | ✓ | ✓ | | ✓ | ✓ | |
| **UFR (Dipstick)** | ✓ | | | | | ✓ | |
| **Serum creatinine** | ✓ | ✓ | ✓ When required /on TDF | | | ✓ | |
| **Blood urea** | ✓ | | | | | | |
| **Serum electrolytes** | ✓ | | | When required | | | |
| **Hepatitis B s Ag** | ✓ | | | | | | |
| **HCV antibody** | ✓ | | | When required | | | |
| **Pregnancy test** | | | | When required | | | |
| **Toxoplasma Ab** | ✓ | | | When required | | | |
| **CMV Ab** | ✓ | | | When required | | | |
| **STI screening** | ✓ | | | When required | | | ✓ |
| **VDRL** | ✓ | | | | | | ✓ |
| **Pap Smear** | ✓ | | | | | | ✓ |
| ***CD4 cell count** | ✓ | | | | | ✓ | ✓ |
| ****Viral load** | ✓ | | | | ✓ | ✓ | ✓ |

**Reference**


- (Reference: BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals (2019 interim update)

# 2.5 Drug toxicities and side effects

Dr. P. Weerasinghe

Adverse effects were the most common reason for drug discontinuation, substitution and poor adherence in the past era. However, newer ARV drugs show lesser adverse effects compared to past. As lifelong ART is now recommended for all, detection of drug related toxicities are very important to minimize adverse effects.

ART associated toxicities can range from severe life-threatening acute reactions to chronic insidious toxicities. In the case of severe adverse effects immediate discontinuation of all ART is recommended. When restarting ART, caution should be taken to avoid ARV drugs with overlapping toxicities. Less severe toxicities can be managed symptomatically or with substitution of specific ARV drug.

### Toxicities and adverse effects of ARV drugs

Toxicities and adverse effects that are considered as life threatening medical emergencies (severe effects) are marked in bold, adverse effects that expected by more than 10 % of treated patients (frequent effects) are marked in italics while neither severe nor frequent effects are in normal font.

Table 2.6. Toxicities and adverse effects of ARV drugs

| System / Involvement | | Type of Toxicity or adverse effects and Agents (ARV) |
|---|---|---|
| | **Hypersensitivity reaction**<br>(excluding rash alone or Steven-Johnson Syndrome ) | **ABC associated HSR (Hypersensitivity reaction)**<br>Median onset 9 days after ABC, 90 % develop within 6 weeks<br>Symptoms: fever, rash, malaise, nausea, vomiting, diarrhoea, headache , myalgia, arthralgia, dyspnoea and respiratory symptoms<br>**NVP: Hypersensitivity syndrome of hepatotoxicity and rash**<br>Symptoms: fatigue, myalgia, arthralgia, blisters, oral lesions, conjunctivitis, facial oedema,<br>**RAL: reported in concomitant use of drugs causing hypersensitivity reactions.**<br>**DTG: less than 1 % of patients** |
| **Skin manifestations** | Steven Johnson Syndrome / Toxic Epidermal Necrolysis | **NVP > EFV, ETR (etravirine), RPV (rilpivirine)**<br>Some reported cases for DRV /r, LPV /r, ATV/r, RAL |
| | Rash | All NNRTIs<br>ATV, DRV, LPV/r<br>All INSTIs |

| | | |
|---|---|---|
| | | DRV contains sulphonamide moiety and should be used with caution in patients with sulfonamide allergy. Most patients with sulfonamide allergy can tolerate DRV well. |
| | Pigmentation | FTC - Hyperpigmentation<br>AZT -Nail, skin and mucosal pigmentation |
| **Metabolic manifestations / changes** | Lactic acidosis | **Reported with AZT,**<br>But not common with ABC, 3TC, FTC, TAF, TDF |
| | Lipoatrophy<br>Loss of subcutaneous fat in the limbs, face and buttocks | Associated with exposure to *AZT*<br>But not with ABC, 3TC, FTC, TDF, TAF |
| | Lipohypertrophy<br>Accumulation of visceral, truncal, dorsocervical and breast fat | EFV, PI and RAL containing regimens |
| | Dyslipidaemia<br>Hypertriglyceridaemia with or without elevated LDL level | *RTV* or COBI boosted<br>EFV<br>Elevated TG and LDL levels may see with *LPV/r* than with other RTV boosted PIs<br>Improvement seen with switch to ATV /r |
| | Insulin resistance and Diabetes | LPV /r but not with boosted ATV or DRV |
| | Weight gain | Weight gain has been associated with the initiation of ART and subsequent viral suppression.<br>Greater with INSTIs than with other drug classes. *DTG>RAL*<br>Weight gain is more **with TAF** compared to TDF |
| **Neurological manifestations** | Neuropsychatric events | *EFV related neuropsychiatric events*<br>*Insomnia, somnolence, dizziness, Impaired concentration, depression, psychosis,* **suicidality (Suicidal thoughts, plans and attempts)**<br>(ataxia, encephalopathy reported months to years after treatment and considered as delayed onset neurotoxicities)<br>RPV: Depression, sleep disturbances, **suicidality.**<br>*INSTIs-Insomnia, depression and suicidal attempts have been reported with INSTI's use in patients with pre-existing psychiatric conditions.* |
| **Renal Manifest** | Acute / chronic renal disease | TDF: Chronic kidney disease, *Acute kidney injury, Fanconi syndrome* |

| | | |
|---|---|---|
| | | If baseline eGFR is < 60 ml / min/1.73m$^2$, should not start TDF.<br>TAF: less impact on renal biomarkers. However, currently approved only for patient with eGFR > 30 ml / min |
| | Nephrolithisis<br>Stone or crystal formation | ATV |
| | Increase in serum creatinine | RPV, DTG, COBI Inhibit creatinine secretion without reducing renal glomerular function<br>*EVG /c ( Elvitegravir / cobicistat )* |
| **Cardiac Manifestations** | Conduction defects | ATV/r: Electrocardiographic abnormalities ( PR and QRS interval prolongation )<br>LPV /r: PR prolongation<br>RPV, EFV: QT prolongation |
| | Myocardial infarction | ABC: has been associated with increased cardiovascular events in some observational studies |
| | | Boosted DRV, LPV /r<br>Associated with cardiovascular events in some studies |
| **Hepatic Manifestations** | Liver steatosis | AZT - Hepatic steatosis |
| | hepatotoxity | NVP, RPV, EFV, LPV /r, DRV /r |
| | | TDF: hepatomegaly with steatosis |
| | Indirect hyperbilirubinaemia | *ATV: Indirect hyperbilirubinaemia*<br>*Can cause clinical jaundice* without concomitant hepatic transaminase elevation |
| | **Haematological** | AZT associated severe anaemia and neutropaenia |
| | **Bone mineral density changes** | Decline in bone mineral density has been observed upon initiation of some ART regimens<br>TDF associated low BMD, Osteomalacia, *Increased fracture risk* |
| | **GI related** | ABC - Nausea & diarrhoea<br>AZT - Nausea<br>*PI - Nausea & diarrhoea, LPV/r is known to cause diarrhoea more than ATV/r or DRV /r*<br>*RTV - Nausea & diarrhoea*<br>RAL - Nausea<br>DTG - Nausea<br>EVG /c – **Nausea** & diarrhoea |

| | | |
|---|---|---|
| | **Gynaecomastia** | EFV |
| | **Myopathy** | AZT induced myopathy, **rhabdomyolysis**<br>RAL, DTG - Increase CPK levels, **rhabdomyolysis**, myositis reported |

### Monitoring and management of ARV toxicities

There are two main approaches for monitoring of the safety and toxicity of ART

1. Symptoms direct approach
2. Specific laboratory monitoring: for patients with specific high-risk factors using certain drugs

Some ARV toxicities could be anticipated by carefully evaluating risk factors and monitoring those patients accordingly.

Gastro-intestinal toxicities are the commonest adverse effects experienced within hours or days after starting ART. However, many of these symptoms are usually self-limiting and there is no need to discontinue ART. Mild to moderate side effects can be managed with symptomatic treatment.

Table 2.7. Key types of toxicities, associated risk factors and suggested management

| ARV drug | Risk factors | Suggested Monitoring and Management |
|---|---|---|
| **TDF related renal toxicity** | • Underlying renal disease<br>• Age >40 years<br>• BMI <18.5 (or body weight <50 kg)<br>• Untreated diabetes mellitus<br>• Untreated hypertension<br>• Concomitant use of a boosted PI or nephrotoxic drugs (NSAID, Ledipsavir) | • Serum creatinine, eGFR is recommended in baseline and follow up<br>Periodic monitoring of:<br>• Urine Albumin Creatinine Ratio<br>• Urine Protein creatinine ratio<br>• Urine sugar to detect tubular and glomerular dysfunction<br>Children on TDF:<br>• Growth monitoring is very important<br>• Correct dosing is extremely important in children to minimize toxicity<br>If TDF related renal disease is evident - Substitution with AZT or ABC or TAF. |
| **TDF related decrease in bone mineral density** | • History of osteomalacia (in adult) rickets ( in children)<br>• Pathological fractures<br>• Osteopaenia<br>• Bone mineral density loss<br>• Vit D deficiency | • Switching from TDF to alternative ART regimen has been shown to increase BMD<br>• Serum phosphate and Dual energy X -Ray absorptiometry testing (DEXA scan) are helpful in identifying early bony changes with TDF |
| **AZT related haematological toxicity** | • CD4 count of <200 cells/mm3<br>• Anaemia at baseline | • Monitor Hb after 1 month of initiation, then at least every 3 monthly<br>• if severe anaemia -blood transfusion |

| | | |
|---|---|---|
| | | • Should not start patients with Hb < 7 g/dl<br>• replace by an ARV with minimal or no bone marrow toxicity (eg. ABC or TDF) |
| **AZT related lactic acidosis** | • BMI > 25 (or body weight > 75kg)<br>• Prolong exposure to nucleoside analogues | • Discontinue ART and give supportive treatment. After clinical resolution, resume ART, replacing the offending NRTI. ABC, TDF and 3TC are less likely to cause this type of adverse effect. |
| **EFV related CNS toxicity** | • Psychiatric illness<br>• Genetic factors<br>• Concomitant use of drugs with neuropsychiatric effects | • Some symptoms may subside after 2 - 4 weeks, can persist up to months in some cases<br>• Bedtime dose<br>• Taking without food may reduce the symptoms<br>• Consider using 400 mg /d dose<br>• Persistent and severe symptoms need substitution |
| **Hepatotoxicity related to RPV, EFV, LPV /r, DRV /r** | • HCV and HBV coinfection<br>• Concomitant use of hepatotoxic drugs<br>• Underlying liver disease | • If ALT >5-fold the basal level, discontinue ART and monitor. After resolution, replace the drug most likely to be associated with another one |
| **ABC related toxicities** | • Presence of HLA-B*5701 allele | • Do not use ABC in the presence of HLA B 5701 allele<br>• Never re-challenge as it can cause severe and potentially life-threatening reaction even if HLA B 5701 negative |
| **ATV/r related ECG changes** | • Patients with pre-excising conduction system disease<br>• Concurrent use of other drugs which may prolong the PR or QRS intervals<br>• Congenital long QT syndrome<br>• Hypokalaemia | • Use with caution. |
| **ATV/r related Hyper bilirubenimia** | • Presence of uridine diphosphate (UDP) glucoronyl transferase 1A1*28 allele | • This is a benign condition but potentially stigmatizing<br>• Consider substitution if adherence is compromised |

| | | |
|---|---|---|
| **ATV related Nephrolithiasis** | • History of nephrolithiasis | • Adequate hydration may reduce the risk<br>• Substitute with suitable drug |
| **DRV/r related skin rash** | • Sulphur allergy | • DRV contains sulphonamide moiety and should be used with caution in patients with sulfonamide allergy. Most patients with sulfonamide allergy can well tolerate DRV<br>• ARV substitution if very severe |
| **RAL related myopathy and rhabdomyolysis** | • Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis including statins. | • Substitute |

Table 2.8. Laboratory indications to change ARVs due to toxicity

| **Laboratory indications to change ARVs due to toxicity** | | |
|---|---|---|
| **Haemotology** | Haemoglobin | Less than 7.0 g/dl |
| | Neutrophil count | Less than 750/mm$^3$ |
| | Platelets | Less than 50,000mm$^3$ |
| **Blood Chemistries** | Glucose (fasting non diabetics) | Less than 39 mg/dl or more than 251mg/l |
| | AST (SGOT) | More than 5 x upper limit of normal |
| | ALT (SGPT) | More than 5 x upper limit of normal |
| | Alkaline phosphatase | More than 5 x upper limit of normal |
| | Bilirubin | More than 2.5 x upper limit of normal |
| | Amylase, lipase | More than 2 x upper limit of normal |

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- Guidelines for use of Antiretrovirals in adults. AIDS info 2020
- Clinical Guidelines: Antiretroviral Therapy WHO 2016
- Clinical Guidelines: Antiretroviral Therapy WHO 2010

# 2.6 Key ARV drug interactions

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### Key ARV drug Interactions

Pharmacokinetic (PK) drug-drug interactions between antiretroviral (ARV) drugs and concomitant medications are common and occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. These PK interactions may result in increase or decrease in exposure of ARV drug or the other drug. Changes in drug exposures could lead to reduced efficacy and/or increased drug related toxicities. Prescribers should be aware of the drugs that the patients are on including herbal remedies, dietary supplements and other alternative medicines before initiating ARV. Thorough review of concomitant medications during each clinic visit is mandatory for optimal patient management in order to avoid undesired potential drug interactions and to take necessary actions when drug interactions are unavoidable.

### 1. Anti-tuberculosis drugs

As tuberculosis is the commonest co-infection among PLHIV, anti-tuberculosis drugs are commonly used along with ARVs. A key contraindicated drug combination is rifampicin with Protease Inhibitors (PIs). When patients with HIV/TB co-infection have boosted PIs in their ARV regimen, rifampicin need to be substituted with rifabutin. If rifabutin is not available, LPV/r can be used for the duration of TB treatment by doubling the standard dose of LPV/r or increasing the dose of RTV. For children, using triple NRTI (AZT+3TC+ABC) regimens also could be considered.

Rifampicin is also known to reduce plasma concentration of DTG significantly and increasing the dose of DTG to twice-daily schedule may be necessary.

There is limited information on drug interactions between ARV and new anti-tuberculosis drugs such as bedaquiline and delamenid, used extensively in drug-resistant or multi drug-resistant (XDR/MDR) TB. As bedaquiline is primarily metabolized by CYP3A4, concomitant use of EFV and PIs can interfere with drug concentration.

### 2. Hormonal contraceptives

There may be drug interactions between some NNRTIs and RTV-boosted PIs with hormonal contraceptives, which can reduce the effectiveness of both the hormonal contraceptive and ARVs. There are generally fewer interactions of hormonal contraceptives with NRTIs and newer NNRTIs such as doravarine and rilpivirine.

The contraceptive efficacy of injectable formulations of either IM or SC depot medroxyprogesterone acetate (DMPA) is unaffected by ARVs and could be used without restrictions. There is a potential for reduced efficacy of long-acting progestogen only implants, combined oral contraceptives and progesterone only pills when used in patients on EFV.

### 3. Anti-fungals

Itraconazole and ketoconazole are often used for fungal infections. Studies have shown that NVP may decrease the concentrations of these antifungal agents to sub therapeutic levels. Alternative

antifungals such as fluconazole could be used to ensure adequate treatment of fungal infections among these PLHIVs

Due to the significant interaction between EFV and ketoconazole/ itraconazole it is advised to use an alternative antifungal such as fluconazole.

Protease inhibitors interact with most of the antifungals, except amphotericin B, fluconazole, miconazole and nystatin and flucytosine.

### 4. Statins

BHIVA recommends CVD risk minimization for people with 10-year cardiovascular risk exceeding 10%, calculated from QRISK2. Boosted PIs may lead to increased concentrations of simvastatin and lovastatin which may increase the risk of serious events such as myopathy, including rhabdomyolysis, hence contraindicated. Alternative lipid lowering drugs should be used to prevent these toxicities.

### 5. Antihistamines

Concomitant use of boosted PIs and NNRTIs with some antihistamine agents (such as astemizole and terfenadine) has been associated with severe and life-threatening reactions, such as cardiac arrhythmia. Alternative antihistamine agents include loratidine and cetirizine.

### 6. Other interactions

I. DTG should not be co-administered with cation Magnisium/Aluminium containing antacids, laxatives and multivitamin or calcium/ iron supplements because of the risk of chelation. If combined, DTG should be administered two hours before or six hours after taking medications containing polyvalent cations.

II. DTG should not be co-administered with the drugs such as carbamazepine, phenobarbital or phenytoin which reduced DTG exposure.

III. Co-administration of metformin and DTG increases metformin concentration significantly. A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin in order to maintain glycaemic control. It is recommended to limit the total daily dose of metformin to 1000 mg when co-administering with DTG. Monitoring renal function during co-administration and monitoring blood glucose when starting and stopping co-administration is recommended. As metformin is eliminated renally, patients with moderate renal impairment may be at increased risk for lactic acidosis due to increased metformin concentrations.

IV. Atazanavir/ritonavir (ATV/r) should not be co-administered with proton pump inhibitors (PPI) as this will lead to reduction of blood concentration of ATV significantly. If co-administration is unavoidable, close clinical monitoring is recommended and doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded and must be taken approximately 12 hours prior to ATV/r.

V. Boosted PIs which are potent CYP3A4 inhibitors should not be used simultaneously with domperidone. As domperidone is metabolized by CYP3A4, inhibitors of CYP3A4 could potentially increase domperidone exposure and increase the risk of cardiac adverse effects (QT interval prolongation).

**Raltegravir-with Strong inducers of drug-metabolizing enzymes (eg, Rifampicin, carbamazepine, phenobarbital, phenytoin)**

Given that raltegravir is metabolized primarily via Uridine diphosphate Glucuronyl Transferase 1A1 (UGT1A1), caution should be used when co-administering raltegravir with strong inducers of UGT1A1 (e.g. rifampicin). Rifampicin reduces plasma levels of raltegravir. If co-administration with rifampicin is unavoidable, doubling of the dose (800 mg twice daily) of raltegravir can be considered in adults. There are no data to guide co-administration of raltegravir with rifampicin in patients below 18 years of age.

The impact of other strong inducers of drug metabolizing enzymes, such as carbamazepine, phenytoin and phenobarbital, on UGT1A1 is unknown. If coadministration with any of these drugs is unavoidable, raltegravir should be used as 400 mg twice daily regimen with close monitoring of antiretroviral response.

Co-administration of raltegravir with antacids containing divalent metal cations such as magnesium, calcium and aluminium may reduce raltegravir absorption by chelation, resulting in a decrease of raltegravir plasma levels. Therefore, co-administration of raltegravir with aluminium and/or magnesium, or calcium containing medicines is not recommended. However, if coadministration is unavoidable, administration of raltegravir should be separated with a gap of at least 4 hours.

Table 2.9. Key ARV related drug interactions and management*

*Section revised in 2021 interim update

| ARV drug | Key interactions | Suggested management |
|---|---|---|
| **AZT** | Ribavirin and pegylated-interferon alpha-2a | Substitute AZT with TDF |
| **Boosted PI (ATV/r, DRV/r, LPV/r)** | Rifampicin | Substitute rifampicin with rifabutin<br>Adjust the dose of LPV/r or substitute with three NRTIs (for children) |
| | Halofantrine and lumefantrine | Use an alternative antimalarial agent |
| | Lovastatin and simvastatin | Use an alternative cholesterol-lowering agent |
| | Hormonal contraceptives | Use alternative or additional contraceptive methods |
| | Methadone and buprenorphine | Adjust methadone and buprenorphine doses as appropriate |
| | Astemizole and terfenadine | Use alternative antihistamine agent |
| | TDF | Monitor renal function |
| | Simeprevir | Use alternative DAA |
| | Ombitasvir + paritaprevir + ritonavir plus dasabuvir | Use alternative DAA |

| | | |
|---|---|---|
| **DTG** | Carbamazepine, phenobarbital and phenytoin | Use alternative anticonvulsant agent |
| | Polyvalent cation products containing Mg, Al, Fe, Ca and Zn | Use DTG at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: Fe-, Ca-, Mg- or Zn-multivitamin supplements; mineral supplements, cation-containing laxatives and Al-, Ca- or Mg-containing antiacids. Monitor for virological efficacy |
| **EFV** | Amodiaquine | Use an alternative antimalarial agent |
| | Methadone | Adjust the methadone dose as appropriate |
| | Hormonal contraceptives | Use alternative or additional contraceptive methods to prevent HIV transmission and unintended pregnancies, as EFV may lower efficacy of some long-acting hormonal contraceptives |
| | Astemizole and terfenadine | Use an alternative antihistamine agent |
| | Simeprevir | Use alternative DAA |
| | Ombitasvir + paritaprevir + ritonavir plus dasabuvir | Use alternative DAA |
| **NVP** | Rifampicin | Substitute NVP with EFV |
| | Methadone | Adjust the methadone dose as appropriate |
| | Astemizole and terfenadine | Use alternative antihistamine agent |
| | Itraconazole and ketoconazole | Use an alternative antifungal agent |
| | Simeprevir | Use alternative DAA |
| | Ombitasvir + paritaprevir + ritonavir plus dasabuvir | Use alternative DAA |

AZT zidovudine, ATV atazanavir, DAA direct-acting antiviral (agent), DRV darunavir, DTG dolutegravir, EFV efavirenz, LPV lopinavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r ritonavir, TDF tenofovir.

For more information please visit - www.hiv- druginteractions.org and www.hep-druginteractions.org.

**References**


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# 2.7 Substitution of ART

Dr. V. Dharmakulasinghe

## Switching ARV drugs due to adverse effects

Some patients experience treatment-limiting toxicities associated with ART. In these cases, ART must be modified. ART associated adverse events can range from acute and potentially life-threatening to chronic and insidious. Serious life-threatening events (e.g. hypersensitivity reaction due to ABC, severe hepatotoxicity, or severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen later, without overlapping toxicity.

Toxicities that are not life-threatening (e.g. urolithiasis with ATV or renal tubulopathy with TDF) can usually be managed by substituting another ARV agent for the presumed causative agent without interrupting ART.

Other chronic, non–life-threatening adverse events (e.g. dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the adverse event with pharmacological or nonpharmacological interventions. Management strategies must be individualized for each patient.

Switching a patient from an effective ARV agent or regimen to a new agent or regimen must be done carefully and only when the potential benefits of the change outweigh the potential risks of altering treatment. The fundamental principle of regimen switching is to maintain viral suppression. It is critical that providers review the following information before implementing any treatment switch:

- Patient's medical and complete ARV history
- Prior virologic responses to ART (if available)
- HLA-B* 5701 status (if ABC is being considered)
- Comorbidities
- The patient's pregnancy status, ability to use effective contraceptives, and desire for pregnancy
- Hepatitis B virus (HBV) status. Patients with evidence of chronic HBV infection should not discontinue ARVs active against HBV (e.g. TDF, tenofovir alafenamide, lamivudine, emtricitabine)
- Adherence history
- Prior intolerances to any ARVs
- Concomitant medications and supplements, considering any potential drug interactions with ARVs.

The patient's willingness to accept dosing schedule must also be assessed.

Table 2.10: Major ART - associated adverse events and the options for appropriate switches between agents in an ARV regimen.

| Adverse Event | ARV Agent(s) or Drug Class | |
|---|---|---|
| | Switch from | Switch to |
| **Hypersensitivity Reaction** | ABC | Any appropriate ABC sparing regimen (TDF, AZT) |
| | EFV, NVP | Non NNRTI (DTG or RAL, PI/r) |
| | DTG, RAL | Non-INSTI ART (EFV, PI/r) |
| **Renal Effects**<br>Including proximal renal tubulopathy and elevated Creatinine | TDF | ABC, AZT<br>TAF (for patients with CrCl >30 mL/min, unless on chronic hemodialysis), NRTI-sparing regimens, or regimens using only 3TC or FTC as the NRTI may be considered if appropriate |
| **Nephrolithiasis** | ATV/r | DTG, RAL, boosted DRV, boosted LPV |
| **Bone Density Effects** | TDF | ABC, AZT or TAF<br>NRTI-sparing regimens or regimens using only 3TC or FTC as the NRTI may be considered if appropriate |
| **Bone Marrow Suppression** | ZDV | Regimen not including ZDV (TDF or ABC) |
| **Cardiac Conduction Defects** | EFV, ATV, DRV | INSTI-based regimen (DTG or RAL) |
| **Cardiovascular Events**<br>Myocardial infarction, ischemic stroke | ABC | TDF, AZT or TAF |
| | RTV- boosted PI regimens | RAL, DTG |
| **Dyslipidemia**<br>Hypertriglyceridemia (with or without elevated LDL level) | RTV—boosted LPV<br>EFV-based regimens | DTG, RAL |
| **Insulin Resistance** | LPV/r | INSTI, NNRTI, |
| **Jaundice and Icterus** | ATV/r | INSTI (DTG or RAL) or DRV/r, LPV/r, NNRTI (EFV) |
| **Neuropsychiatric Side Effects**<br>(Dizziness, suicidal ideation, abnormal dreams, depression, ataxia, encephalopathy) | EFV | INSTIs (DTG or RAL), PI/r may be used, but monitoring is recommended (see comments column) |
| **Rash** | NNRTIs (especially NVP and EFV) | INSTI-based regimen (DTG or RAL), PI |

| | | |
|---|---|---|
| **Rash** | DRV/r | ATV/r, or another drug class (e.g., INSTI) |

Peripheral lipoatrophy (loss of subcutaneous fat of the limbs, face, and buttocks) is associated with prior thymidine analog (AZT) use. Despite switching from these ARVs, fat recovery remains slow (may take years) and incomplete.

**References**


- WHO Interim guidelines, updated recommendations on first line and second line antiretroviral regimens and post exposure prophylaxis and recommendations on early infant diagnosis of HIV December 2019
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# 2.8 Maintaining treatment adherence

Dr. P. Premadasa, Dr. P. Batagalla

### How to assess treatment adherence?

Adherence requires ongoing assessment and monitoring. This should be part of each clinic visit, as factors that influence adherence are dynamic and require different approaches to address them as they change over time. This is particularly apparent for adolescents who are undergoing rapid physical, psychological and emotional changes.

- Patients may find it difficult to remember missed doses exactly. An adherence diary, calendar, phone apps and pillboxes can be useful in keeping track of doses and recording adherence.
- Overstating adherence is a potential disadvantage of self-reporting. Creating a conducive environment and maintaining a patient–health care provider relationship that encourages honesty and openness is a critical component of accurate adherence assessment.
- Simply establishing the number of doses missed or identifying non-adherence is not sufficient to solve adherence issues. Addressing non-adherence requires an understanding of what influences adherence. It involves the health provider exploring together with the patient in a sensitive and supportive way to identify the barriers to adherence and potential strategies to address those barriers.
- Therapeutic drug level monitoring (TDM) is the best way to assess treatment adherence but not done routinely. Viral load monitoring is an indirect way of assessing the treatment adherence.

Barriers to drug adherence can be explored through the use of open-ended questions such as:

- Think about the time you took your medication(s). Tell me about it. What helped you to take it at the scheduled time?
- Think about the time you missed your tablets. Tell me about it. What was the reason for missing the dose at the scheduled time?
- What do you think you could do to prevent this from happening again?
- How do you think we can assist you to prevent this from happening?

### Interventions for poor adherence

Patients may need support to make the most effective use of their medicines (e.g. further information and discussion, or practical changes to the type of medicine or the regimen).
Address the patient's beliefs and concerns that has resulted in reduced adherence.
Interventions might include:

- Suggesting to record the time that they take medicine

- Suggesting to use an alarm (phone or watch), or linking an established daily behaviour with taking medication. Eg; taking ARV with a morning cup of tea may help.
- Encouraging patients to monitor the improvement of their condition eg: weight, CD4 count, viral load
- Simplifying the dosing regimen
- Using suitable patient preferred packaging –eg: storage, travel pack, pillbox
- Suggesting techniques to limit the risk of involuntary disclosure. HIV-related stigma can compromise adherence to ART, and not taking medication in front of others can be protective.

Side effects can be a problem for some patients. If this is the case you should:

- Discuss the benefits, side effects and long term effects with the patient to allow them to make an informed choice
- Consider adjusting the dosage
- Consider switching to another medicine
- Consider what other strategies might be used (for example, the timing of medicines).

PLHIV may not raise adherence concerns so should be encouraged to do so, and provided with feedback, at each visit. Interventions to support adherence should be tailored to address specific relevant perceptual and practical barriers. A three-step 'perceptions and practicalities approach' may be helpful:

- Identify and address any doubts about the personal need for ART
- Identify and address specific concerns about taking ART
- Identify and address practical barriers to adherence

**References**


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# 2.9 Treatment failure

Dr. N. Widanage, Dr. T. Ratnayake

### Identification and management of treatment failure

Timely identification of treatment failure is important to limit development of resistance and minimize onward transmission.

Viral load testing is recommended as the preferred monitoring approach to diagnose and confirm treatment failure. It is advisable to assess clinical and immunological status in parallel with viral load testing to identify treatment failure and to change the failing ART regimen.

Virological failure is defined by a persistently detectable viral load exceeding 1000 copies/mL (two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of starting a new ART regimen.

Assessing and managing a patient who is experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.

### Management of treatment failure

- Initial evaluation
- Carry out an assessment of adherence
- Check for drug-drug and drug-food interactions
- Drug tolerability
- Assess HIV RNA level and CD4 T lymphocyte (CD4) cell count trends over time
- Obtain past ART history, and prior and current drug-resistance test results

Drug-resistance testing should be performed while the patient is taking the failing antiretroviral (ARV) regimen or within 4 weeks of treatment discontinuation.

### Key considerations in the management

In general, adding a single ARV agent to a virologically failing regimen is not recommended, because this may risk the development of resistance to all drugs in the regimen.

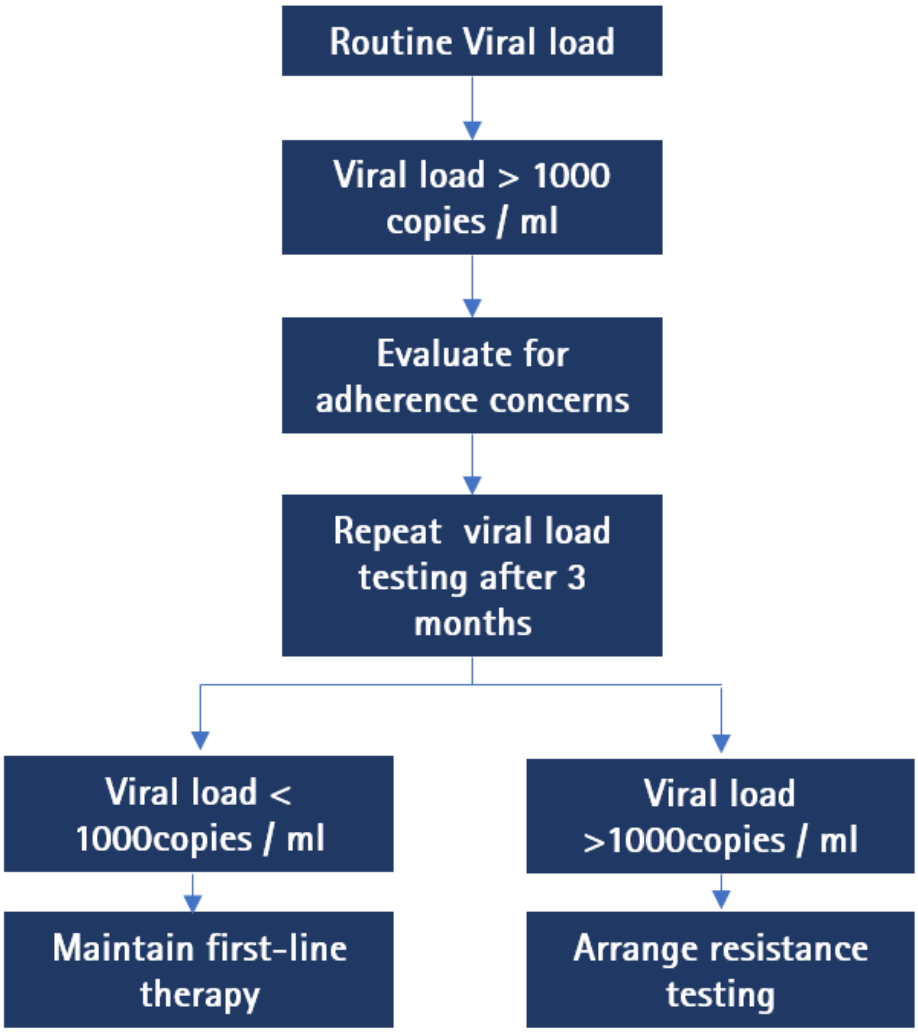
A new regimen should include at least two, and preferably three, fully active agents. A fully active agent is one that is expected to have uncompromised activity based on the patient's ART history and current and past drug-resistance test results. A fully active agent may also have a novel mechanism of action.

For some highly ART-experienced patients with extensive drug resistance, maximal virological suppression may not be possible. In this case, ART should be continued with regimens that are designed to minimize toxicity, preserve CD4 counts, and delay clinical progression.

It is crucial to provide continuous adherence support to all patients before and after regimen changes due to virological failure.

Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA, a decrease in CD4 count, and an increase in the risk of clinical progression. Therefore, this strategy is not recommended in the setting of virological failure.

Figure 3. Flow chart for detecting and confirming virological failure

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# 2.10 Antiretroviral resistance

Dr. P. Premadasa, Dr. P. Batagalla

The ability of HIV to mutate and reproduce itself in the presence of antiretroviral drugs is called HIV drug resistance (HIVDR). The consequences of HIVDR include treatment failure and transmission of resistant strains.

Drug resistance develops when mutations in HIV strains occur, so that previously effective HIV medication is no longer successful in suppressing viral replication. All current antiretroviral drugs are at risk of becoming partly or fully inactive because of the emergence of drug resistant strains.

### Types of drug resistance

WHO classify HIVDR into three main categories,

Acquired HIVDR (ADR)– resistance developed due to viral replication in the presence of ARV medicines, commonly due to suboptimal drug levels.

Transmitted HIVDR (TDR)– occurs when previously uninfected individuals are infected with virus that already has drug-resistant mutations.

Pre-treatment HIVDR – refers to resistance which may have been transmitted at the time of infection (TDR) or may be acquired through previous short term exposure to ART (post-exposure prophylaxis, re-initiating ART after a period of interruption etc.)

### Causes for drug resistance

Development of ART resistance is mainly due to sub-optimal ART levels in the blood. There can be many reasons leading to ART resistance

- Poor ART adherence
- Drug-drug interactions
- Drug – food interactions (poor absorption)
- Treatment interruption
- Virus related factors (innate resistance to ART, high pre-treatment viral load)

Drug resistance is suspected on a patient who is on ART;

- for at least 6 months and
- viral load is above 1000 copies/ml on two consecutive viral load measurements 3 months apart with satisfactory adherence

### When to do drug resistance testing

If a patient's viral load is detectable, first step in the management is to assess patients ART adherence. All the measures need to be taken to ensure good ART adherence, if found to be poor and repeat viral load in three months after having ART with satisfactory adherence. If the adherence

has been acceptable, need to exclude any possible drug-drug or food interactions. Proceeding to the resistance assay is indicated in the absence of these. (Figure- 3)

### Virologic response definitions

The following definitions are used to describe the different levels of virologic response to ART.

| | |
|---|---|
| Virologic Suppression | A confirmed HIV RNA level below the level of detection of available assays. |
| Virologic Failure | The inability to achieve or maintain suppression of viral replication to an HIV RNA level <1000 copies/mL. |
| Virologic Rebound | Confirmed HIV RNA level ≥200 copies/mL after virologic suppression. |
| Virologic Blip | After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression. |
| Low-Level Viremia | Confirmed detectable HIV RNA level <200 copies/mL. |

HIV drug resistance testing has been developed to evaluate the susceptibility of HIV strains to individual ARV drugs. There are two different types of HIV drug resistance tests that are typically used, genotypic assays and phenotypic assays. Genotypic assays determine if certain viral genes have developed drug resistance mutations. Phenotypic assays test a virus' ability to grow in varying ARV drug concentrations.

HIV drug resistance testing can inform how drug resistance may have contributed to virological failure and will aid the clinician in selecting an appropriate treatment regimen for the individual.

Drug resistance test is not recommended if the viral load is below 1000 copies/ml or if the patient has stopped taking ART more than 4 weeks back, leaving the wild type of virus to predominate.

### Common mutations and ART resistance

Mutation in HIV genome can be due to insertion, deletion or replacement of an amino acid in a particular location of the amino acid sequence. Some drugs easily develop resistance and even a single mutation is enough to cause resistance (NNRTIs and NRTIs), whilst some drugs are more durable and need multiple mutations to cause resistance (PIs).

Some mutations confer resistance only to a particular drug and some mutations cause resistance to the whole ART classes. In addition, some mutations can increase susceptibility to a particular ART (e.g. I50L which increases susceptibility to all PIs other than Atazanavir).

Some of the commonly detected mutations are as follows;

| | |
|---|---|
| NRTIs | M184V (3TC), K65R (TDF) |
| NNRTIs | K103N/S (EFV), V106A/M (NVP) |
| PIs | L10F (LPV), I50L (ATV) |

## How to manage drug resistance – Management principles

Discuss with the patient why resistance may have developed. This may include poor adherence, ART interruption, interactions with co-medications or food. All possible measures need to be implemented to prevent the development of ART resistance in the future.

Change HIV medications to a regimen that does not include drugs to which HIV is resistant.

- often, we have to change to an entirely new class of drugs to avoid resistance
- the drugs to which the HIV was resistant, cannot be used in future regimens
- Ideally 3 fully active drugs or at least 2 active drugs need to be used in the new regimen

Continue to monitor the patient's viral load for response to the new medications and development of any further resistance

### Management of multiple or 3 class resistance

If maximal virological suppression cannot be achieved, the goals of ART will be to preserve immunologic function, prevent clinical progression and minimize the development of further resistance that may compromise future regimens.

Management principles of patients with multiple or three class resistance includes the following;

- Use of past and current genotypic and phenotypic resistance assay results to guide therapy
- Identification of active or partially active drugs as much as possible based on above assays
- To consider ART drug with a different mechanism of action

In general, adding a single fully active ARV drug to the regimen is not recommended because of the risk of the rapid development of resistance.

**References**


- Waters L. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update) Writing Group. 2016.
- WHO | HIV drug resistance. WHO [Internet]. 2019 [cited 2020 Aug 20]; Available from: http://www.who.int/hiv/topics/drugresistance/en/
- CDC, HIV drug resistance and drug resistance testing. Center of Disease Control and Prevention [Internet]. August 2017 [cited 2020 Aug 20]; Available from: https://www.cdnetwork.org/wp-content/uploads/2017/08/HIV-Drug-Resistance-and-Drug-Resistance-Testing.pdf
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- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. [cited 2020 Oct 19]; Available. from: https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf.
- Shafer, R. W., & Schapiro, J. M. (2008). HIV-1 drug resistance mutations: an updated framework for the second decade of HAART. AIDS reviews, 10(2), 67–84.

# 2.11 Second and third line regimes

Dr. U. Jayasinghe

## Preferred second line and alternative ART regimens for adults and adolescents

DTG in combination with an optimized NRTI backbone may be recommended as a preferred second line regimen for PLHIV for whom on non DTG based regimens which are failing.

Table 2.11. Preferred second line and alternative ART regimens for adults and adolescents

| Failing first line regimen | Preferred second line regimen | Alternative second line regimen |
|---|---|---|
| TDF + 3TC (or FTC) + EFV (or NVP) | AZT + 3TC + DTG | AZT + 3TC + ATV/r (or LPV/r or DRV/r) |
| AZT/ABC + 3TC + EFV (or NVP) | TDF + 3TC (or FTC) + DTG | TDF + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r) |
| TDF + 3TC (or FTC) + DTG | AZT + 3TC + ATV/r (or LPV/r) | AZT + 3TC + DRV/r |
| TDF+ FTC+ PI (LPV/r, ATV/r) | AZT +3TC+ DRV/r +/- DTG | *AZT+3TC+DRV/r 600/100mg bd (BHIVA guidelines) |

## Third line regimens

Third line ART therapy is defined as an ARV regimen in a patient who has failure to first line and second line therapy. Such regimen may contain new drug classes such as coreceptor inhibitors and attachment inhibitors. Eg: Maraviroc and Enfuvirtide

Third line ART for adults may consist of boosted Darunavir (DRV/r) and Dolutegravir (DTG) or Raltegravir (RAL) with or without one or two NRTIs.

(DRV/r + DTG (or RAL) +-1-2 NRTIs)

If DTG based 1st or 2nd line regimen - DRV/r+2NRTIs + or- NNRTI

References


- Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection June 2016
- WHO Interim guidelines, updated recommendations on first line and second line antiretroviral regimens and post exposure prophylaxis and recommendations on early infant diagnosis of HIV December 2019

# ART in children

3

# 3.1 First line ART regimes for children

Dr. D.O.C de Alwis

## When to start ART in children

Recommendations:

- ART should be initiated in all infants and children with HIV infection.
- Rapid ART initiation (defined as initiating ART immediately or within days of diagnosis), accompanied by a discussion of the importance of adherence and provision of subsequent adherence support, is recommended for all children with HIV.

Table 3.1. Preferred and alternative ART regimens for children and neonates

| Population | Preferred regimen | Alternative regimen | Special circumstances |
|---|---|---|---|
| Children | ABC /AZT+3TC+ LPV/r<br>ABC + 3TC + DTG[a] | ABC/AZT + 3TC+ NVP<br>ABC + 3TC + LPV/r<br>ABC + 3TC + RAL[b]<br>TAF+3TC(FTC)+DTG[c] | ABC + 3TC + EFV (or NVP)<br>AZT + 3TC +EFV[d] (or NVP)<br>AZT + 3TC + LPV/r (or RAL)<br>TAF[e]+ 3TC(FTC) +DTG |
| Neonates | AZT + 3TC + RAL[f] | AZT + 3TC + NVP | AZT + 3TC + LPV/r[g] |

[a] For age and weight groups with approved DTG dosing. DTG is approved for children weighing 15 kg and more. Children weighing more than 20 kg can take adult 50 mg film coated tablet.

[b] RAL should be used as an alternative regimen only if LPV/r solid formulations are not available.

[c] For age and weight groups with approved DTG dosing.

[d] EFV should not be used for children younger than three years of age.

[e] For age and weight groups with approved TAF dosing.

[f] Neonates starting ART with an RAL-based regimen should transition to an LPV/r solid formulation as soon as possible.

[g] LPV/r syrup or granules can be used if starting after two weeks of age.

- ABC can be used for children > 3 months. HLAB 5701 need to be done.
- For children younger than 3 years, a PI based regimen is the preferred approach, if not feasible consider NVP based regimen. Consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained.
- For children more than 3 years, EFV can be used.
- For children <3 years who develop TB while on ART regimen containing NVP or LPV/r, ABC+3TC+AZT is an option.

- TDF – Can be used for children weighing >30 kg.
- Atazanvir/r can be considered for children more than 3 months.
- DTG is approved for use among children older than six years and weighing more than 15 kg and is widely available for children weighing at least 20 kg who can take 50mg film coated adult tablets. Among children for whom approved dosing of DTG is not available, raltegravir (RAL) is considered an effective option and is approved for use from birth. RAL successfully reduces viral load among highly viraemic infants and is safe and well tolerated among neonates and infants at high risk of infection.

**References**


- Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en).
- Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2016 (http://www.who.int/hiv/pub/guidelines/arv2016/download/en).
- AIDS info Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

## 3.2 Monitoring children on ART

Dr. D. Mendis

This section will consider monitoring of HIV positive children at baseline, immediately following initiation of ART and routinely afterwards.

**Initial evaluation of children with HIV diagnosis**

- Growth and cognitive development
- Age-appropriate medical history and physical examination
- STI screening according to the exposure or history
- OI screening as appropriate
- Age-appropriate vaccination
- Adherence issues and potential barriers has to be addressed with the parents or caregiver

**1-2 weeks of initiation of ART**

- Identification of adverse effects and assessment of adherence and support for adherence

**2-4 weeks of initiation of ART**

- Assessment of adverse effects, toxicities and adherence
- Significant viral load declining should be observed after 4 weeks to 8 weeks of ART

**Children who are stable on ART**

- Assess adherence
- History, new adverse effects and toxicities and physical examination
- If laboratory evidence of toxicity is identified frequent monitoring is recommended

Table 3.2. Timing of CD4 and Viral load monitoring

| CD4 count monitoring | Viral load monitoring |
|---|---|
| At base line | At baseline |
| At 3 months | At 3 months |
| At 6 months | At 6 months |
| Annually, if virally suppressed | At 12 months |
| | if virally suppressed, once in 6 months |

Table 3.3. Clinical and laboratory monitoring of children before and after initiation of ART

| Laboratory Testing | Baseline | 1-2 weeks | 2-4 weeks | At 3 months | At 6 months | Annually |
|---|---|---|---|---|---|---|
| Medical History and Physical Examination | ✓ | ✓ | ✓ | ✓ | | ✓ |
| Adherence | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| VL | ✓ | | | ✓ | ✓ | ✓ |
| CD4 | ✓ | | | ✓ | | ✓ |
| FBC | ✓ | | ✓ | ✓ | | ✓ |
| LFT/RFT | ✓ | | ✓ | ✓ | | ✓ |
| Lipid Profile | ✓ | | | | ✓ | ✓ |
| FBS/RBS | ✓ | | | | ✓ | ✓ |
| Urine analysis | ✓ | | | | ✓ | ✓ |
| HBV S antigen | ✓ | | | | | |
| HCV Antibody | ✓ | | | | | |
| Toxoplasma Ab | ✓ | | | | | |
| CMV Ab | ✓ | | | | | |
| Pregnancy test | When required | | | | | |
| STI Screening | When required | | | | | |

References


- AIDS info- Guideline for the use of Antiretroviral Agents in Paediatric HIV Infection. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf

## 3.3 Second line ART regimes in children

Dr. I. Malwatta

According to WHO estimates, 20% of children who are in need of ART by 2020 and onwards are expected to experience virological failure at some point. Recommending potent and effective second-line regimens for infants and children is difficult because of the current lack of experience in resource-limited settings and the limited formulations available. This challenge highlights the importance of choosing potent and effective first-line regimens and the need for optimal adherence to ensure their durability and effectiveness.

The Paediatric Antiretroviral Drug Optimization Group has endorsed the rapid introduction of integrase inhibitors for infants and children, with a preference for DTG over RAL. DTG in combination with an optimized NRTI backbone may be recommended as a preferred second-line regimen for children living with HIV for whom non-DTG-based regimens are failing, provided that the approved DTG dosing is available. For those taking a first-line regimen containing DTG that has failed, a boosted PI-containing regimen should be used.

Table 3.4. Preferred second-line ART regimens for children

| Population | | Failing first-line regimen | Preferred second-line regimen | Alternative second line regimens |
|---|---|---|---|---|
| Children and infants | Less than 3 years | 2 NRTIs + LPV/r | 2 NRTIs + DTG/RAL | Maintain the failing LPV/r-based regimen and switch to 2 NRTIs+ EFV at 3 years of age |
| | | 2 NRTIs + NVP | 2 NRTIs + DTG/RAL | 2 NRTIs+ LPV/r+ ATV/r |
| | 3 years to 10 years | 2NRTI + DTG | 2NRTI + LPV/r (or ATV/r) | 2NRTI + DRV/r |
| | | 2 NRTIs + LPV/r | 2NRTI + DTG/ RAL | 2 NRTIs + EFV |
| | | 2 NRTIs + EFV | 2 NRTI+ DTG/RAL | 2NRTI + LPV/r (or ATV/r) |
| | | 2NRTI+ NVP | 2NRTI + DTG/RAL | 2NRTI + LPV/r (or ATV/r or DRV/r) |

Recommendations

- After failure of a first line LPV/r-based regimen, children younger than 3 years should be switched to a DTG or RAL-based second-line regime.
- After failure of a first line LPV/r-based regimen, children older than 3 years should be switched to a second-line regimen containing two NRTIs plus DTG or RAL or EFV.
- After failure of a first-line NNRTI-based regimen, children should be switched to an integrase inhibitor (DTG or RAL) or boosted PI-based regimen (LPV/r or ATV/r are preferred).
- After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC.
- After failure of a first-line regimen containing AZT + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC).
- TDF can be given for children weighing >30 kg.
- TAF (tenofovir alafenamide) can be used as an alternative NRTI in children weighing at least 25 kg.
- ATV/r can be used as an alternative to LPV/r in children older than 3 months. However, the limited availability of suitable formulations for children younger than 6 years, the lack of an FDC and the need for separate administration of the RTV 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.

**References**


- Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2016 (http://www.who.int/hiv/pub/guidelines/arv2016/download/en).
- Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection December 2018
- Update of recommendations on first- and second-line antiretroviral regimens July 2019
- AIDS info - http://aidsinfo.nih.gov/contentfles/lvguidelines/pediatricguidelines.pdf

# Prevention of mother to child transmission of HIV

4

# 4.1 Prevention of MTCT of HIV

Dr. I. Rajapaksha, Dr. K. Dharmaratne

Fertility desires of reproductive aged women living with HIV are rising with the availability of services to eliminate mother to child transmission (EMTCT) of HIV. WHO has certified Sri Lanka as a country which has achieved elimination of MTCT of HIV in 2019. Improvements in life expectancy and quality of life for HIV-positive women coupled with accessibility for EMTCT services will encourage HIV positive women to consider the possibility of becoming pregnant. HIV positive women planning to have children should receive pre-conception counselling on the importance of treatment adherence and virologic suppression. Choice of ARV therapy should be individualized and should be discussed in full with every woman taking their concerns and preferences into account; decisions should be in accordance with the standard treatment guidelines.

All women planning on pregnancy should start folic acid supplementation before pregnancy and continue up to 12 weeks of gestation.

**Women already on ART**

Women conceiving on an effective ART regimen should continue their treatment.

Women planning pregnancy while on effective ART regimen containing Dolutegravir, need appropriate information on current evidence on neural tube defects to take informed decisions. If women identify pregnancy after first trimester, DTG should be initiated or continued for the duration of the pregnancy.

**Women not on ART**

All pregnant women newly diagnosed with HIV should start ART during pregnancy and advised to continue lifelong treatment. Initiating ART as early as possible in pregnant women is recommended. For a woman who is already pregnant and found positive best third drug is DTG as neural tube defect due to DTG occur only in first 28 days in pregnancy.

**What to start?** *

Section revised in 2021 interim update

| | Recommended | Alternative |
|---|---|---|
| NRTI backbone | Tenofovir DF + emtricitabine<br>Abacavir + lamivudine | Zidovudine + lamivudine |
| Third agent | Dolutegravir<br>Efavirenz<br>Atazanavir /r | Raltegravir 400 mg bd<br>Darunavir /r |

Integrase inhibitor based regimen (raltegravir or dolutegravir) can be considered as third agent with women with high baseline viral load (>100,000copies/ml) as it causes fast reduction in viral load.

Dolutegravir may be considered as third agent from 6 weeks of gestation. Twice daily Darunavir/ritonavir can also be considered as third agent.

### Using DTG in pregnancy *

Section revised in 2021 interim update

1. For a woman on dolutegravir wishing to conceive:
    a. The risk of neural tube defects with preconception DTG

        Tsepamo study - appears to be about 0.2% or less, a potential excess of only one neural tube defect per 1000 DTG exposures at conception compared with a general population prevalence of 0.06% in countries with food folate fortification

        Two separate risk—benefit analyses indicate that the benefits of first-line DTG-based ART compared with EFV-based ART among individuals living with HIV, including women of childbearing potential, significantly outweigh the potential risks.

    b. Two randomized controlled trials investigated the use of DTG-based regimens among pregnant and breastfeeding women and found DTG to be more effective than NNRTI-based regimens. The potential signal of neural tube defects for women of childbearing potential has been examined extensively; the risk is lower than initially observed and does not affect its use for women of childbearing potential.

    c. All women choosing to continue dolutegravir while planning to conceive will be supported in this decision and advised to commence or continue folic acid 5 mg.

2. For a woman on dolutegravir who becomes or is pregnant:
    a. We acknowledge the neural tube has closed within 28 days of conception but the mechanism of some of the reported abnormalities remains uncertain. If dolutegravir is the best ART choice for the woman, the neural tube defect risk of 0.2% or less should be discussed and if a woman accepts this risk then dolutegravir can be continued in pregnancy.

    b. We do not recommend switching from dolutegravir if the pregnancy is confirmed to be already past 6 weeks' gestation unless there are other reasons to consider switching.

    c. If the physician/woman choose(s) to switch, use a regimen for which there are the most safety data in pregnancy, such as efavirenz or atazanavir/r.

## Late-presenting woman not on treatment

A woman who presents after 28 weeks should commence ART without delay. If the viral load is unknown or >100,000 HIV RNA copies/mL, a three drug regimen that includes raltegravir 400 mg twice daily or dolutegravir 50 mg once daily is suggested.

An untreated woman with confirmed or presumed HIV infection, presenting in labour at term should be given a stat dose of nevirapine 200mg and commence on fixed dose zidovudine+lamivudine and raltegravir (400 mg bd) or Dolutegravir (50 mg daily) as the preferred additional agent. Oral administration of zidovudine using 600mg loading dose and 300mg every 3 hours can be considered.

**In preterm labour,** if the infant is unlikely to be able to absorb oral medications consider the addition of double dose tenofovir DF to the woman's treatment described above.

**References**


- BHIVA pregnancy guideline- https://www.bhiva.org/file/5bfd30be95deb/BHIVA-guidelines-for-the-management-of-HIV-in-pregnancy.pdf
- British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018 (2020 third interim update)
- Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO
- CDC guideline

## 4.2 Infant prophylaxis

Dr. M. Pathiraja

Infant prophylaxis prevents HIV infection in infants who were exposed to the infection in utero, perinatal and breast feeding period.

The transmission risk to the infant depends on maternal and fetal factors. Maternal viral load at the time of delivery is the most important factor and if it is not suppressed the risk of transmission is high.

All newborns exposed to the HIV infection perinatally, should receive ARV prophylaxis to prevent risk of transmission.

ARV drugs as prophylaxis or treatment should be started as early as possible within 4 hours of birth considering the following scenarios.

**xis is defined as** giving one or more ARV drugs, to a newborn of, a HIV positive woman, without evidence of documented o prevent perinatal acquisition of HIV infection.

**HIV therapy is given for** newborns who are at highest risk of perinatal acquisition of HIV infection in utero, perinatal or ing period.

Newborns with documented evidence of HIV infection are started on HIV therapy with 3 drug regimens (ART).

Table 4.1. Neonatal Antiretroviral management according to the risk of HIV infection in newborn

| Level of perinatal HIV transmission risk | ART management |
|---|---|
| **Low risk infants** | |
| Infants born to mothers on ART during pregnancy with satisfactory adherence and with maternal viral load undetectable (<50 copies/ml) close to the delivery, receiving replacement feeding. | Infant post exposure prophylaxis<br>NVP daily or ZDV twice a day for 4 - 6 weeks |
| **High risk infants** | |
| Infants born to mothers with confirmed HIV infection<br>• Who are not on antepartum or intrapartum ARV<br>• Only on intrapartum ARV<br>• Who were on antepartum or intrapartum ARV but not attained undetectable viral load at the time of delivery<br>Mothers with acute HIV infection during pregnancy or breast feeding. (Breast feeding should be stopped.) | Presumptive HIV therapy<br>ZDV+3TC+NVP (in treatment dose)<br>or<br>ZDV+3TC+RAL (in treatment dose)<br>For the first 6 weeks of life |

| **Presumed new born HIV exposure** | |
|---|---|
| Infants born to mothers with one positive HIV screening test but still not confirmed or<br>Infants with positive HIV test born to a mother with unknown HIV status | Presumptive therapy with ZDV+3TC+NVP (in treatment dose)<br>or<br>ZDV+3TC+RAL (in treatment dose)<br>from birth to 6 weeks<br>ARV should be discontinued as soon as possible with negative confirmatory test of the mother. |
| **HIV infected infant** | |
| Having two positive virologic tests from two separate blood samples | Three drug regimen with treatment dose |

- ART other than Zidovudine, Lamivudine and Nevirapine are not recommended for infants <37 weeks as there are no safety data.
- For term babies: ZDV, NVP, 3TC, FTC, RAL can be given.
- For term babies: 2 weeks of birth onwards LPV/r can be used.
- If the baby becomes positive while on the presumptive therapy, NVP should be replaced with LPV/r at the post menstrual age (time from mother's first day of last menstrual period to birth and the time elapsed after birth) ≥42 weeks or ≥14 days after birth.
- Changing to RAL can be done at any time in babies born after post menstrual age ≥37 weeks and who weigh ≥ 2 kg.
- New born antiretroviral dosing recommendations are given in the following link.

  Clinicalinfo.hiv.gov/en/guidelines/paediatric-arv

  Refer Annexure 6- Dosing schedule of ARV drugs for the new born

**References**


- Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection June 2016
- BHIVA guidelines for the management of HIV in pregnancy 2018
- CDC guideline; Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

# Vaccination

5

# 5.1 Vaccination in HIV

Dr. D. Mallikarachchi

## General principles of immunization in HIV-infected children

Vaccines may be less effective in HIV infected children. However, these children also have an increased risk of infectious diseases and may have more severe illness. Therefore, HIV infected children should be protected from vaccine preventable diseases. Hence completing immunization is important, but consideration should be given to the most appropriate time for immunization. It is important to immunize the HIV infected children prior to the impairment of their immune system or after immune reconstitution occurs with ART.

Table 5.1: Immunization schedule for HIV infected children**

| Age | Standard schedule | Child with HIV | Remarks |
|---|---|---|---|
| **0-4 weeks** | BCG | If vaccinated with BCG at birth are at an increased risk of developing disseminated BCG disease. Therefore, BCG vaccination should be delayed until ART has been started and the infant is confirmed to be immunologically stable (CD4 >25%). | Neonates born to women of unknown HIV status should be vaccinated as the benefits of BCG vaccination outweigh the risks.<br>Neonates of unknown HIV status born to HIV infected women should be vaccinated if they have no clinical evidence suggestive of HIV infection, regardless of whether the mother is receiving ART. However, if the mother is having a detectable viral load at the time of delivery it is better to postpone BCG till HIV is excluded in the infant. Exclusion of HIV in the infants will take 4-6 moths. |
| **2 months** | Pentavalent (DTP-HepB-Hib) & OPV (1st dose)<br>fIPV (fractional IPV) -1st dose | Pentavalent (DTP-HepB-Hib) + inactivated polio vaccine*** - 1st dose<br>Pneumococal conjugate vaccine (PCV)-1st dose | OPV and fIPV are not recommended in infants with HIV infection |

| | | | |
|---|---|---|---|
| **4 months** | Pentavalent (DTP-HepB-Hib) & OPV -2nd dose<br><br>fIPV (fractional IPV) -2nd dose | Pentavalent (DTP-Hep B-Hib)+inactivated polio vaccine*** -2nd dose<br>PCV -2nd dose | OPV and fIPV are not recommended in infants with HIV infection |
| **6 months** | Pentavalent (DTP-HepB-Hib)& OPV -3rd dose | Pentavalent (DTP-HepB-Hib)+inactivated polio vaccine*** -3rd dose<br><br>PCV -3rd dose | OPV is not recommended in infants with HIV infection |
| **9 months** | MMR | MMR | MMR- should be postponed in severe immunodeficiency |
| **12 months** | Live JE | Hep A 1st dose (2nd dose 6-12 months apart) | Live JE is not recommended for HIV infected children<br>Children with severe immunosuppression may have a suboptimal response to Hep A vaccine |
| **13-15 months** | | Varicella- 2 doses 3 months apart.<br>PCV booster dose | Patients who are severely immunosuppressed should not receive the vaccine. |
| **18 months** | DTP& OPV -4th dose | DTP+ inactivated Polio vaccine*** | OPV is not recommended for children with HIV infection |
| **3 years** | MMR 2nd dose | MMR 2nd dose | Patients who are severely immunosuppressed should not receive the vaccine. |
| **5 years** | DT+OPV | DT+Inactivated polio***<br>Pneumococcal polysaccharide vaccine | OPV is not recommended for children with HIV infection |
| **10 years** | HPV (quadrivalent)<br>2 doses (females)<br>(0,6 months) | HPV (quadrivalent)<br>3 doses (both females and males)<br>(0,2,6 months) | |
| **11 years** | aTd | aTd | |

** Adopted from National Immunization Schedule

*** IPV dose and Route – 0.5ml IM

## General principles of immunization in HIV infected adults

### Live vaccines

Persons with symptomatic HIV infection or CD4 counts <200 cells/µl should not be given live vaccines. Vaccination may be reconsidered when immune restoration occurs with ART.

HIV infected adults with a CD4 count of 200-300 cells/µl have a moderate immunodeficiency. When administering live vaccines for them it is important to weigh the risk and benefits before vaccination.

Co-administration of multiple live vaccines to HIV infected individuals is not recommended due to issues related to safety, immunogenicity and efficacy. It is recommended to have at least an interval of four weeks between vaccinations.

### Inactivated vaccines

In persons with CD4 counts <200 cells/µl, the response to inactivated vaccines is reduced. Delaying vaccination till immunorestoration could be considered in these patients. However, if the risk of exposure is high, vaccination could be done. If indicated vaccination could be repeated following immunorestoration on ART.

### Vaccination of adults with HIV infection

Table 5.2: Vaccination of adults with HIV infection

| Vaccine | Indication | Primary course | Boosting | Remarks |
|---|---|---|---|---|
| **Haemophilus influenzae type b (Hib)** | At risk | Single dose | None | Could be given regardless of the CD4 cell count |
| **Hepatitis A** | At risk | Two or three doses | Ten yearly if at risk. | Three doses at 0,1, and 6 months if the CD4 cell count is <350 cells/µL and two doses at 0 and 6 months if the CD4 cell count is >350 cells/µL. |
| **Hepatitis B** | All non-immune | Four doses**** (at 0, 1, 2, 6 months) | If HBsAb ≥10- <100 IU/L –need one | Could be given at all CD4 cell counts. Screen HBsAb levels |

| | | | | |
|---|---|---|---|---|
| | | | booster dose and retesting<br>If HBsAb ≤ 10 IU/L need three further vaccine doses monthly and retesting | according to initial response. |
| **Human papillomavirus** | Age and gender related | Three doses of quadrivalent vaccine<br>0, 2 and 6 months apart | None | Could be given regardless of the CD4 cell count |
| **Inactivated polio** | To all non-immune | Five doses<br>(at 0,1,2 months, 5 years and 10 years) | Ten yearly if at risk | Could be given regardless of the CD4 cell count |
| **Influenza** | For all | Single dose | Annually | Could be given regardless of the CD4 cell count |
| **Japanese Encephalitis**<br>Inactivated vero cell derived | At risk | Two doses 1 month apart | One booster dose 1 to 2 years later for those at continued risk with a further boost after 10 years. | Could be given regardless of the CD4 cell count |
| **Meningococcal**<br>(conjugated) | At risk | Two doses 2 months apart | Five yearly if at risk | Could be given regardless of the CD4 cell count |
| **MMR** | To all non-immune | Two doses at least 1 month apart | None | Could be given when the CD4 cell count is >200 cells/µL |
| **Pneumococcal**<br>(polysaccharide) PPSV23 and Pneumococcal (Conjugate)-PCV13/10 is preferred | For all | One dose of PCV13/10 followed by one dose of PPSV23 at least 8 weeks later. Second dose of PPSV23 at least 5 years after the previous dose. One final PPSV23 at 65 years or older | None | Could be given regardless of the CD4 cell count |

| | | | | |
|---|---|---|---|---|
| **Rabies vaccine** | For exposed non immune | Rabies immunoglobulin + five doses of the vaccine IM at 0,3,7,14 and 30 days | None | Could be given regardless of the CD4 cell count |
| **Tetanus-Diphtheria (aTd)** | To all non immune | Five doses at 0, 1, 2 months, 5 years and 10 years | Ten yearly if at risk | Could be given regardless of the CD4 count |
| **Tetanus toxoid** | To all non immune | Five doses at 0, 1, 2 months, 5 years and 10 years | Ten yearly if at risk | Could be given regardless of the CD4 count |
| **Typhoid** Vi Capsular polysaccharide | At risk | Single dose | Three yearly if at risk | Could be given regardless of the CD4 count |
| **Varicella** | All non immune | Two doses 3 months apart | None | Could be given when the CD4 cells count is >200 cells/µL |
| **Yellow fever** | At risk age <60 years and CD4 cell count is >200 cells/µL | Single dose | Ten yearly if at risk | Age >60 years, CD4 cell count is <200cells/µL and pregnant women should not receive the vaccine |

**** Yeast based vaccine 40µg / dose

## Recommendation for pre-exposure vaccination in HIV-infected adults

**Haemophilus influenzae type b vaccine (Hib)**

Vaccine has been shown to produce protective antibodies in HIV infected individuals but the response can vary with the CD4 cell count. It is recommended that HIV positive individuals with following conditions are at risk of having infection and should receive one dose of a Hib containing vaccine whether or not they were immunized previously and regardless of CD4 count, ART use and viral load.

- Asplenia
- Splenic dysfunction
- Complement deficiency

### Hepatitis A vaccine

It is recommended to do pre-vaccination screening for Hepatitis A immunity in HIV positive adults who are at risk of Hepatitis A. Following categories could be considered as at risk for Hepatitis A infection.

- Close contacts with Hepatitis A
- Men who have sex with men
- Injecting and non-injecting drug users
- Persons who have chronic liver disease or conditions that can lead to chronic liver disease
- Those with occupational exposure to Hepatitis A
- Persons who require frequent blood /blood product transfusions
- Persons with special needs living in residential institutions and their carers
- Persons who travel to countries with high or intermediate endemicity of infection

If serologically negative for Hepatitis A, they should be offered monovalent Hepatitis A vaccine. The immune response to Hepatitis A vaccine is generally reduced in HIV positive individuals compared to HIV negative individuals. But the response improves with increasing CD4 cell counts and viral load suppression on ART. If the CD4 count is less than 200 cells / µL, or when the patient is having symptomatic HIV infection, it is preferable to differ vaccination until several months after initiation of ART and an improvement of the CD4 count. However, it should not be deferred in patients who are clinically unlikely to achieve an increase in the CD4 cell count.

HAV IgG can be done at least 1 month after the last dose of vaccination to identify the non-responders. Non responders should be revaccinated. The vaccine is safe and well tolerated in HIV positive individuals including those who receive three doses over 6 months.

### Hepatitis B vaccine

HIV infection affects the response to Hepatitis B vaccine and the HBsAb seroconversion strongly correlates with CD4 cell count and viral load. Revaccination of non-responders once the CD4 count is >350 cells/µL, suppression of viral load with ART and the use of larger and more frequent vaccine

doses are some of the strategies available to improve the vaccine response among HIV infected individuals. Duration of vaccine induced protection is unknown in HIV positive individuals and in general, post vaccination antibody levels are lower and disappear more quickly than in HIV uninfected individuals.

When using recombinant vaccines, high dose (40 µg -2 doses of 20 µg/mL vaccine) vaccination should be offered. Four vaccine doses should be given at 0, 1, 2, and 6 months. It is recommended to measure the HBsAb levels 4-8 weeks after the last vaccine dose.

Antibody level >100IU/L are regarded as ideal, whereas a level <10 IU/L is classified as non-responsive. It is recommended that individuals with HBsAb levels ≥10 but <100 IU/L should receive one booster dose. If retesting of HBsAb level shows antibody level between ≥10- 100 IU/L regular annual HBsAb testing is needed to guide subsequent boosting requirement.

Individuals who have HBsAb levels <10 IU/L after the primary vaccine course should receive three further vaccine doses at monthly intervals. It is better to delay the revaccination until the viral load is suppressed on ART and the CD4 count has increased > 350 cells/µL.

Screening of HBsAb levels with longer intervals (2-4 yearly) are indicated for individuals with initial HBsAb levels >100 IU/L, CD4 count >350 cells/µL and viral load suppression on ART. Other individuals should undergo yearly HBsAb screening.

### Human papillomavirus vaccine

HIV infected individuals are at higher risk of HPV acquisition, persistence and at increased risk of HPV related malignancies. The response to vaccine is highest in those receiving ART and showing high CD4 cell count and suppressed viral load. Studies are still on-going to demonstrate the duration of vaccine induced protection. Even though younger individuals are more likely to benefit from the vaccine, older men and women may continue to have at least a partial benefit from vaccination.

It is recommended that previously unvaccinated HIV infected men and women aged up to 26 years should be offered HPV vaccination regardless of CD4 count, ART use and viral load. Previously unvaccinated HIV positive men having sex with men aged up to 40 years should be offered HPV vaccination regardless of CD4 count, ART use and viral load.

It may be useful to offer HPV vaccination for previously unvaccinated HIV positive women aged up to 40 years regardless of CD4 count, ART use and viral load. In ART naïve patients with CD4 cell count <200 cells /µL, vaccination may be postponed until the patient is established on ART.

It is recommended that three doses of the quadrivalent vaccine need to be administered at 0,1-2, and 6 months to HIV infected individuals. If the schedule is interrupted, vaccine series need to be completed rather than restarted. Ninevalent (9vHPV) can replace quadrivalent vaccine for both men and women once available.

### Inactivated polio vaccine

Inactivated polio vaccine can produce neutralizing antibodies in HIV positive adults and children and in patients with CD4 count <300 cell/µL. It is safe and well tolerated. It is recommended that individuals who are unvaccinated should receive 3 vaccine doses at monthly intervals followed by 2 reinforcing doses after 5 and 10 years. Fully vaccinated individuals could receive booster doses every 10 years if at risk of exposure. Fractionated IPV is not recommended.

### Inactivated influenza vaccine

HIV infected individuals are at four to eight-fold risk of influenza and are 1.5 times more likely to die compared to HIV uninfected individuals. Vaccination against influenza has been identified as an effective preventive strategy.

Vaccine response is lower compared to HIV negative individuals and correlate with CD4 cell count and viral load. Vaccine may have low immune response especially when the CD4 count is less than 200 cells/µL. However, as the vaccine is still effective in preventing and reducing the complications in patients with HIV infection, it is recommended to offer annual inactivated influenza vaccine to all HIV infected individuals especially for HIV infected pregnant women.

### Japanese encephalitis vaccine

Live JE vaccine is not recommended in HIV infected patients. There is insufficient evidence on the safety, immunogenicity and clinical efficacy of JE vaccination in HIV positive adults. However, it is recommended that HIV infected individuals be offered an inactivated Vero cell derived JE vaccine with two doses given 1 month apart. A booster dose could be given 2 years later for those at continued risk with a further booster planned after 10 years. This vaccine is not available in Sri Lanka at present.

### Meningococcal vaccine

Patients with HIV infection are at higher risk of invasive meningococcal infection especially those with CD4 cell count <200 cells/µL and viral load >400 copies/ml. However, HIV infection alone is not currently an indication for meningococcal vaccine. It is recommended that HIV positive individuals should follow the general indications for meningococcal vaccination and should be offered the vaccination as needed. Individuals who are close contacts of patients with meningococcal disease should be offered antibiotic prophylaxis and appropriate vaccination. Due to the low immunity associated with polysaccharide vaccine, two doses of conjugated vaccine given at an interval of two months are recommended for individuals with HIV infection. The individuals who received MenACWY should be offered a booster dose every five years if there is an on-going risk

### MMR vaccine

The prognosis of rubella and mumps does not show much difference between HIV infected individuals and the general population. However, measles could be life threatening in persons with advanced HIV infection. Therefore, it is recommended to offer two doses of MMR vaccine at least 1 month apart to measles seronegative HIV infected patients with CD4 cell counts > 200 cells/µl. However, based on the likelihood of exposure, vaccination may be postponed in patients with CD4 cell count <200 cells/µL who have not started on ART.

After a significant exposure to measles, HIV infected individuals should be screened for measles IgG within 3 days regardless of a history of previous vaccination. After a risk assessment about the need and the mode of post exposure prophylaxis, measles seronegative adults:

- with CD4 count >200 cells/µL preferably on ART with a stable viral load could receive MMR vaccine within 3 days of contact or IM preparation of human immunoglobulin (HNIG) within 6 days of contact.

- with CD4 counts <200 cells/µL could be given HNIG within 6 days.

However, the protection afforded with HNIG/IVIG will be short lived.

It is also recommended to give MMR vaccine to rubella seronegative HIV positive women of childbearing age provided their CD4 count is >200cells/µL and they are not pregnant. Vaccine responses are reduced in HIV infected individuals but effective ART can improve the response.

### Pneumococcal vaccine

HIV infected individuals are at higher risk of developing pneumococcal disease and show an increased risk of mortality. Studies conducted on clinical efficacy of pneumococcal polysaccharide vaccine (PPSV23) in HIV positive adults have shown inconsistent findings. However, serological studies conducted on pneumococcal conjugate (PCV) vaccine have shown immunogenicity in HIV infected persons. With both vaccines, the response is low in HIV positive individuals compared to HIV negative individuals. However, PCV vaccine has demonstrated superiority with certain serotypes over PPSV in serological studies.

It is recommended to give pneumococcal vaccine to HIV infected individuals irrespective of the CD4 cell count, ART use and viral load.

One dose of PCV 13/10 could be administered followed by one dose of PPSV23 at least 8 weeks later. Second dose of PPSV23 should be administered at least 5 years after the previous dose. One final dose of PPSV23 should be administered at 65 years or older. This dose should be given at least 5 years after the most recent dose of PPSV23.

### Rabies vaccine

When giving post exposure prophylaxis, each case should be assessed individually. Following categories should be considered as non-immune for rabies and should be given rabies immunoglobulin (RIG) and five doses of a cell culture derived vaccine intramuscularly at 0,3,7,14 and 30 days.

- Unvaccinated
- Partially vaccinated (< 3 doses)
- Given a complete course of vaccination (5 doses) but without serological evidence of an adequate antibody response
- Uncertain vaccination history
- CD4 cells<500 cells/µL and not receiving ART

In patients who previously received 5 doses of the vaccine and had adequate antibody response with a CD4 count >500 cells/µL, viral suppression (>6 months) and on ART may be managed with 2 intramuscular doses given at 0 and 3-7 days without RIG.

After full course of vaccination all patients should undergo serological testing 2 weeks after the last vaccine dose and non-responders are offered a double dose or more frequent vaccine doses after obtaining specialist advice.

### Tetanus-Diphtheria vaccine (aTd)

HIV infected adults who require vaccination against tetanus and diphtheria could be given aTd vaccine regardless of CD4 cell count, ART use and viral load. It is recommended to give three vaccine doses at 1 month intervals, followed by 2 reinforcing doses after 5 and 10 years.

### Tetanus toxoid

The vaccine has been shown to be immunogenic in HIV infected individuals even though the response is less compared to HIV non infected individuals. However, the immunity improves following successful ART.

If the patient is unvaccinated for tetanus, it is recommended to give the adult tetanus vaccine regardless of CD4 count, ART use and viral load in three vaccine doses given at 3-month intervals, followed by two reinforcing doses after 5 and 10 years. Fully vaccinated individuals should receive a booster dose every 10 years.

Following a potential exposure,

i. Individuals with uncertain or incomplete vaccination, 3 vaccine doses at monthly intervals should be given regardless of type of wound and level of risk.
ii. Individuals who have previously received three vaccine doses with a clean wound and negligible risk should receive one dose if the last dose received was >10 years previously.
iii. Individuals who received at least three vaccine doses with tetanus prone wound should receive tetanus immunoglobulin and 1 dose of vaccine if the last dose received was >10 years previously.

### Typhoid vaccine

HIV infected individuals are at higher risk of developing infections with Salmonella and more likely to develop complications. It is recommended to offer Vi capsular polysaccharide vaccine to HIV infected individuals who are likely to be exposed to poor sanitary conditions. The vaccine should be given at least 2 weeks before the expected exposure. The booster dose could be given every 3 years for those who remain at risk.

### Varicella zoster vaccine

HIV infected individuals who acquire chicken pox are at higher risk of developing severe and fulminant disease. In addition, they are at increased risk of developing VZV reactivation especially with low CD4 count and with a viral load of >400 copies/ml. Even with ART the disease burden is 3-5 times higher compared to HIV negative individuals.

Chicken pox vaccine was shown to be safe and immunogenic in children with asymptomatic or mildly symptomatic HIV infection. However, only limited data are available in HIV positive adults.

Two doses of the varicella vaccine 3 months apart are recommended for varicella seronegative patients who have CD4 cell count >200 cells/µl, and on ART.

### Yellow fever vaccine

It is recommended that HIV infected individuals aged <60 years and with CD4 cell count >200 cells/µL who are planning to travel to countries in which there is risk of exposure should be offered the vaccination after counselling on benefits and risks of vaccination. One vaccine dose at least 2 weeks

before travel is recommended. Higher CD4 counts and a suppressed viral load on ART are likely to maximize safety and the efficacy of vaccination.

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# Annexures

6

## List of annexures

| | |
|---|---|
| Annexure 1 | Depression screening questionnaire and brief screening tool (PHQ-9) |
| Annexure 2 | FRAX fracture risk |
| Annexure 3 | QRISK2 calculation |
| Annexure 4 | Vaccination against hepatitis B (HBV) if not already immune |
| Annexure 5 | The details of individual ARV |
| Annexure 6 | Dosing schedule of infant prophylaxis |

## Annexure 1 - Depression screening questionnaire

Can be screened using either ICD 10 or DSM (V) criteria

**ICD 10 Criteria for diagnosis of depression**

Depressed mood, loss of interest and enjoyment, and increased fatigability are usually regarded as the most typical symptoms of depression, and at least two of these, plus at least two of the other symptoms described below.

a) reduced concentration and attention

b) reduced self-esteem and self-confidence

c) ideas of guilt and unworthiness (even in a mild type of episode)

d) bleak and pessimistic views of the future

e) ideas or acts of self-harm or suicide

f) disturbed sleep

g) diminished appetite

Minimum duration of the whole episode is about 2 weeks.

**DSM (V) Criteria for diagnosis of depression**

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

   Note: Do not include symptoms that are clearly attributable to another medical condition.

   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty and hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
   3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A-C represent a major depressive episode.

**Brief Screening tool for Depression (PHQ – 9)**

This is an easy-to-use patient questionnaire which is self-administered.

**PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)**

| Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)* | Not at all | Several days | More than half the days | Nearly every day |
|---|---|---|---|---|
| **1.** Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| **2.** Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| **3.** Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| **4.** Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| **5.** Poor appetite or overeating | 0 | 1 | 2 | 3 |
| **6.** Feeling bad about yourself — or that you are a failure or have let yourself or your family down | 0 | 1 | 2 | 3 |
| **7.** Trouble concentrating on things, such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| **8.** Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |
| **9.** Thoughts that you would be better off dead or of hurting yourself in some way | 0 | 1 | 2 | 3 |

FOR OFFICE CODING 0 + _____ + _____ + _____
=Total Score: _____

**If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?**

| Not difficult at all | Somewhat difficult | Very difficult | Extremely difficult |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

**Sinhala translation of the PHQ- 9**

## සෞඛ්‍ය සම්බන්ධ ප්‍රශ්නාවලිය ( PHQ-9)

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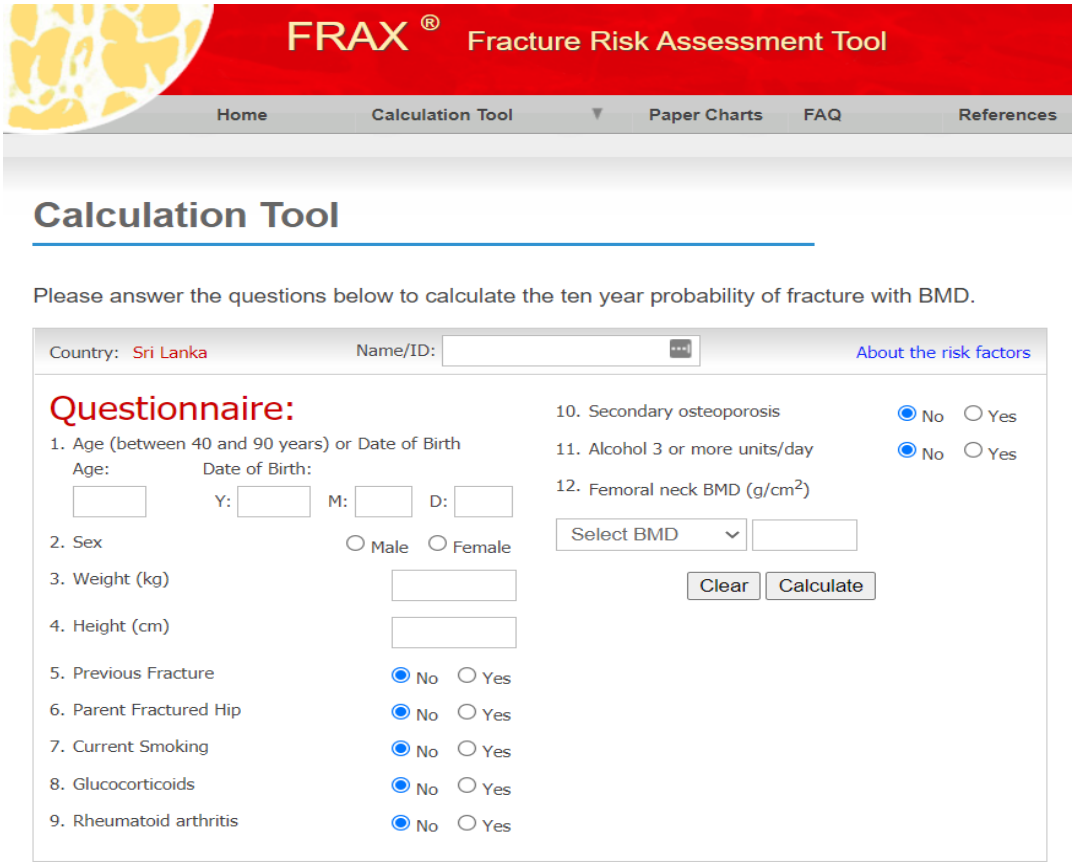
| | කිසිසේත්ම නැත | දින කිහිපයක් | සතියක් හෝ වැඩිකාලයක් | සෑම දිනකම |
|---|---|---|---|---|
| 1. එදිනෙදා කටයුතු කිරීමට එපරම් උනන්දුවක් නොදැක්වීම | | | | |
| 2. බලාපොරොත්තු රහිත බවක් දැනීම | | | | |
| 3. නින්ද නොයෑමක් හෝ වැඩියෙන් නිදාගැනීමට සිතීම | | | | |
| 4. වෙහෙසකාරී බවක් හෝ දුර්වල බවක් දැනීම | | | | |
| 5. කෑම අරුචිය හෝ අධික ලෙස ආහාර කැනීමට සිතීම | | | | |
| 6. ඔබ ගැන අවනක්ෂේරුවක් හෝ පරාජිත හැඟීමක් දැනීම. | | | | |
| 7. පුවත් පතක් කියවීම හෝ රූපවාහිනිය නැරඹීම වැනි දේ කෙරෙහි අවධානය අඩු බවක් දැනීම | | | | |
| 8. ඔබ සෙමින් ගමන් කරන බවක් හෝ සෙමින් කතා කරන බවක් නිසීම හෝ වෙනදාට වඩා වැඩි කලබල බවක් නොපෙන්නුන් බවක් නිසීම | | | | |
| 9. ඔබට මියදිවී යාහී කරගැනීමට සිතීම | | | | |

| | |
|---|---|
| 10.ඔබට ගැටලුවක් අහිමු අවස්ථාවකදී එම ප්‍රශ්නය නිසා ඔබගේ පෞද්ගලික වැඩ කටයුතු කිරීමට පවුලේ වැඩකටයුතු කිරීමට හෝ වෙනත් පුද්ගලයන් සමඟ සුහදව කටයුතු කිරීමට ඔබට කොතරම් අපහසු වී තිබෙද ? | කිසිසේත්ම අපහසු නැත .....<br>තරමක් අපහසුය .....<br>ඉතා අපහසුයි .....<br>අතිශයින්ම අපහසුයි ..... |

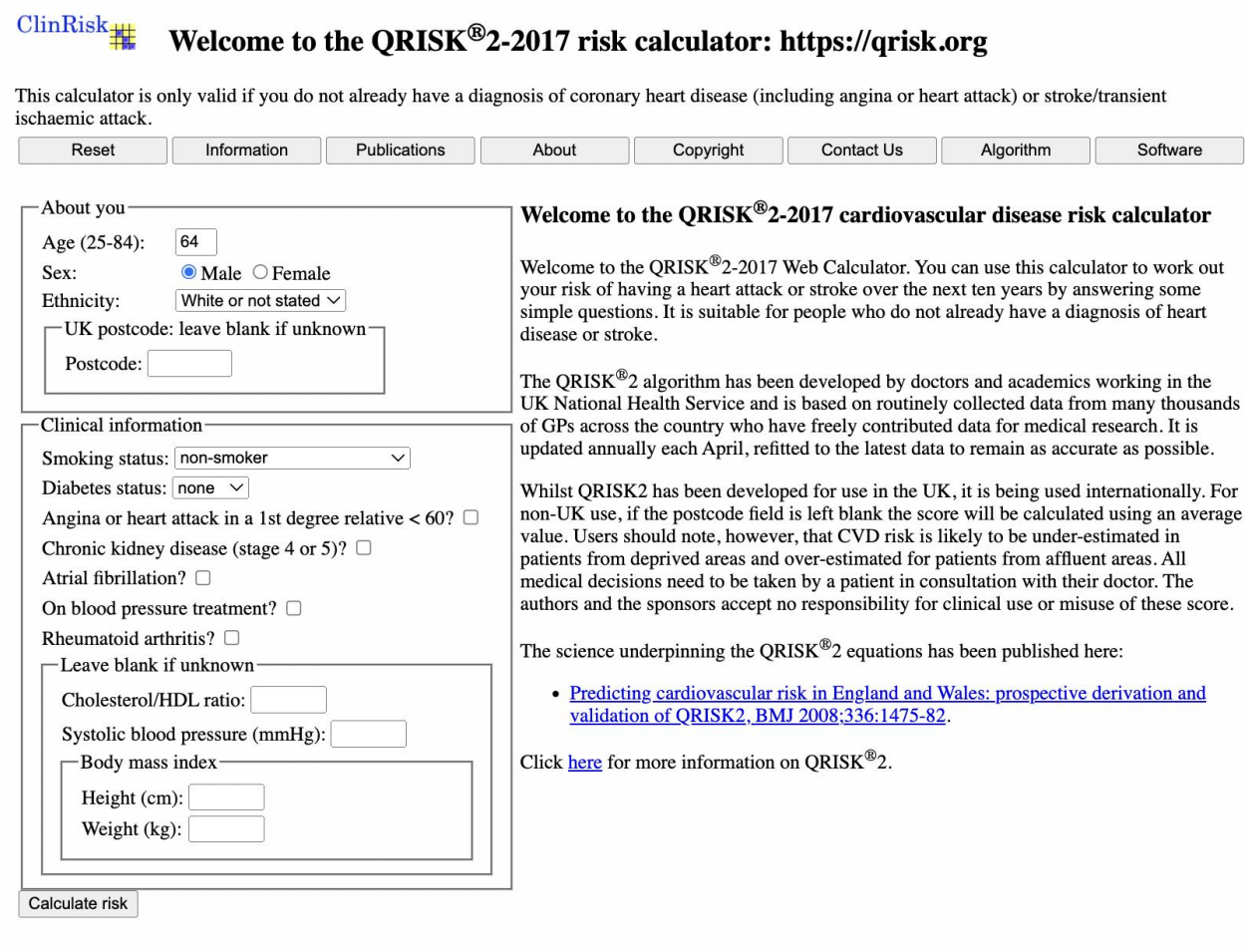
## Annexure 2 - FRAX® Fracture Risk Assessment Tool




Link - https://www.sheffield.ac.uk/FRAX/tool.aspx?country=45

| | |
|---|---|
| Age | The model accepts ages between 40 and 90 years. If ages below or above are entered, the programme will compute probabilities at 40 and 90 year, respectively. |
| Sex | Male or female. Enter as appropriate. |
| Weight | This should be entered in kg. |
| Height | This should be entered in cm. |
| Previous fracture | A previous fracture denotes more accurately a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture. Enter yes or no (see also notes on risk factors). |
| Parent fractured hip | This enquires for a history of hip fracture in the patient's mother or father. Enter yes or no. |
| Current smoking | Enter yes or no depending on whether the patient currently smokes tobacco (see also notes on risk factors). |
| Glucocorticoids | Enter yes if the patient is currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5mg daily or more (or equivalent doses of other glucocorticoids) (see also notes on risk factors). |
| Rheumatoid arthritis | Enter yes where the patient has a confirmed diagnosis of rheumatoid arthritis. Otherwise enter no (see also notes on risk factors). |
| Secondary osteoporosis | Enter yes if the patient has a disorder strongly associated with osteoporosis. These include type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease |
| Alcohol 3 or more units/day | Enter yes if the patient takes 3 or more units of alcohol daily. A unit of alcohol varies slightly in different countries from 8-10g of alcohol. This is equivalent to a standard glass of beer (285ml), a single measure of spirits (30ml), a medium-sized glass of wine (120ml), or 1 measure of an aperitif (60ml) (see also notes on risk factors). |
| Bone mineral density (BMD) | (BMD) Please select the make of DXA scanning equipment used and then enter the actual femoral neck BMD (in g/cm2). Alternatively, enter the T-score based on the NHANES III female reference data. In patients without a BMD test, the field should be left blank (see also notes on risk factors) (provided by Oregon Osteoporosis Center). |

## Annexure 3 - QRISK2 calculator (Cardiovascular risk calculator)




There is no HIV-specific CVD risk calculator for those of non-white ethnicity; one approach might be to use the QRISK2 equation and apply a correction for HIV status of 1.6

**Reference**

British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update)

## Annexure 4 - Vaccination against hepatitis B (HBV) if not already immune

High dose (40 µg,-2 doses of 20 µg/ml vaccine) vaccination should be offered.

Four vaccine doses should be given at 0, 1, 2, and 6 months.

**Missed doses**

If series is interrupted after the first dose the second dose should be given as soon as possible and the third dose at least 2 months after the second dose. If only third dose is delayed it should be given as soon as possible

**Testing antibody levels following vaccination**

Antibody levels>100IU/L are regarded as ideal, whereas a level <10 IU/L is classified as nonresponsive.

It is recommended that individuals with HBsAb levels ≥10 but <100 IU/L should receive one booster dose. If retesting of HBsAb level shows antibody level between ≥10- 100 IU/L, regular annual HBsAb testing is needed to guide subsequent boosting requirements.

Individuals who have HBsAb levels <10 IU/L after the primary vaccine course should receive three further vaccine doses at monthly intervals. It is better to delay the revaccination until the viral load is suppressed on ART and the CD4 count has increased > 350 cells/µL.

Screening of HBsAb levels with longer intervals (2-4 yearly) are indicated for individuals with initial HBsAb levels >100 IU/L, CD4 count >350 cells/µL and viral load suppression on ART.

Other individuals should undergo yearly HBsAb screening.

Source- STI management guidelines- NSACP 2019

## Annexure 5 - Details of individual ARV

| Generic name | Dose |
|---|---|
| **Nucleoside reverse-transcriptase inhibitors (NRTIs)** | |
| Abacavir (ABC) | 300 mg twice daily or 600mg once daily |
| Emtricitabine (FTC ) | 200mg once daily |
| Lamivudine (3TC) | 150 mg twice daily or 300mg once daily |
| Zidovudine(AZT) | 300mg twice daily |
| **Neucleotide reverse transcriptase inhibitors (NtRTIs)** | |
| Tenofavir –DF (TDF) | 300mg once daily |
| **Non- Neucleotide reverse transcriptase inhibitors (NNRTIs)** | |
| Efavirenz (EFV) | 600mg once daily |
| Etravirine(ETV) | 200mg once daily |
| Nevirapine(NVP) | 200mg once daily for 14 days,<br>followed by 200mg twice daily |
| **Protease inhibitors (PIs)** | |
| Atazanavir+ritonavir (ATV/r) | 300mg+100mg once daily |
| Darunavir +ritonavir (DRV/r) | 800mg+100mg once daily[a] or<br>600mg +100mg twice daily[b] |
| Lopinavir+ritonavir (LPV/r) | 400mg+100mg twice daily |
| **Integrase strand transfer inhibitors (INSTIs)[c]** | |
| Raltegravir (RAL) | 400mg twice daily |
| Dolutegravir (DTG) | 50 mg once daily* |

a For individuals with no previous use of protease inhibitors.

b For individuals with previous use of protease inhibitors.

c In the presence of rifabutin, no dose adjustment required. In the presence of rifampicin,dose should be adjusted as, RAL – 800mg twice daily: DTG -50mg twice daily

* TDF (Tenofovir 300 mg, Lamivudine 300 mg, Dolutegravir 50 mg fixed dose combination) can be used once daily in adolescents living with HIV weighting at least 30 kg.

Source-Updated recommendations on ART: WHO -2018: Annexure 3

## Annexure 6 - Dosing schedule of ARV drugs for the newborn

| Name of the ART | POA (weeks) | Dose | Dosing Interval |
|---|---|---|---|
| **Zidovudine (AZT)**<br>Liquid –10mg/mL | <30 | 2mg/kg | Twice daily |
| | 30-34 | 2mg/kg | Twice daily for two weeks, and three times a day there after |
| | 34-40<br><2kg birth weight<br>>2kg birth weight | <br>4mg/kg<br>See the dosing chart | Twice daily |
| **Lamivudine (3TC)** (Epivir® )<br>Liquid 10 mg/mL | | 2mg/kg twice daily | Stop NVP after 2/52, in view of long half-life, continue other PEP agents for full 4/52 |
| **Nevirapine (NVP)** (Viramune® )<br>Liquid 10 mg/mL | | 2 mg/kg once a day for 1 week, then 4 mg/kg once a day for 1 week | |
| **Raltegravir (RAL)** (Isentress® )<br>100 mg sachets for oral suspension (10 mg/mL) | | 1.5 mg/kg once a day from birth to day 7, then 3 mg/kg twice a day until 4 weeks of age | |

***Dosing chart for AZT for >34/52 POA with > 2kg birth weight**

| | |
|---|---|
| 2.01–2.12 | 8.5 mg |
| 2.13–2.25 | 9 mg |
| 2.26–2.37 | 9.5 mg |
| 2.38–2.50 | 10 mg |
| 2.51–2.75 | 11 mg |
| 2.76–3.00 | 12 mg |
| 3.01–3.25 | 13 mg |
| 3.26–3.50 | 14 mg |
| 3.51–3.75 | 15 mg |
| 3.76–4.00 | 16 mg |
| 4.01–4.25 | 17 mg |
| 4.26–4.50 | 18 mg |
| 4.51–4.75 | 19 mg |
| 4.76–5.00 | 20 mg |

Source - British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018 : 2020 third interim update: Annexure 3)

***Dosing chart for Syrup NVP as prophylaxis for HIV exposed Infants**

| Infant age/weight | Dosing of NVP | Dosing of AZT |
|---|---|---|
| **Birth to 6 weeks** | | |
| Birth weight <2000g with gestational age > 35 weeks[a] | 2mg/kg once daily | 4mg/kg per dose, twice daily |
| Birth weight 2000-2499g[a] | 10mg once daily<br>(1ml syrup once daily) | 10mg twice daily<br>(1ml syrup twice daily) |
| Birth weight > 2500g | 15mg once daily<br>(1.5ml syrup once daily) | 15mg twice daily<br>(1.5ml syrup twice daily) |
| **>6 weeks to 12 weeks** | | |
| | 20mg once daily<br>(2ml syrup once daily or half a 50mg tablet once daily) | No dose established for prophylaxis: use treatment dose<br>60mg twice daily<br>(6 ml syrup twice daily or a 60mg tablet twice daily) |

[a] For premature infants <35 weeks of gestational age should be dosed with expert guidance.

Source- A guide to ART therapy, NSACP -2016

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