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ART in HIV/AIDS Adults and Adolescents

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Abstract

There has been a rapid decline in HIV-related mortality and morbidity due to the wider availability of affordable, more efficacious and less toxic ARVs over the last two decades. ART consists of the use of a combination of at least three ARV drugs from different classes to inhibit the replication of HIV and reduce viraemia to undetectable levels. Continued suppression of viral replication leads to the restoration of immune response, reflected by an increase in the CD4 count. Increase in CD4 count leads to slowing of the disease progression, reduced frequency of OIs, improvement in the quality of life and increased longevity. Successes achieved by ART have now transformed the perception about HIV infection from being a 'virtual death sentence' to a 'chronic manageable illness'. ART was earlier known as Highly Active ART (HAART) and as combination ART (cART).

1. Goals of Antiretroviral Therapy

ART cannot cure HIV infection, as the currently available ARV drugs cannot eradicate the virus from the human body. This is because a pool of latently infected CD4 cells is established during the earliest stages of acute HIV infection. HIV persists within the organs/cells and fluids (e.g., brain, liver and lymphoid tissue) despite prolonged suppression of plasma viraemia to undetectable level by ART. The primary goals of ART are maximal and sustained reduction of plasma viral load and restoration of immunological functions. The reduction in the viral load also leads to reduced transmissibility and reduction in new HIV infections. The defined goals of ART are depicted in Table 1.

Table 1. Goals of ART

Goals of ART	
Clinical goals	Increased survival 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
Preventive goals	Reduction of HIV transmission by suppression of viral load

Due to continued viral suppression, the destruction of CD4 lymphocyte cells is reduced and, over time, there is an increase in the CD4 count, which is accompanied by partial restoration of pathogen-specific immune function. This leads to a reduction in incidence of OIs, reduced morbidity and mortality.

2. Principles of Antiretroviral Therapy

A continuous high level of HIV replication takes place in the body right from the early stages of the infection. At least one billion viral particles are produced during the active stage of replication. The ARVs act on various stages of the HIV viral replication and interrupt the process of viral replication in the body. Figure 1 depicts the various enzymes involved in viral replication and the points where ARVs target the virus. The ARV drugs act on the viral replication in the following steps and their classes are labelled according to the site of their action:

Block binding of HIV to the target cell **(Fusion Inhibitors and CCR-5 co-receptor blockers)**

Block the viral RNA cleavage and one that inhibits reverse transcriptase **(Reverse Transcriptase Inhibitors)**

Block the enzyme integrase, which helps in the pro-viral DNA being incorporated into the host cell chromosome **(Integrase Inhibitors)**

Block the RNA to prevent viral protein production

Block enzyme protease (Protease Inhibitors)

Inhibit the budding of virus from host cells

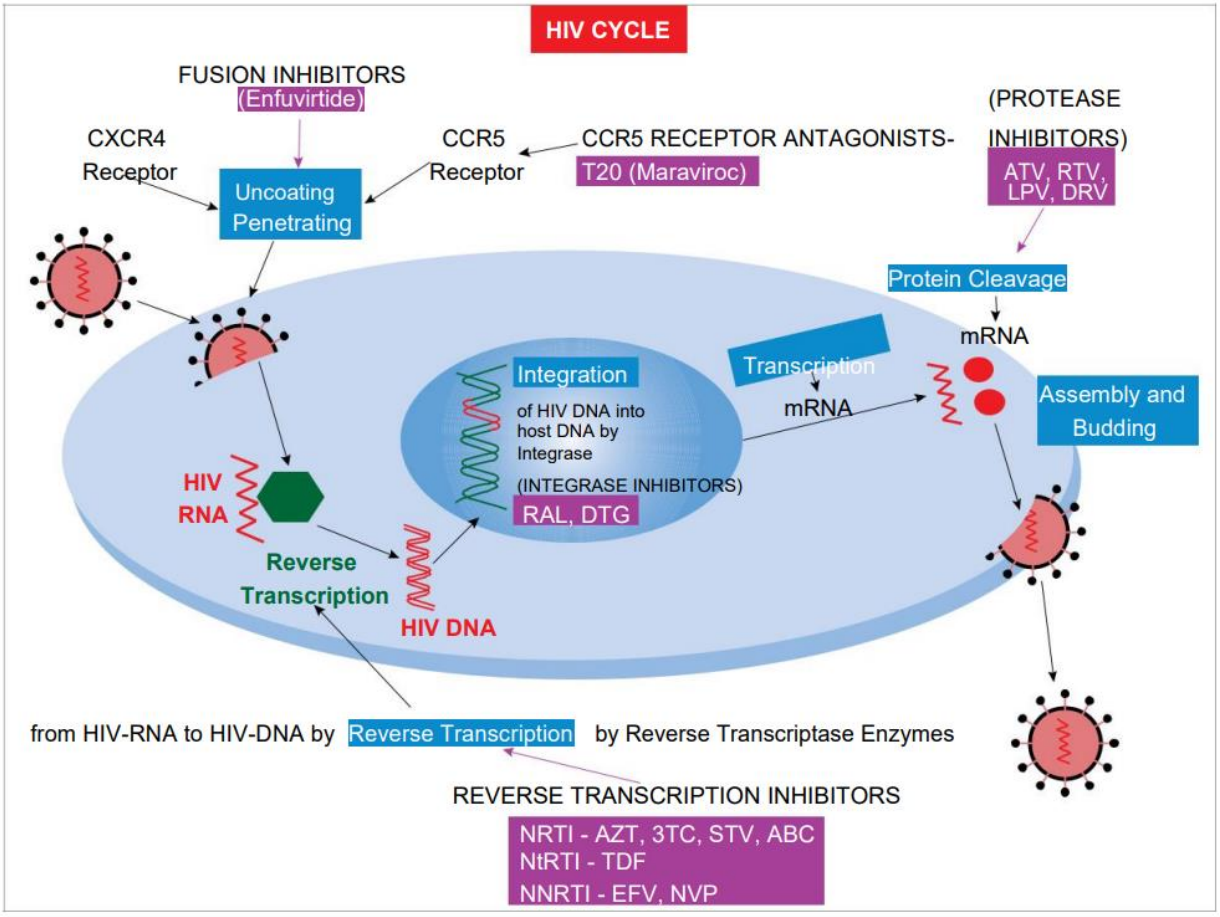

Figure 1. Targets of antiretroviral drugs

Table 2. Classes of ARV Drugs

Nucleoside reverse transcriptase inhibitors (NsRTI)	Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Protease inhibitors (PI)
Zidovudine (AZT)*	**Nevirapine (NVP)***	Saquinavir (SQV)
Stavudine (d4T)	**Efavirenz (EFV)***	**Ritonavir (RTV)***
Lamivudine (3TC)*	Delavirdine (DLV)	Nelfinavir (NFV)
Abacavir (ABC)*	Rilpivirine (RPV)	Amprenavir (APV)
Didanosine (ddI)	Etravirine (ETV)	Indinavir (INV)
Zalcitabine (ddC)	Doravirine (DOR)	**Lopinavir (LPV)***
Emtricitabine (FTC)	**Integrase Inhibitors**	Fosamprenavir (FPV)
Nucleotide reverse transcriptase inhibitors (NtRTI)	**Dolutegravir (DTG)***	**Atazanavir (ATV)***
	Raltegravir (RGV)*	Tipranavir (TPV)
	Elvitegravir (EVG)	**Darunavir (DRV)***
Tenofovir Disoproxil Fumarate (TDF)*	Bictegravir (BIC)	
Tenofovir Alafenamide (TAF)	Cabotegravir (CAB)	
Fusion inhibitors (FI)	**CCR5 entry inhibitor**	**Post attachment maturation inhibitor**
Enfuvirtide (T-20)	Maraviroc (MVC)	Ibalizumab (IBA)
***Available in the national programme**		

3. Clinical Pharmacology of Commonly Used ARV Drugs

3.1 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

The first effective class of ARV drugs discovered was the **Nucleoside analogues,** which act by incorporating themselves into the DNA of the virus, thereby stopping the building process. The resulting DNA is incomplete and cannot create new viruses. **Nucleotide analogues** work in the same way as nucleosides, but they have a non-peptidic chemical structure. The details of individual ARV drugs of this class are listed in Table 3.

Table 3. Commonly used NRTIs

Generic Name	Dose	Adverse effects
Tenofovir Disoproxil Fumarate (TDF)	300 mg once daily	Renal toxicity, bone demineralization
Zidovudine (AZT)	300 mg twice daily	Anaemia, neutropenia, bone marrow suppression, GI intolerance, headache, insomnia, myopathy, lactic acidosis, skin and nail hyperpigmentation

Generic Name	Dose	Adverse effects
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily	Minimal toxicity, rash (though very rare)
Abacavir (ABC)	300 mg twice daily or 600 mg once daily	Hypersensitivity reaction in 3% to 5% (can be fatal), fever, rash, fatigue, nausea, vomiting, anorexia, respiratory symptoms (sore throat, cough, shortness of breath); rechallenging after reaction can be fatal

3.2 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) stop HIV production by binding onto the reverse transcriptase and preventing the conversion of RNA to DNA. These drugs are called 'non-nucleoside' inhibitors because, even though they work at the same stage as nucleoside analogues, as chain terminators, they inhibit the HIV reverse transcriptase enzyme by directly binding to it. The details of individual ARV of this class are shown in Table 4.

Table 4. Commonly used NNRTIs

Generic Name	Dose	Food-related advice	Adverse Effects
Efavirenz (EFV)	600 mg once daily (bedtime administration is suggested to decrease central nervous system side Effects	Avoid taking after high-fat meals	Central nervous system symptoms (dizziness, somnolence, insomnia, confusion, hallucinations, agitation) and personality change. Rash occurs, but less common than with NVP
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily	None	Hepatitis (usually within 12 weeks); sometimes, life-threatening hepatic toxicity. Skin rash occasionally progressing to severe conditions, including Stevens Johnson's syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Patients who develop severe hepatic toxicity or grade 4 skin rashes should not be rechallenged.

3.3 Integrase Inhibitors (Integrase Strand-Transfer Inhibitor [INSTI])

Integrase inhibitors are a class of ART drugs designed to block the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell.

Since integration is a vital step in retroviral replication, blocking it can halt further replication of the virus.

Raltegravir (RAL): Raltegravir was the Integrase inhibitor approved for use in 2007. It is metabolized primarily through uridine diphosphate glucuronosyltransferase 1A1 and has a single inactive glucuronide metabolite.

It is not a substrate, inhibitor or inducer of cytochrome P450 enzymes and it exhibits low potential for drug–drug interactions. It is well tolerated; most reported adverse effects include nausea, headache, diarrhoea, fever, CPK elevation, muscle weakness and insomnia. The major toxicities are given in Table 5. Raltegravir was approved for use in both treatment-naive and treatment-experienced patients, and it had been primarily used for second- or third-line

ART in the national ART programme.

3.4 Dolutegravir (DTG)

It was first approved for its usage by US FDA in 2013. Later, it was recommended by WHO in 2019 and NACO Technical Resource Group approved its usage since July 2020. NACO recommends Dolutegravir as the preferred drug for treatment of HIV-positive adults, adolescents and children (aged more than 6 years with bodyweight more than 20 kg) under the NACP. DTG is an orally bioavailable INSTI with activity against HIV type 1 and 2 (HIV-1/2 and both) infections. Upon oral administration, dolutegravir binds to the active site of integrase, an HIV enzyme that catalyses the transfer of viral genetic material into human chromosomes. This prevents integrase from binding to retroviral DNA, and blocks the strand transfer step, which is essential for the HIV replication cycle. This prevents HIV replication. Dolutegravir is currently the preferred drug in the first-line and also in second-line treatment regimens.

Table 5. Integrase Inhibitors used in National Programme

Generic Name	Dose	Adverse Effects
Dolutegravir (DTG) (Preferred INSTI in programme)	50 mg once daily	✖ Insomnia: Patients with complaints of sleep disturbances need to be reviewed and to be managed accordingly. Sedatives should be added with appropriate consultation if that is affecting the daily routine of the patient. ✖ Headache: If headache is persistent and affecting daily routine of activities, the PLHIV should be referred for expert opinion. ✖ Dizziness ✖ Tiredness ✖ Allergic reactions ✖ Weight gain: Weight gain is a known side effect and strict monitoring is required and information should be given to the PLHIV about the same.
Raltegravir (RAL)	400 mg twice daily	✖ Rhabdomyolysis, Myopathy, Myalgia, diarrhoea, fever, rash, Stevens-Johnson's syndrome, Toxic Epidermal Necrolysis, Hepatitis and Hepatic failure ✖ Insomnia

Dolutegravir has drug interactions with the drugs listed in Table 6.

Table 6. Drug Interactions with Dolutegravir

Key Drug Interaction	Suggested Management
Amodiaquine	Use an alternative antimalarial agent
Carbamazepine	Use DTG twice daily or substitute with an alternative anticonvulsant agent
Phenytoin and phenobarbital	Use an alternative anticonvulsant agent

Key Drug Interaction	Suggested Management
Dofetilide	Use an alternative antiarrhythmic agent
Metformin	Limit daily dose of metformin to 1000 mg when used with DTG and monitor glycaemic control
Polyvalent cation products containing Al, Ca, Fe, Mg and Zn (e.g., antacids, multivitamins and supplements)	Use DTG at least two hours before or at least six hours after supplements containing polyvalent cations
Rifampicin	Use DTG 50 mg twice daily or substitute with rifabutin

3.5 Protease Inhibitors

Protease inhibitors (PIs) work at the last stage of the viral reproduction cycle. They prevent HIV from being successfully assembled and released from the infected CD4 cell. All PIs can produce GI intolerance, altered taste, abnormal liver function test and bone disorder and all have been associated with metabolic abnormalities, such as hyperglycaemia, insulin resistance and increase in triglycerides, cholesterol and body fat distribution (lipodystrophy). The details of individual ARVs of this class are shown in Table 7.

Table 7. Commonly used PIs

Generic Name	Dose	Adverse Effects
Atazanavir/ ritonavir (ATV/r)	300 mg Atazanavir + 100 mg Ritonavir once daily	Unconjugated hyperbilirubinemia, lipid abnormality, hyperglycaemia, fat maldistribution, nephrolithiasis, cholelithiasis, PR prolongation
Lopinavir/ ritonavir (LPV/r) Heat-stable Tablets	200 mg Lopinavir/ 50 mg Ritonavir Fixed dose tablet 2 tablets twice daily	Diarrhoea, nausea, vomiting, abnormal lipid profiles, glucose intolerance
Darunavir (DRV)	600 mg twice a day (when used with Ritonavir 100 mg twice daily)	Hepatotoxicity, skin rash (10%), diarrhoea, nausea, headache, hyperlipidaemia, serum transaminase elevation, hyperglycaemia
Ritonavir (RTV)	100 mg once or twice daily according to the PI to be boosted	Common: GI (diarrhoea, nausea, vomiting, abdominal pain (upper and lower); Rarely, neurological disturbances (including paraesthesia)

Co-administration of antitubercular and ARV agents: Available clinical data suggest that, for most individuals, Rifampicin-based regimens can be successfully combined with the NNRTI, Efavirenz. However, PIs are associated with important drug–drug interactions. Combinations are limited by the alterations in the activity of the hepatic cytochrome P450 (CYP) enzyme system, which may produce sub-therapeutic plasma concentrations of ARV drugs. For example, PIs must often be avoided if the potent CYP inducer Rifampicin is co-administered. Alternatively, Rifabutin, which has efficacy similar to Rifampicin, can be used with appropriate dose reduction instead of Rifampicin. Rifampicin-based regimens also suppress the bioavailability of DTG. However, Rifampicin in FDC can be used with a DTG-based ART regimen with an extra dose of DTG 50 mg (at an interval of 12 hours with the regular dose of DTG) for the entire duration of ATT.

4. Considerations Before Initiation of ART

All people with confirmed HIV infection should be referred to the ART centre for registration

into HIV care, comprehensive clinical and laboratory evaluation to assess baseline status, treatment of pre-existing opportunistic infections, treatment preparedness, counselling and rapid ART initiation, preferably the same day unless contraindicated otherwise.

The following principles need to be kept in mind:

The patient should be adequately prepared, and informed consent should be obtained from the patient or from the caregiver in case the patient is a minor, before initiating HIV care and ART. (For modified consent form, refer to National Operational Guidelines for ART Services, 2021.)

Treatment should be started based on the person's informed decision and preparedness to initiate ART with information and understanding of the benefits of treatment, lifelong course of medication, issues related to adherence and positive prevention.

A caregiver should be identified for each person to provide adequate support. Caregivers must be counselled and trained to support treatment adherence, follow-up visits and shared decision-making.

All patients with clinical stages 3 and 4 and those with CD4 less than 350 cells/mm3 need to be put on CPT. All patients to be screened for TB using the 4-symptom tool (current cough, fever, night sweats and weight loss) and those who do not have TB need to be started on Tuberculosis Preventive Therapy (TPT) / (Isoniazid Preventive Therapy) in addition to ART.

ART should not be started in the presence of an active OI. In general, OIs should be treated or stabilized before commencing ART. Mycobacterium Avium Complex (MAC) and Progressive Multifocal Leukoencephalopathy (PML) are exceptions in which commencing ART may be the preferred treatment, especially when specific MAC therapy is not available.

Some clinical conditions, which may regress following the commencement of ART, include candidiasis and cryptosporidiosis. The following OIs and HIV-related illnesses (Table 8) need treatment or stabilization before commencing ART.

Table 8. Opportunistic infections and HIV-related conditions and ART initiation

Clinical Picture	Action
Any undiagnosed active infection with fever	Diagnose and treat first; start ART when stable
Tuberculosis	✖ ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count (except when signs and symptoms of meningitis are present). ✖ Among PLHIV with TB meningitis, ART should be delayed at least 4 weeks (and initiated within 8 weeks) after treatment for TB meningitis is initiated. Corticosteroids should be considered for adjuvant treatment of TB meningitis.
PCP	Treat PCP first; start ART when PCP treatment is completed.

Clinical Picture	Action
Invasive fungal diseases: **Oesophageal Candidiasis, Penicilliosis, Histoplasmosis**	✖ Start treatment for Oesophageal Candidiasis first; start ART as soon as the patient can swallow comfortably; ✖ Treat Penicilliosis and Histoplasmosis first; start ART when patient is stabilized or OI treatment is completed.
Cryptococcal Meningitis	✖ For people with signs and symptoms of meningitis, ART should be delayed till the results of lumbar puncture are available or patient is stabilized with presumptive treatment. ✖ Due to risk of life-threatening immune reconstitution inflammatory syndrome (IRIS), immediate ART initiation is contraindicated in 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.
Bacterial Pneumonia	Treat Pneumonia first; start ART when treatment is completed.
Malaria	Treat Malaria first; start ART when treatment is completed.
Acute diarrhoea which may reduce absorption of ART	Diagnose the cause and treat diarrhoea first; start ART when diarrhoea is stabilized or controlled.
Non-severe anaemia (Hb <9 g/dl)	Start ART if no other causes for anaemia are found (HIV is often the cause of anaemia).
Skin conditions such as Pruritic Papular Eruption and Seborrhoeic Dermatitis, Psoriasis, HIV-related Exfoliative Dermatitis	Start ART (ART may resolve these problems).
Suspected MAC, Cryptosporidiosis and Microsporidiosis	Start ART (ART may resolve these problems)
Cytomegalovirus Retinitis	Start treatment for CMV urgently and start ART after 2 weeks of CMV Treatment
Toxoplasmosis	Treat Toxoplasmosis first; start ART after 6 weeks of treatment and when patient is stabilized

5. When to Start ART in Adults and Adolescents

In general, the clinical management of an HIV-infected patient revolves around optimizing the treatment regimen, reducing drug toxicity, reducing the pill burden and increasing adherence to the treatment.

The guidelines on when to start ART have evolved over the years towards early and rapid initiation of ART; CD4 count cut-off point for ART initiation moving from less than 200 cells/mm3 in 2004 to less than 350 cells/mm3 in 2011 and then to less than 500 cells/mm3 in 2016. The current recommendation to **TREAT ALL**, regardless of the clinical stage or CD4 count is in the National Programme since 2017. These changes have been based on the evidence from various randomized clinical trials (RCT) and large observational cohorts, which have revealed that with early ART initiation, there is a significant delay in progression to AIDS and reduction in the incidence of TB. These studies are summarized in Figure 2.

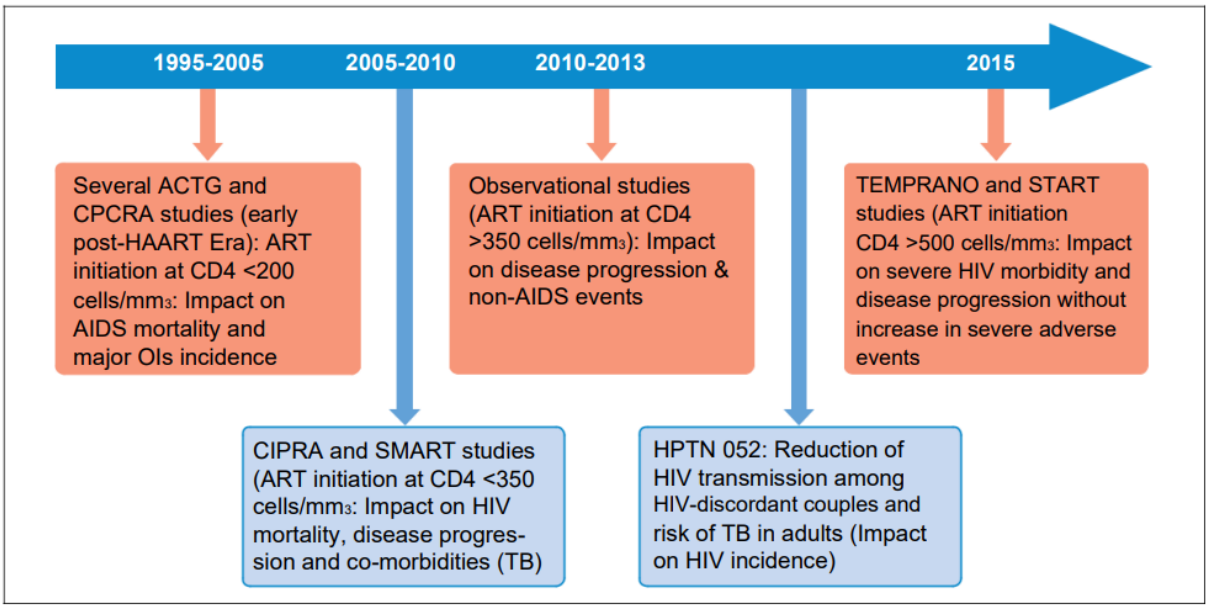

Figure 2. Evolution of CD4 cut-offs for ART initiation over time

5.1 Current NACO Guidelines on When to Start ART

All persons diagnosed with HIV infection should be initiated on ART regardless of the CD4 count or WHO Clinical Stage or age group or population sub-groups.

Ensuring good adherence to treatment is imperative for the success of the treatment as well as for the prevention of drug resistance. To achieve this, counselling must start from the first contact of the patient with the clinical team. Counselling should include preparing the patient for treatment and providing psychosocial support through an identified caregiver/guardian/treatment support and support networks. All patients should undergo two to three counselling sessions (preparedness counselling) before the initiation of ART. The period of waiting for investigations and their results should be utilized for counselling, Cotrimoxazole prophylaxis, TPT in eligible patients, and treatment preparation. All efforts should be made to trace the patients who have missed their visits or are lost to follow-up to initiate ART in all PLHIV registered at the ART centres. NGOs and positive network linkages should be established by each ART centre for its respective locality.

6. What to Start: Antiretroviral Therapy Regimens

Fixed-dose combinations (FDCs) of ARVs are preferred because they are easy to prescribe and easy for patients to take, thereby facilitating improved and desirable treatment adherence. This is essential for PLHIV as the treatment is life-long and we need to minimize the chance of developing drug-resistant mutants in their body and the resultant treatment failure. Further, FDCs have distinct advantages in drug procurement and distribution, essentially the drug stock management itself. National experience has shown that regimens with FDCs are more acceptable, well tolerated and adequately complied with.

6.1 Recommended Choice of First-Line Regimen

In consideration of the WHO guidelines and based on recommendations of NACO Technical Resource Group, it has been decided to include DTG-containing regimens as the preferred first-line treatment for HIV-positive adults, adolescents and children (weighing more than 20 kg/age more than 6 years) under the NACP since July 2020.

Dolutegravir is known to have the following features:

High genetic barrier: It is highly potent and has high genetic barrier. That is why it is an ideal drug.

Rapid viral suppression: It helps in achieving rapid viral suppression. It has been found to reduce the viral copies to <50 copies/ml within 4 weeks and this helps reduce the chances of transmission.

Fewer toxicities and side effects: DTG-based

regimens are expected to have fewer side effects as compared to NNRTI-based regimens. These have lesser allergic reactions and chances of neuropsychiatric events compared to NNRTI-based regimens.

Minimal drug interactions: DTG has minimal drug interactions with concomitant medications PLHIV might be on.

Effective against HIV-2: DTG-based regimens can be prescribed for PLHIV infected with HIV-2 or combined HIV-1 and HIV-2. Prior to the availability of DTG in the programme, those infected with HIV-2 were being initiated with two NRTIs plus boosted PI regimen. With DTG in the programme, this will further bring harmonization across patient populations.

No need for substitution of DTG-based ART regimen in PLHIV if co-infected with TB or HBV or HCV.

The regimens described in this chapter are for HIV-1, HIV-2 and HIV-1 & 2 infected individuals unless specified otherwise.

The basic principle for **first-line ART** for treatment-naive adult and adolescent patients is to use a triple drug combination from two different classes of ARVs.

The first-line ART essentially comprises of a NRTI backbone, preferably Non-Thymidine (Tenofovir plus Lamivudine) and one INSTI, preferably DTG. Based on the evidence supporting better efficacy and fewer side effects, the **preferred first-line ART regimen for all PLHIV with age >10 years and weight >30kg is as follows:**

Tenofovir (TDF 300 mg) + Lamivudine (3TC 300 mg) + Dolutegravir (DTG 50 mg) regimen (TLD) as FDC in a single pill once a day (at a fixed time every day as per patient's convenience)

This regimen has the advantage of harmonization in the treatment of all adults, adolescents, pregnant women including those with HIV-1, HIV-2, HIV-1 & 2, women exposed to single dose nevirapine in the past and those co-infected with TB or Hepatitis.

It is a simple, potent and well-tolerated regimen that offers the advantage of a decentralized service delivery and monitoring. It also simplifies the supply chain and minimizes monitoring requirements.

In cases where the preferred first-line ARV regimen of TDF+3TC+DTG cannot be used, the alternative regimens are mentioned in Table 9.

Table 9. Alternate first-line ART in adults and adolescents

Condition	Alternate First-line Regimen
PLHIV with body weight <30 kg	ABC 600 mg + Lamivudine 300mg, one tablet + DTG (50 mg) once daily in the morning or any fixed time every day as per patient's convenience
All patients with high (above ULN for laboratory) serum creatinine values (Calculate Creatinine clearance*)	ABC 600 mg OD, Lamivudine (as per creatinine clearance**) and DTG 50 mg once daily in the morning or any fixed time every day as per patient's convenience
PLHIV on Rifampicin-containing ATT Regimen	Tenofovir (300 mg) + Lamivudine (300 mg) + Dolutegravir (50 mg) – FDC one tablet once daily (in the morning or any fixed time every day as per patient's convenience) + Additional dose of DTG 50 mg to be provided (12 hours after taking their regular dose) until 2 weeks after completion of ATT
Women of childbearing potential who do not wish to take DTG-based ART after adequate and optimal counselling* **	Tenofovir (300 mg) + Lamivudine (300 mg) + Efavirenz (600mg) If Efavirenz is contraindicated (HIV-2/HIV-1&2/prior NNRTI exposure) then Tenofovir (300 mg) + Lamivudine (300 mg) + [Lopinavir (200 mg) + ritonavir (50 mg) twice daily]

*For all patients with high serum creatinine values (above ULN for laboratory), calculate creatinine clearance.

**Lamivudine, along with Abacavir, may be used in full dose if creatinine clearance is more than 30 ml per minute, with patient being closely monitored.

***Women of childbearing potential receive full information and medical guidance that is appropriate to their situation and are supported in making an informed decision.

6.2 General Guidance

A single pill of TLD should be taken preferably at bedtime, and instances where additional dose of DTG is indicated should be taken preferably in the morning.

Patients with severe Diabetes and Hypertension should be monitored more closely for TDF toxicity.

Patients starting on DTG should be monitored for blood glucose (six monthly) and weight gain (on monthly visits). Appropriate physical activity should be advised to prevent weight gain.

Guidance on laboratory investigations is mentioned in the laboratory investigations.

6.3 Considerations for ART in Adolescents

According to WHO, adolescence is the period between 10 and 19 years of age. During this period, healthy HIV-infected adolescents pass through well-described stages of physical, psychological and sexual maturation for which appropriate support and care are required.

An estimated 1.74 million adolescents (10–19 years old) were living with HIV globally in 2019. HIV-related deaths among adolescents are estimated to have tripled since 2000, making HIV the second leading cause of death among adolescents worldwide with 34,000 (23,000–50,000) estimated number of adolescents dying of AIDS-related causes in 2019 (UNAIDS, 2019).

Adolescence is marked by rapid physical, neuro-developmental, emotional and social changes. Adolescents have significantly lesser access to ART and coverage of ART than adults, high risk of loss to follow-up, suboptimal adherence and special requirements for comprehensive care, including psychosocial support and sexual and reproductive healthcare. Adolescents also face significant barriers to the access of essential health and support services, especially because of policy and legal barriers related to the age of consent.

Perinatally infected adolescents are more likely to experience chronic diseases and neurodevelopmental growth and pubertal

delays in comparison to their age-matched peers. Older adolescents who acquire HIV behaviourally do not present the same clinical features but face potentially greater challenges in dealing with stigma and lack of family and community support to access care.

Physicians giving care and treatment to such adolescents should consider the following issues:

Disclosure

Developmental delays

Transition difficulties from childhood to adulthood that may influence choice of appropriate ART regimens

Adherence issues

Psychosocial support needs

Physical and sexual issues

6.4 Rapid ART Initiation for Newly Diagnosed PLHIV at ART Centre

The introduction of the 'Treat All' recommendation supports the rapid initiation of ART, including the offer of same-day initiation where there is no clinical contraindication. Rapid ART initiation is defined as **"ART initiation within seven days from the day of HIV diagnosis"**. Following a confirmed HIV diagnosis and clinical assessment, same-day /rapid ART initiation should be offered to all PLHIV adequately prepared and ready for initiation. However, if an active OI is present, ART initiation may be deferred as required.

PLHIV should be assessed for readiness for ART initiation using the algorithm provided in Figure 3 (with concurrent sample collection for CD4 testing and baseline investigation). This algorithm focusses on clinical screening of PLHIV for potential presence of common OIs/advanced HIV disease/comorbid conditions:

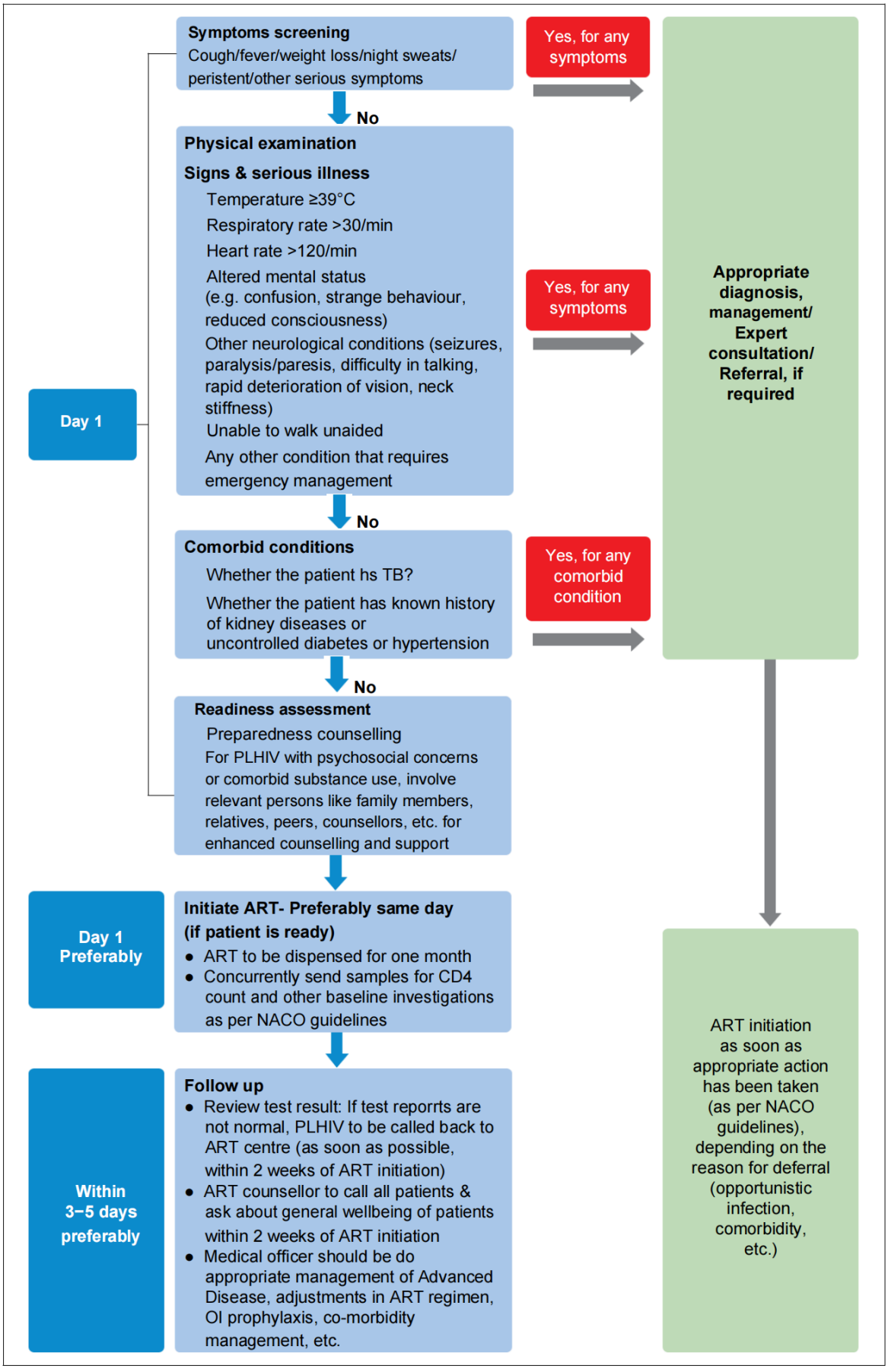

Figure 3. Rapid ART initiation algorithm in PLHIV

PLHIV who do not have any such conditions can be fast tracked for ART initiation giving them the benefits of timely ART initiation, such as reduction in incident TB and other OIs, achieving quick viral load suppression, prevention of transmission and better health outcomes. Additionally, it will also reduce travel inconvenience and financial burden for PLHIV.

PLHIV who have any such symptoms would require further evaluation for diagnosis and management of common OIs/advanced HIV disease/comorbid conditions before ART initiation.

7. Monitoring of Patients on ART

Follow-up and monitoring are essential in patients initiated on ART to track clinical progress, monitor well-being and to identify adverse drug reactions and toxicities.

ART monitoring includes clinical monitoring and laboratory monitoring. Clinical monitoring includes monitoring of adherence to ART as well. The client should be monitored every month for clinical progress, side effects of the ARVs and treatment adherence. Clinical and laboratory evaluations are carried out at specified intervals for patients on ART.

A combination of clinical and laboratory monitoring is to be carried out in all PLHIV after initiation of ART as depicted in Table 10.

Table 10. Monitoring and follow-up schedule for patients on ART

Monitoring Tool	When to Monitor
Body weight Height / length in children	Every visit
Treatment adherence	Every visit
Clinical monitoring and T-staging	Every visit
4-symptom TB screening	Every visit
Screening for common NCD; Hypertension, Diabetes mellitus	Every 6 months or symptom directed
Laboratory evaluation based on ART regimen	Every 6 months or symptom directed
CD4 Count	CD4 must be done every 6 months*
Viral load	At 6 months, 12 months and then every 12 months**

***CD4 Count:**

1. As routine virological monitoring is available, CD4 testing should be done every 6 months and can be discontinued in PLHIV (except those with HIV-2 infection) when CD4 count reaches greater than 350 cells/mm$_3$ and viral load is less than 1000 copies/ml (when both tests are conducted at the same time).
2. CD4 monitoring should be restarted for any patient if
   a. the patient has been switched due to treatment failure, that is, virologic failure (Plasma Viral Load ≥1000 copies/ml) or
   b. when deemed necessary for clinical management by the clinician at any point in time

**For patients on second/third-line ART, Plasma Viral Load testing to be done every 6 months

The various monitoring indicators are listed below:

7.1 Clinical Monitoring

Monthly clinical evaluation

Body weight, overall well-being, any new symptoms/signs, 4-symptom screening for TB at every visit

Monthly treatment adherence evaluation, pill count, self-reported adherence

Adherence to ART must be assessed at each visit and adherence must be reinforced through counselling at each visit.

Adverse reactions of ART/OI drugs

Drug–drug interactions, look for all concomitant drug use (prescribed and over the counter)

Look for IRIS

7.2 Immunological Monitoring

CD4 testing should be done every 6 months.

As routine virological monitoring is available, CD4 testing should be done every 6 months and can be discontinued in PLHIV (except those with HIV-2 infection) when CD4 count reaches greater than 350 cells/mm3 and plasma viral load is less than 1000 copies/ml (when both tests are conducted at the same time).

Virological monitoring: At 6 months and 12 months after ART initiation and then every 12 months

7.3 Interpretation of Plasma Viral Load Testing Results

PLHIV with plasma viral load report <1000 copies/ml should continue the same ART regimen. Next viral load testing should be done as per guidelines.

PLHIV with plasma viral load report ≥1000 copies/ml should undergo step-up enhanced adherence counselling for three months. ART centre counsellor should provide intensive support to improve adherence.

Repeat viral load testing should be done once treatment adherence is > 95% for three consecutive months.

If repeat plasma viral load report is <1000 copies/ml, patient should be continued on same ART regimen.

If repeat plasma viral load report is ≥1000 copies/ml, patient should be referred electronically to SACEP (e-SACEP) for further management.

In case of PLHIV with high viral load, declining CD4 counts and poor clinical conditions, ART Medical Officer may refer the patient to SACEP, even based on a single viral load report, for further management.

7.4 Laboratory Monitoring

The laboratory monitoring of PLHIV on ART is also very important. Regular monitoring of the patient's laboratory parameters is crucial to identify ARV-related toxicities, inter-current illnesses, drug–drug interactions and other metabolic abnormalities. The frequency of monitoring and the parameters to be monitored depend on the components of the regimen. The summary of the laboratory monitoring recommended under the programme is presented in Table 11 Additional laboratory tests outside this schedule may be performed as clinically indicated by the ART medical officer.

Table 11. Laboratory monitoring of individual ARV drugs

For all patients on ART, we need to do CD4, Hb, TLC, DLC, ALT (SGPT) and serum creatinine once every six months								
Tests for monitoring patients on ART (Follow-up tests): Drug-specific tests frequency as below								
In regimen ARV drug Monitoring	test Monitoring	Baseline	15th Day	First month	Third month	Sixth month	6 months Then every	At 12 months
On Tenofovir-based ART	Serum creatinine	Yes	&	&	&	Yes	Yes	&
	Urine for protein	Yes	&	&	&	Yes	Yes	&
On Zidovudine-based ART	CBC	Yes	Yes	Yes	Yes	Yes	Yes	&
Efavirenz-containing ART	Lipid profile	Yes	&	&	&	&	&	Yes
Atazanavir-containing ART	LFT Lipid profile	Yes	&	&	&	Yes	Yes	&
Lopinavir-containing ART	Lipid profile & Blood sugar	Yes	&	&	&	Yes	Yes	&
Dolutegravir- containing ART	ALT (SGPT) & blood sugar	Yes				Yes	Yes	&

The prevalence of lipid abnormalities is significantly frequent in patients on ART, particularly if they are on Stavudine, Efavirenz or boosted PIs. In case of these patients and those with significant risk factors for coronary artery disease, a fasting lipid profile should be done at 6 months or earlier as required. Otherwise, yearly evaluations suffice. This is expected to decrease since DTG is not known to have significant lipid abnormalities.

Fasting blood sugar is recommended as part of the baseline screening of all patients to be started on ART, as currently one of the major causes of morbidity in India is diabetes mellitus.

More frequent visits or additional laboratory monitoring may be required if the patient develops any symptoms or side effects of the ARVs or experiences difficulties in adherence to ARVs due to any reason, including clinically indicated reasons as per the discretion of the medical officer.

8. Conclusion

Once the patient has stabilized and CD4 starts improving, the patient does not have any OI or adverse events and has been adherent to ART for at least 6 months, the frequency of visits can be reduced to once in 3 months.

Taking ART is a lifelong commitment, and the first 6 months of therapy are especially important. Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART. However, certain OIs and/or IRIS and/or early adverse drug reactions such as drug hypersensitivity may develop, especially in the first 3 months of treatment. ART significantly decreases the overall mortality, but death rates are highest in the first 3 months of ART initiation in PLHIV with advanced HIV disease. As the immune system recovers, there may be exacerbation of previously sub-clinical coexisting infections (e.g., TB), resulting in an apparent worsening of the disease. It is to be remembered that this is not due to failure of therapy, but due to the success of the therapy and resulting immune reconstitution. Complications are most common during the first few weeks of treatment, especially among people starting ART with advanced HIV disease, those with severe immunodeficiency and existing co-infections and/or comorbidities, very low haemoglobin, low BMI, very low CD4 counts or those who are severely malnourished. Poor adherence during this period is also associated with the risk of early treatment failure and rapid development of drug

resistance.

8.1 CD4 Recovery

In most adults and children, CD4 cell counts rise by 40 to 60 cells/year when ART is initiated, and immune recovery starts. Generally, this increase occurs during the first year of treatment, achieves a plateau and then continues to rise further during the second year. However, severe immunosuppression may persist in some individuals who do not experience a significant rise in CD4 cell count with treatment, especially those with a very low CD4 cell count at the time of initiation of ART. Failure to achieve some CD4 recovery should alert the healthcare provider to potential adherence problems or primary non-response to ART and consideration should be given to continue prophylaxis for OIs such as CPT.

Several other factors can influence CD4 cell counts apart from laboratory-related variables. These include the following:

Concurrent infections, specifically hepatitis;

Leukopenia of varying aetiology, especially caused by ART itself and steroids or other immunosuppressive therapies;

Pregnancy can also lead to lower values.

Diurnal variation occurs; CD4 cells are lower at noon, and highest in the evening around 8 pm.

Psychological stress seems to play a negligible role, even though patients often assume the contrary.

Several factors can influence the extent of immune reconstitution during ART. The degree of viral suppression is crucial: the lower the viral load, the more pronounced the effect. The absolute increase in CD4 count is higher if CD4 counts were high at the start of ART. Presence of naive CD4 T-cells at the time of ART initiation is a particularly important factor for long-term immune reconstitution/recovery. Hence CD4 response may vary widely, and we need to focus son viral suppression.

Patients with declining CD4 but undetectable plasma viral load should be evaluated for recent viral infection, immunization and CD4 variability; if all these have been ruled out, one may consider the possibility of HIV-2 or HIV-1 and HIV-2 co-infection.

8.2 Plasma Viral Load

Within the first few weeks of therapy, the plasma viral load should start decreasing and after 6 months, a plasma viral load test should be done to evaluate the response to ARVs. Plasma viral load testing should be done at 6 months after initiation of ART, again at 12 months and once the viral load is suppressed, every 12 months. Most people will achieve viral suppression at 24 weeks of initiation of treatment.

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