Guideline

Antiretroviral therapy-an Update

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Antiretroviral therapy (ART) consists of use of combination of at least three antiretroviral drugs from different groups to inhibit the replication of HIV and reduce viraemia to undetectable levels. Durable suppression of viral replication leads to a restoration of immune response and slowing of the disease progression reflected by increase in CD 4 count, reduced frequency of Opportunistic Infections, improvement in the quality of life and increased longevity.

The primary goals of ART are maximal and durable reduction in plasma viral levels and restoration of immunological functions. The reduction in viral load also leads to reduced transmissibility and reduction in new infections. However there is no cure for HIV so far and treatment is life long

Considering the lifelong management, one has to sequence the drug therapy in view of easy and repeated viral mutability. In addition to drugs, monitoring facilities such as CD4 counts, viral load estimation and drug resistance assay are required for follow-up.

How ART works?

The antiretroviral drugs act on various stages of replication of HIV in the body and interrupt the process of viral replication. The ARV drugs act at following steps in viral replication:

(i) block binding of HIV to target cell (Fusion Inhibitors),

(ii) block the viral RNA cleavage and one that inhibits reverse transcriptase (Reverse Transcriptase Inhibitors),

(iii) block the enzyme integrase, which helps in the proviral DNA being incorporated into the host cell chromosome (Integrase Inhibitors)

(iv) block the RNA to prevent viral protein production,

(v) block enzyme protease (Protease Inhibitors),

(vi) inhibit the budding of virus from host cells,

Most commonly used drugs target the virus mainly by inhibiting the enzymes reverse transcriptase (RT) inhibitors and protease inhibitors (PIs) and are depicted in Table 1

The major points in ART are- When to start treatment, with which drugs and how to monitor the therapy?. The guidelines in this regard by various international agencies are in Table 2

When To Start Art :

The guidelines on When to start ART have been evolving over the years towards earlier initiation of ART at CD4 count of less than 200 cells/per year in 2004 to less than 350 in 2010 and moving to less than 500 in 2013 and now recommendation is to TREAT ALL irrespective of clinical stage or CD4 count . These are based on evidence from various RCTs

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The Current global recommendation is to treat all plhiv regardless of cd4 count or clinical stage. this includes all pregnant women irrespective of duration of pregnancy.

Editorial Comments :
- **Treat all whenever diagnosed**
- **Single pill TDF + 3TC+EFV preferred regiment**
- **Adherence of 95% necessary for treatment success.**

What regimen to start

As regards What ART Regimen to start in a treatment naïve patient, the principle is to start a combination of at least three agents from different classes of ARV drugs as this gives maximal achievable suppression of HIV replication over a prolonged period of time and reduces the chances of emergence of drug resistant strains. The current guidelines on ART regimen in first line ART by NACO are depicted in Table 3

This regimen of TDF+3TC+EFV in single pill has many advantages like simplicity, regimen is very effective, well tolerated and available as a single, once-daily FDC and therefore easy to prescribe and easy for patients to take It, which also facilitates adherence, harmonizes regimens across range of populations (Adults, Pregnant Women (1st trimester), Children >3 years*, TB and Hepatitis B),simplifies drug procurement is safe in pregnancy, Efficacious against HBV, is preferred NNRTI for people with HIV and TB & HIV and HBV co-infection and is now affordable for most patients.

Table 1 — *Classes of ARV Drugs*

Nucleoside reverse transcriptase inhibitors (NRTIs)	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Protease Inhibitors (PIs)	Integrase Inhibitors
Zidovudine (AZT)	Nevirapine (NVP)	Atazanavir(ATV)	Raltegravir (RAL)
Lamivudine (3TC)	Efavirenz (EFV)	Ritonavir (RTV)	Dolutegravir
Abacavir (ABC)	Etravirine	Lopinavir (LPV)	
Didanosine (ddI)		Saquinavir (SQV)	Fusion Inhibitor(FI)
Emtricitabine (FTC)		Darunavir (DRV)	
Stavudine (d4T)		Indinavir (IDV)	Enfuviritide(ENF)
		Nelfinavir (NFV)	CCR 5 co-receptor antagonists
		Amprenavir (APV)	
		Fosamprenavir, (FPV)	
		Tipranavir (TPV)	
Nucleotide reverse transcriptase inhibitors (NtRTI)			Maraviroc (MVC)
Tenofovir (TDF)			

Monitoring Of Therapy :

Frequent and regular follow-up especially during the initial months of the treatment is very important in order to ensure timely

Table 2 — *Comparison of ART guidelines by different agencies*

	US DHHS July 2016	IAS-USA October 2016	BHIVA July 2015-16	EACS Oct 2016	WHO June 2016	NACO 2016
			When to Start ART?			
Initiation of ART at CD4 cut off	Regardless of count	Regardless of count	Regardless of count	Regardless of count (immediate if CD4 < 350)	Regardless of count (priority to CD4 <350)	Regardless of CD 4 count or clinical stage
Tuberculosis Co-infection	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load (on priority)	Regardless of CD 4count or clinical stage
Hepatitis B Co-infection	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Regardless of CD 4count or clinical stage
Hepatitis C **Co-infection**	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Start ART before HCV treatment; acceptable to defer if CD4 >500	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Regardless of CD 4count or clinical stage
Pregnant women	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Regardless of CD4 count or Viral load	Regardless of WHO clinical stage and CD4 count and continued lifelong	Regardless of CD 4count or clinical stage
			What to start?			
Preferred first line ART	• TDF/TAF plus FTC plus DTG or EVG/c or RAL or DRV/r • DTG plus ABC plus 3TC (HLA-B*5701 negative)	• TAF plus FTC plus DTG or EVG/c or RAL • DTG plus ABC plus 3TC (HLA-B*5701 negative)	TDF/TAF plus FTC plus ATVr/r or DRV/r or DTG or EVG/c or RAL or RPV (if VL < 1 lakh)	• TAF/TDF plus FTC plus DTG or EVG/c or RAL or RPV or DRV/c or DRV/r • ABC plus 3TC plus DTG	TDF + 3TC (or FTC) + EFV	TDF+3TC+EFV
			How to monitor?			
CD4	• Every 3 to 6 months • Annual - After 2 years of ART (VL consistently suppressed, CD4 consistently 300-500	• Pretreatment CD4 < 200: 3 to 4 monthly until CD4 > 350 for 1 year (VL suppressed) and then 6 monthly for 2 years. • VL suppressed for 2 years and CD4 > 500: No repeat monitoring unless VL/OI	• 3 months of ART – still <350 – repeat at 6 months • If > 350 on two occasions >1 year apart, no further CD4	• Every 3-6 months • Annual - if stable on ART and CD4 > 350	• 6 monthly (frequency Can be reduced if VL suppressed on two occasions)	• 6 monthly
Viral load	• Initiation or modification of ART: 2 to 4 weeks (8 weeks) • Stable (>2years) patients: 3-4 months (6 months)	• Every 4 to 6 weekly after ART until VL is undetectable • After viral suppression 3 monthly for 1 year then 6 monthly	• 1, 3 and 6 months after starting ART • Every 6 monthly	3-6 months	• At 6 months and then Every 6–12 months (Targeted/ routine)	Presently following targeted VL testing for those with clinical or immunological failure, soon expanding to routine VL monitoring

US DHHS, US Department of Health and Human Services; IAS-USA, International Antiviral Society–USA; BHIVA, British HIV Association; EACS, European AIDS Clinical Society; WHO, World Health Organization, NACO-National AIDS Control Organisation, India
3TC = lamivudine; ABC = abacavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; CD4 = CD4 T lymphocyte; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

diagnosis and management of adverse events, to work with the patient on adherence issues and to diagnose any clinical manifestations like OIs and immune reconstitution inflammatory syndrome (IRIS). Generally, morbidity and mortality on ART occurs in the first 3 to 6 months of initiation of therapy. The various monitoring indicators are as below:

· Clinical monitoring

o Monthly Clinical Evaluation

§ weight, overall wellbeing, any fresh symptoms, routine four symptom screening for TB on every visit

o Monthly Treatment Adherence Evaluation, pill count, self-reported

o For Adverse reactions of ART / OI drugs

o For drug interactions, look for concomitant drugs

o For IRIS (Immune Reconstitution Inflammatory Syndrome)

· Immunological monitoring

o CD4 count (every 6 months but for virlogically suppressed patients, frequency can be reduced or stopped)

· Virological monitoring (at 6 months, 12 months and every 12 months)

Some laboratory parameters to be monitored regularly are depicted in Table 4

Antiretroviral drug toxicity :

Antiretroviral drugs have a broad range of toxicities, ranging from low-grade intolerance which may be self-limiting to life-threatening side-effects and are depicted in Table 5. Differentiating between complications of HIV disease and ART toxicity is very important. Considerations should also include intercurrent illness (e.g. hepatitis A, malaria, etc.) or reactions to medications other than ARVs, eg, isoniazid-induced hepatitis or rash induced by Cotrimoxazole. However, most of the toxicity/effects can be adequately co-managed with good clinical monitoring at all the levels of the health care system. As a general principle, mild toxicity does not require discontinuation of ART or substitution. Symptomatic treatment may be given. Moderate or severe toxicities may require substitution with a drug of the same ARV class but with a different toxicity profile. Severe life-threatening toxicity requires discontinuation of all ARV drugs until the patient is stabilised and the toxicity is resolved.

Table 3 — *ART Initiation regimen for ARV naïve adults*

Preferred regimen	FDC of TDF + 3TC (or FTC) + EFV
Alternative regimens	AZT + 3TC + EFV (or NVP)
	TDF + 3TC (or FTC) + DTGa
	TDF + 3TC (or FTC) +NVP
Special circumstances b	Regimens containing ABC and boosted PIs

a Safety and efficacy data on DTG for pregnant and breastfeeding women and TB co-infection are still pending. b Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug–drug interactions, drug procurement and supply management issues, or for other reasons. 3TC lamivudine, ABC abacavir, AZT zidovudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, NVP nevirapine, PI protease inhibitor, TDF tenofovir.

Treatment Failure: When to Change and What to Change :

The adherence to ART is one of the most crucial determinants of success of ART on long term basis. The adherence of 95% or more is crucial for patients to achieve desirable suppression of viral replication. However even with good adherence levels, resistance occurs to ARV drugs over a period of time due to viral mutation and this requires change of ARV drugs. The virological failure appears first followed by immunological failure which finally leads to clinical failure. It is desirable to switch the entire regimen from first to second line as soon as virological failure is detected. Table 6 depicts the criteria for suspecting and confirming treatment failure.

The second line regimen for patients failing on first line ART is AZT + 3TC + ATV/r for those on TDF in first line regimen (and TDF+3TC+ATV/r for those on AZT or d4T based regimen in first line).

HIV/Tuberculosis Co-Infection :

Initiation of treatment for active TB should always be on priority followed by initiation of ARV therapy as per the guidelines and should be started as soon as the patient is stabilised on ATT. In HIV-infected patients with TB who are not currently on ART, and who are provided Rifampicin-based anti-TB treatment, initiate ART

Table 4 — *Recommended tests for monitoring patients on ART*

Tests for monitoring patients on ART(Follow up tests)
For all patients on ART, need to do CD4, Hb, TLC, DLC, ALT (SGPT), Bl urea once in every six months
Drug specific tests frequency as below :

Monitoring tool	Test	baseline	15th Day	1st Month	2nd Month	3rd Month	6th Month	Than every 6 months
On Zidovudine based ART	CBC	Yes	Yes	Yes	Yes	Yes	Yes	Yes
On Tenofovir Based ART	Serum Creatinine	yes	-	yes	-	yes	Yes	Yes
Nevirapine Containing ART	ALT(SGPT)	Yes	Yes	Yes	-	-	Yes	Yes
Efaviranz containing ART	Lipid profile	Yes	-	-	-	-	Yes	Yes
Atazanavir containing ART	LFT	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lopinavir containing ART	Lipid Profile and Blood sugaryes	Yes	-	-	-	-	Yes	Yes

It is preferable /desirable to monitor patients with viral load at 6 & 12 months after initiation of ART & then viral load every 12 months once viral suppression achieved. For stable patients with virological suppression, frequency of CD4 can be reduced or stopped.CD4 test is required for CPT initiation/stopping CPT, and for primary and secondary prophylaxis for some OIs
Any other can be done earlier based on clinician's assessment/ discretion and as per availability.

Table 5 — Common ARV drug toxicities and overlapping Toxicities

Drugs	Short term toxicities	Medium term toxicities
Zidovudine	Headache, nausea, vomiting, malaise, Diarrhoea Anaemia (Macrocytic)	Bone Marrow suppression Anaemia (Macrocytic) Bone Marrow suppression Hyper pigmentation Lactic Acidosis Proximal myopathy
Tenofovir	Nephrotoxicity (low incidence), Fanconi syndrome and rarely Acute Renal Failure	
Efavirenz	Drowsiness, dizziness Confusion, Vivid dreams Skin Rashes Hepato toxicity (very rare)	
Nevirapine	Skin Rashes Hepato toxicity	
Overlapping Toxicities	Drugs	
Bone marrow suppression	Zidovudine, Cotrimoxazole, Dapsone, Pyrimethamine, Ganciclovir, Amphotericin B, Ribavirin	
Hepatotoxicity	Nevirapine, Atazanavir, Lopinavir, Ritonavir, Isoniazid, Rifampicin, Pyrazinamide, Fluconazole, Cotrimoxazole	
Peripheral neuropathy	Stavudine, Isoniazid, Alcohol	
Pancreatitis	Stavudine, Cotrimoxazole, Alcohol	

directly with EFV. No lead in dose is required for EFV. Nevirapine or PIs should not be administered along with Rifampicin because of the enzyme inducing effect of Rifampicin which renders NVP levels sub therapeutical. EFV blood levels are also decreased in presence of Rifampicin, but remain at therapeutic levels. It is recommended to use the standard dose of EFV (usually 600 mg/day) in patients receiving EFV and Rifampicin or use Rifabutin if patient is on LPV/r based ART. Details on initiation guidelines have already been discussed.

HIV and Hepatitis B, C Co-Infection :

Liver-related morbidity and mortality is very common in patients on ART. The common cause for liver related deaths is co-infection with hepatitis viruses. It is recommended that all HIV-infected patients should be screened for HBsAg, anti-HBcAb (if possible), HCV-RNA and HCV genotype at the baseline. It should be ensured that additional baseline investigations like LFTs, PT, serum proteins, HbeAg and HBV-DNA are also done. Appropriate treatment for co infections need to be instituted at the earliest and the drug-drug interactions with ARVs need to be kept in mind

Conclusion :

Antiretroviral therapy is quite effective in suppressing viral replication, delaying the progression of disease and has changed the management of HIV disease dramatically. Millions of lives and millions of new infections have been saved due to ART. Present day ART with initiation with single pill FDC regardless of CD4 count offers an hope to reach out to more and more people to begin the end of AIDS epidemic.

Table 6 — *Defining Antiretroviral Failure*

WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens

Failure	Definition	Comments
Clinical failure	Adults and adolescents New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)[a] after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure
Immuno-logical failure	Adults and adolescents CD4 count at or below 250 cells/mm3 following clinical failure[b] or Persistent CD4 levels below 100 cells/mm3	Without concomitant or recent infection to cause a transient decline in the CD4 cell count Current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure.
Virological failure	Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test	An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed

[b] Previous guidelines defined immunological failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation. The option of CD4 cell count at or below 250 cells/mm³ following clinical failure is based on an analysis of data from Uganda and Zimbabwe

Recommended readings :

1 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services, USA. July 2016. Available at http://www.aidsinfo.nih.gov/guidelines

2 Guidelines for Management of HIV-Infected Adults and Adolescents Including Post-exposure Prophylaxis, NACO. Ministry of health and Family Welfare, 2013). Available at http://naco.gov.in/NACO/Quick_Links/Publication/Treatment_Care__Support/.

3 WHO consolidated Guidelines on Antiretroviral Therapy for HIV Infection: Recommendations for a public health approach July, 2016. Available at http://www.who.int/hiv/pub/guidelines

4 National Guidelines on Second line ART for adults and adolescents, December 2014, National AIDS Control Organisation, Ministry of Health and Family Welfare. (updated April 2012).