Review Article

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Antiretroviral therapy in Indian setting: When & what to start with, when & what to switch to?

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With the rapid scale up of antiretroviral therapy, there is a dramatic decline in HIV related morbidity and mortality in both developed and developing countries. Several new safe antiretroviral, and newer class of drugs and monitoring assays are developed recently. As a result the treatment guideline for the management of HIV disease continue to change. This review focuses on evolving science on Indian policy - antiretroviral therapy initiation, which drugs to start with, when to change the initial regimen and what to change.

Key words Antiretroviral drugs - antiretroviral therapy - ART - CD4 - HIV - IRIS - viral load

Highly active antiretroviral therapy (HAART) is the cornerstone of management of patients with HIV infection. Initiation of widespread use antiretroviral therapy marked declines in the incidence of most AIDS defining conditions and mortality both in the developed and developing world[1,2]. Suppression of HIV replication is an important component to prevent HIV associated morbidity and mortality as well as in improving the quality of life in patients with HIV infection. Adequate suppression requires strict adherence of antiretroviral therapy. This has been facilitated by the co-formulation of antiretroviral drugs and the development of once daily regimens. This review focuses on issues like when to initiate antiretroviral therapy, what drugs to start with, when to change the initial regimen and what to change to in Indian settings.

Box 1. Goals of antiretroviral therapy

- To achieve maximal and durable virologic suppression (ideally a viral load < 50 copies/ml)
- To reconstitute and preserve immunologic function
- To reduce morbidity and mortality, associated with both HIV infection and use of antiretrovirals (ARVs)
- To improve quality of life

When to initiate ART? (Table I)

Strong evidence based on randomized controlled trials exists for initiating ART amongst asymptomatic patients with CD4<350/mm^3 [12,13]. Large observational studies have demonstrated the effectiveness of ART amongst patients with CD4<500mm^3 in reducing mortality and clinical events including non-AIDS defining events[14,15]. There is limited evidence about the prevalence of non-AIDS defining events from resource

Table I. Indications and conditions to initiate antiretroviral therapy

Condition	Initiating ART
AIDS defining illness current/past	Yes
Asymptomatic	
CD4 (per µl)	
<350	Yes
350-500	Consider
>500	No
Irrespective of CD4 counts	
Tuberculosis	Yes
Pregnancy	Yes
HIVAN[3]	Yes
HBV when HBV treatment indicated[4]	Yes
HCV infection[5]	Yes
Elderly[6,7]	Yes
Malignancy[8]	Yes
VL> 1,00,000 copies/µl[9]	Yes
Serodiscordant relationship[10]	Consider
Underlying CV risk factors[11]	Consider
Acute HIV infection	No

VL, viral load; CV, cardiovascular
Superscript numerals denote reference numbers

limited settings (RLS). Studies have also consistently demonstrated the usefulness of ART in preventing sexual transmission of HIV and this can be considered for the decision of when to initiate ART[16,17]. The benefit of initiating ART in the setting of acute HIV infection is limited and consequently this has to be done only in the context of clinical trial[18-20].

Assessing patient readiness prior to initiating ART

Although no readiness measure has accurately predicted adherence, it is essential to prepare a patient prior to initiating ART[50-52]. Issues that need to be discussed include conceptual understanding of treatment and its benefits, the importance of high level lifelong adherence to drugs and the consequences of sub-optimal adherence (more expensive second line regimens, progression of clinical disease) .Only after ensuring that patient has understood the consequences of initiating and being on ART, should treatment be initiated.

Box 2. Why initiate ART early?

- Better survival[15]
- Potent, durable and convenient regimens are readily available
- Decrease risk of non-AIDS defining complications[15]
- Prevent neurocognitive decline[21-28]
- Reduce immune activation, inflammation, thrombogenesis[29,30]
- Greater likelihood of CD4 normalization[31,32]
- Lesser risk of development of immune reconstitution inflammatory syndrome[33-37]
- Lesser likelihood of developing antiretroviral (ARV) resistance[38]
- Lesser risk of development of toxicities[39]
- Prevention of transmission[9,17]
- Cost-effective[40,41]

Superscript numerals denote reference numbers

Box 3. When is it best to initiate ART in the setting of acute opportunistic infection (OI)?

- Most OIs: as soon as possible[42,43]
- Cryptococcal meningitis: after induction phase of anti-fungal treatment[44-46]
- TB[47,48]
  - CD4<50/mm^3: Around 2 wk of initiation of anti-TB treatment
  - CD4>50/mm^3: Around 8 wk of initiation of anti-TB treatment
- CNS OIs[49]
  - Careful monitoring for immune reconstitution inflammatory syndrome (IRIS)

What to start with? (Table II)

An non nucleoside reverse transcriptase inhibitor (NNRTI) based regimen is preferred over protease inhibitors (PI/r) based regimens considering similar potency, convenience, lesser expense and lower prevalence of primary resistance in the population[53-55]. Efavirenz (EFV) is preferred over nevirapine (NVP) when concomitant use of rifampicin is indicated, patients preference for once daily (lower pill burden) regimen and if pre-therapy CD4 count is >250/mm^3 and >400/mm^3 in women and men respectively[56-60]. Nevirapine is preferred over EFV in women planning pregnancy and those with underlying severe psychiatric illness.

Tenofovir/Emtricitabine or Lamivudine is the preferred backbone because it has similar virologic

Box 4. Choice of first line regimens

Preferred

TDF/XTC/EFV or NVP

Alternative

AZT/3TC/EFV or NVP

Consider (only in special situations)

ABC/3TC/EFV

ddI/3TC/EFV

Use only when no other options available

D4T/3TC/EFV or NVP

AZT, zidovudine; d4T, stavudine; 3TC, lamivudine; FTC, emtricitabine; ABC, abacavir; ddI, didanosine; TDF, tenofovir; NVP, nevirapine; EFV, efavirenz

Table II. Various antiretroviral drugs (ARVs)* approved for therapeutic use

N (t)RTIs	NNRTIs	PIs	Entry inhibitors	Integrase inhbitors
Zidovudine (AZT)	Nevirapine (NVP)	Saquinavir (SQV)	Enfuvitride (ENF)	Raltegravir (RAL)
Stavudine (d4T)	Efavirenz (EFV)	Indinavir (IDV)	Maraviroc (MRV)	
Lamivudine (3TC)		Ritonavir (RTV)		
Abacavir (ABC)	Etravirine (ETV)	Nelfinavir (NFV)		
Didanosine (ddI)	Delaverdine (DLV)	Lopinavir (LPV/r)		
Tenofovir (TDF)		Atazanavir (ATV)		
		Darunavir (DRV)		
Dideoxycytidine (ddC)		Fos-Amprenavir (f-APV)		
		Tipranavir (TPV)		

*Available in India
N(t) RTIs, nucleoside reverse transcriptase inhibitor; NNRTI, non nucleoside reverse transcriptaswe inhibitor; PI, protease inhibitor
XTC: FTC or 3TC

response as compared to zidovudine/lamivudine (AZT/3TC) but has been associated with lower toxicity particularly in women[61-64]. Further advantages associated with TDF/XTC include low pill burden (one pill once a day when combined with EFV), better sequencing options after failure of first line regimen, concomitant treatment of underlying undiagnosed HBV infection, and it has been proven to be cost-effective in an analysis in India[65-67]. Tenofovir use has been associated with renal toxicity (although clinical effect is modest) and bone toxicity, and further research to characterize the incidence and risk factors for these need to be carried out in India[68-72].

AZT/3TC is preferred in women who plan pregnancy/or are pregnant but has been associated with higher short-term haematological and long term morphologic and metabolic toxicities[73-79]. Stavudine (d4T) should be avoided because of long term toxicity concerns that are often irreversible[80-82].

Boosted protease inhibitors need to be used as the third drug in first line regimen along with nucleoside reverse transinptases (NRTs) backbone in certain clinical situations (Table III).

Certain antiretroviral combinations are less potent or can interact with other medications (Table IV). Various laboratory assays are performed before initiating therapy to choose appropriate drug regimen and on follow up to identify early toxicities and efficacy of the regimens. Table V describes various assays to be performed on patients initiating ART.

The utility of virologic monitoring has been debated. Trials have shown no advantage in using viral loads to monitor treatment response (especially disease progression and mortality) as compared to immunological and clinical monitoring[91-93]. Additionally, using CD4 criteria for failure to identify virologic failure has poor positive predictive value and low sensitivity[94]. However, not monitoring virologically is associated with identification of failure late as the gap between virologic and immunologic failure can be many years. This leads to exposure of the virus to a failing regimen amplifying resistance and further cross resistance can compromise future regimens[95-102,134]. Hence after achieving virologic suppression, viral load may be monitored at least once a year. In patients in whom virologic monitoring can be done more frequently (*e.g.* every 3-6 months), CD4 counts may be monitored on an yearly basis after achieving good immunologic response.

Table III. Clinical situations for use of protease inhibitors/ritonavir (PI/r) in first line regimens

- HIV-2 or HIV-1/HIV-2 infection[83-85] (LPV/r, DRV/r, SQV/r, no ATV/r)
- Pregnancy with CD4>250/mm^3
- Exposure to sdNVP in pregnancy (esp within 1 yr of receipt)[86]
- Dual toxicity to NVP and EFV

SQV, saquinavir; r, ritonavir; LPV/r, lopinavir; ATV, atazanavir; DRV, darunavir

Table IV. Antiretrovirals (ARVs)* not recommended for use

ARVs/regimens	Reason
Mono, dual therapy	Sub-optimal potency and development of Resistance
3NRTIs, 4NRTIs	Less potent[87,88]
TDF + ddI + NNRTI	Higher risk of failure and drug-drug interaction[89]
TDF + ABC	Non-additive, resistance[90]
d4T+AZT	Antagonist
d4T + ddI	Additive toxicity
Unboosted PIs	Poor bioavailability

*Available in India. N(t) RTIs, nucleoside reverse transcriptase inhibitor; NNRTI, non nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

Table V. Mnitoring patients on ART

	Baseline	Subsequent frequency
Clinical evaluation	Yes	4 wk, 12 wk, 6 months and q3mo
Rapid HIV ELISA	Yes	
CD4	Yes	q6mo
PVL	Optional	At 6 mo, 1 yr and q1yearly
CBC	Yes	2 wk, 4 wk, 3 mo (AZT) and q6mo
Urine Creatinine and eGFR	Yes	Q6mo (esp with TDF)
LFTs	Yes	As clinically indicated
Fasting lipid	Yes	Q1yearly & before changing regimen
Fasting sugar	Yes	Q1yearly & before changing regimen
HbsAg	Yes	
Anti-HCV/HCV RNA	Yes (esp high risk)	
Syphilis serology	Yes	
Phosphorus, electrolytes	No	Q6mo (esp with TDF)
TB screening (X-ray chest)	Yes (esp with symps)	As clinically indicated
Cervical PAP smear	Yes	Annually
Genotypic resistance testing	Optional	As indicated (at ARV failure)

PVL, plasma viral load; CBC, cell blood count; LFT, liver function test

Box V. When to change ART?

- Substitution (only after confirmed virologic suppression)
  - Toxicity (*e.g.* TDF for AZT anaemia)
  - Simplification (*e.g.* bid to qd regimens)
  - Cost (*e.g.* from EFV to NVP)
  - Drug-drug interaction (*e.g.* from NVP to EFV when initiating rifampicin)
  - Pregnancy (*e.g.* from EFV to NVP or TDF to AZT)
  - Proactive (*e.g.* from d4T to TDF)
- Switching (for ART failure)

Complications in the use of ART

Immune reconstitution inflammatory syndrome (IRIS)

Occurring in a sub-population of HIV infected individuals after initiation of ART, IRIS is associated with inflammatory response to clinical or sub-clinical pathogens or non-pathogenic antigens[103]. Definitions for diagnosis of TB and cryptococcal IRIS have been proposed, however for most other no clear definitions exist[104,105]. Two types have been described: paradoxical IRIS is the worsening of well controlled underlying infection while unmasking IRIS is the occurrence of new manifestations in a patient apparently well prior to initiation of ART[35,106-113]. The major risk factor for development of IRIS is a low pre-therapy CD4 count (usually<50/mm^3)[35,114-117]. Differential diagnosis includes anti-microbial resistance, ARV toxicity or progression of underlying OI. No clear strategies exist for management of IRIS, however, 4 wk of steroids treatment (1.5 mg/kg/day for 2 wk followed by 0.75 mg/kg/day for 2 wk) has been found to be effective for treatment of mild to moderate paradoxical TB IRIS.

Box VI. Definition of ART failure

Virologic failure
- Rebounders: Confirmed re-emergence of virus (defined as viral load>1000 copies/ml) after virologic suppression
- Non-responders: Inability to achieve virologic suppression after initiation of ART (defined as VL<400 copies at 6 months and <50 copies/ml at 12 months)

In patients not monitored on viral load, immunologic and clinical criteria for failure include

Immunologic failure
- Confirmed drop > 30% drop in CD4 count from peak value
- Non-improvement in CD4 count>100 cells in the first year of initiating or changing ART

Clinical failure
- Development of new AIDS defining condition 3 months after initiation or change in ART regimen

ARV toxicities

A range of toxicities is associated with use of ART[68,69] Table VI. Some of these toxicities are acute and also certain medications can cause chronic toxicities (Tables VII & VIII). While some are mild and self-limited, some can be fatal and irreversible. It is important to forewarn the patients about the same and a discussion on these issues should be part of the discussion prior to initiating ART.

Immunologic and/or clinical failure is an indication to determine viral load (targeted viral load) to identify disconnect or true failure. The disadvantage of

Table VI. Spectrum of adverse events to antiretrovirals and the management plan

ARV drug	Common associated toxicity	Suggested substitute
TDF	Asthenia, headache, diarrhoea, nausea, vomiting, flatulence	If used in first-line therapy AZT/ABC (or d4T if no other choice)
	Renal insufficiency, Fanconi syndrome (risk factors: background renal disease, concomitant use of nephrotoxic medications and PI/r, conditions associated with potential nephrotoxicity *e.g.* DM, HTN) [70,119-123]	
	Osteomalacia	
	Decrease in bone mineral density[124,125]	
	Severe acute exacerbation of hepatitis may occur in HBV – coinfected patients who discontinue TDF[126]	
AZT	Bone marrow suppression:	**If used in first-line therapy TDF (or d4T if no other choice) if used in second-line therapy d4T.**
	Macrocytic anaemia or neutropenia[73,74,127-129]	
	Gastrointestinal intolerance, headache, insomnia, asthenia, skin and nail pigmentation	
	Lactic acidosis with hepatic steatosis[130]	
EFV	Persistent and severe CNS toxicity (dizziness, vivid dreams, depression, confusion)[131]	**NVP**[133,134]
	Rash, hypersensitivity reaction Stevens-Johnson syndrome	**PI/r intolerant to both NNRTIs**
	Hepatitis[132]	
	Hyperlipidaemia	
	Male gynaecomastia	
	Potential teratogenicity (first trimester of pregnancy or women not using adequate contraception)	
NVP	Hypersensitivity reaction	**EFV**
	Stevens-Johnson syndrome rash[135, 136]	**PI/r, if intolerant to both NNRTIs**
	Hepatic toxicity[132,137]	
	Hyperlipidaemia	
ATV/r	Indirect hyperbilirubinaemia[138-140]	**LPV/r, DRV/r, SQV/r**
	Clinical jaundice	
	Prolonged PR interval - first degree	
	Symptomatic AV block[141]	
	Hyperglycaemia	
	Fat maldistribution	
	Possible increased bleeding	
	episodes in individuals with	
	haemophilia	
	Nephrolithiasis[142]	
LPV/r	GL intolerance, nausea, vomiting,	**ATV/r**[145]**, DRV/r**[146,147]
	Diarrhoea	
	Asthenia	
	Hyperlipidaema (especially hypertriglyceridaemia)[143,144]	
	Elevated serum transaminases	
	Hyperglycaemia	
	Fat maldistribution	
	Possible increased bleeding	
	Episodes in patients with haemophilia	
	PR interval prolongation	
	QT interval prolongation	

Superscript numerals denote reference numbers

AZT, zidovudine; TDF, tenofovir; d4T, stavudine; AC, abacavir; EFV, efavirenz; NVP, nevirapine; ATV, atazanavir; LPV, lopinavir; r, ritonavir; DRV, darunavir; SQV, saquinavir; PI, protease inhibitor

Table VII. Managing ARV toxicities: Acute

Adverse event	ARVs	Clinical presentation	Prevention	Management
GI disturbance	ZDV, ddI NVP All PIs	Nausea Vomiting Diarrhoea Abdominal distress	Taking with or after food	Mostly self-limiting Symptomatic treatment Substitute if severe
Rash	NVP ABC EFV ATV	Diffuse maculopapular With/without pruritus Severe reaction: with fever and hepatitis or mucus membrane involvement (SJS)	Always use NVP in lead in dose Do not double NVP dose when rash present Do not use prophylactic steroids/ antihistamines Cross sensitivity to sulpha (DRV)	**Mild-moderate rash: antihistamine [148]** **Severe rash: Discontinue* and never re-challenge**
CNS symptoms	EFV NVP	Drowsiness, abnormal dreams, impaired concentration	Educate patient Take 2-3 h before sleeping Take on empty stomach	**Self limiting, resolves in 1-3 wk**
Hepatitis	NVP All PIs EFV	Nausea, anorexia, vomiting Sometimes jaundice	Monitoring ALT/AST. Avoid NVP in women with CD4>250 & men with CD4 >400/µl Careful use in HBV/HCV co-infected patients Indirect hyperbilirubinaemia with ATV and IDV	**Symptomatic: discontinue permanently** **Asymptomatic: ALT>5 times discontinue**
Hypersensitivity reaction (HSR)	ABC	Fever, rash, malaise, nausea, headache, diarrhoea and respiratory worsens with continuation of ABC: hypotension, respiratory distress, vascular collapse	HLA-B5701 screening[149-151] Patient education and early identification	**Permanently discontinue** **Never re-challenge** **Antipyretics and fluid support**
Anaemia, leucopenia (can also later {years} after initiating treatment)	**ZDV**	Fatigue, breathlessness, palpitations	Avoid in anaemic patients and in patients with advanced disease Monitor Hb levels as recommended	**Discontinue and never re-challenge** **Transfusions or growth factors if severe**

*While discontinuing NNRTIs, the long half life has to be taken into account to avoid functional monotherapy and development of resistance. Normally the NRTI backbone is continued for at least 1 wk after NNRTI discontinuation, or briefly a PI based regimen may be prescribed for the patient. Superscript numerals denote reference numbers.
AZT, zidovudine; TDF, tenofovir; d4T, stavudine; AC, abacavir, ddI, didanosine; EFV, efavirenz; NVP, nevirapine; ATV, atazanavir, LPV, lopinavir; r, ritonavir; DRV, darunavir; SQV, saquinavir; PI, protease inhibitor

immunologic/clinical monitoring is late identification of failure causing increased accumulation of drug resistant mutations that can compromise efficacy of future regimens[100,134]. Patients on failing regimen should be switched to secondline regimens (Table IX). Antiretroviral resistance testing should be used to guide the second line regimens if the patient has access.

Preferred choice of PI/r in second line includes ATV/r, DRV/r[159], and alternative is LPV/r.

The essential principle of constructing an effective second/third line regimen is to combine at least two or preferably three fully active drugs. These drugs should ideally include one from a new class (*e.g.* PI/r if NNRTI based first line regimen) or those drugs from the same class of drugs with the least likelihood of resistance as determined by genotypic resistance testing (GRT). Choosing an active drug using GRT has better outcomes than based on expert opinion alone[160-163]. Genotypic resistance testing has to be performed when the patient is on or within 2 wk of discontinuation of a failing regimen.

An expert consultation is advisable. Early identification of second line regimen failure is critical (*e.g.* virologic failure) to preserve effective ARV

Table VIII. Managing ARV toxicities: Long term

Adverse event	ARVs	Clinical presentation	Prevention	Management
Peripheral neuropathy	d4T, ddI	Numbness and pain in lower limbs	Identify early because sometimes irreversible	**Early substitutions**
			Avoid using d4T/ddI	**Symptomatics**[152,153]
			Avoid using with pre-existing neuropathy or drugs causing neuropathy	
Lactic academia	NRTIs especially d4T, ddI, ZDV	Nausea	Identify early	**Permanently substitute**
Lactic acidosis		Fatigue		
		Abdominal discomfort	High risk in	**Thiamine/Riboflavin**
		Breathlessness	women	
		Increased lactate	Obese	**Haemodialysis**
		Acidosis	Pregnancy	**Ventilation SOS**
Pancreatitis[154]	d4T, ddI	Abdominal pain, nausea and vomiting	Avoid in patients with h/o pancreatitis	**Substitute offending agent**
	Drugs causing increase in triglycerides	High amylase/lipase levels	Avoid ddI use with d4T, TDF (use low dose ddI), Ribavarin	**Medical management of pancreatitis**
Lipoatrophy	d4T. ZDV	Fat loss in face, extremities, buttocks	Avoid d4T	**Substitute offending agent**[81]
Lipohypertrophy	PIs	Increase visceral fat in abdomen	Identify early because can be irreversible	**No specific treatment available**
Lipodystrophy[155,156]				**Liposuction**
Hyperlipidaemia	d4T	Increase TC, LDL, TG, decrease HDL	Avoid these drugs when possible	**Substitute to lipid friendly (TDF, NVP, ATV)**
	EFV		Identify early by measuring fasting lipids as recommended in follow up	
	All PI/r	LPV/r		**Assess cardiac risk**
		Increase TG		**Lifestyle changes**
				Statins, Fibrates
Insulin resistance	d4T	Polyuria, polydipsia, polyphagia	Avoid offending agents particularly with pre-existing diabetes	**Substitute offending agent**
Diabetes	PIs	Fatigue		**Lifestyle modification**
		Increased fasting glucose	Monitor sugar	**Drugs: OHAs**
		Impaired glucose tolerance test		**Insulin**
Nephrotoxicity	TDF	Asymptomatic	Hydration,	**Substitute**
	IDV	Nephrogenic DI	Avoid other nephrotoxic drugs	**Usually reversible**
		Fanconi	Monitor creatinine, urinalysis, potassium and phosphorpus closely	**Supportive care**
		Decreased Creatinine clearance, proteinuria, hypophosphate		
Osteonecrosis[157, 158]	**All PIs**	**Pain**	**Limiting risk factors**	**Decompression,**
	D4T	**B/L femoral heads**	**Alcohol, dyslipidaemia**	**Joint replacement**

Note: Discontinuing the offending agent would also mean substituting with an alternative drug to ensure efficacy of the regimen
AZT, zidovudine; TDF, tenofovir; d4T, stavudine; AC, abacavir; EFV, efavirenz; NVP, nevirapine; ATV, atazanavir; LPV, lopinavir; r, ritonavir; DRV, darunavir; SQV, saquinavir; IDV, indinavir; PI, protease inhibitor. Superscript numerals denote reference numbers

Table IX. Choice of second line regimens

First line	Second line regimen
TDF/FTC/EFV or NVP	AZT/3TC/PI/r
ABC/3TC/EFV	AZT/3TC/PI/r
ddI/3TC/EFV or NVP	AZT/3TC/PI/r
AZT/3TC/EFV or NVP	TDF + FTC ± AZT* + PI/r
D4T/3TC/EFV or NVP	TDF + FTC ± AZT* + PI/r

**in case of late identification of failure*

N(t) RTIs, nucleoside reverse transcriptase inhibitor; NNRTI, non nucleoside reverse transcriptaswe inhibitor; PI, protease inhibitor; AZT, zidovudine; TDF, tenofovir; d4T, stavudine; AC, abacavir; EFV, efavirenz; NVP, nevirapine; ATV, atazanavir; LPV, lopinavir; r, ritonavir; DRV, darunavir; SQV, saquinavir; IDV, indinavir

options. CCR5 inhibitors, second generation NNRTIs and entry inhibitors are available in resource rich settings to construct salvage regimens[164-167].

Clinical investigators, industry, federal government, patient advocates and clinical trial networks are involved in the process of drug development and clinical trials. As a result, new HIV therapies and new therapeutic strategies are continually emerging and makes this disease as yet another chronic manageable disease.

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