Chapter

90

Antiretroviral Therapy for HIV Infection

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INTRODUCTION

The HIV/AIDS is now twenty five years old and, in these 25 years, more than 60 million people have been infected by human immunodeficiency virus (HIV). As on December 2006, nearly 39.5 million people globally are living with HIV/AIDS[1]. During this period, lot of efforts have gone into understanding the structure of viruses, its molecular biology and the pathogenesis of disease. The information thus obtained has led to development of a number of antiretroviral drugs and treatment strategies. The results from meta-analysis of various trials involving these drugs have changed the world's outlook towards HIV/AIDS from a 'virtual death sentence' to a 'chronic manageable disease'.

Zidovudine (AZT, ZDV) was the first drug to be approved in 1986 for treatment of HIV infection. For many years, Zidovudine was the only drug available for the treatment of HIV infection. During early nineties, the results from use of dual therapy showed significant benefits in terms of delaying the disease progression, clinical improvements and increase in CD4 counts, but, it was restricted mainly to the developed world due to high costs.

In the year 1996, another class of drugs known as 'Protease Inhibitors' were shown to reduce the viral load significantly. The triple drug combination therapy reduced the hospitalization rates of HIV infected individuals and opportunistic infections were reduced significantly.

Presently, we have 24 anti-retroviral agents approved by US FDA, of which 15 are currently available in India. The efficacy of drugs is well documented, options available are several and large numbers of patients are on antiretroviral therapy (ART). As we are treating more and more patients with ART, issues about availability of monitoring facilities like viral load, drug resistance testing, availability of pediatric formulations and second line ARV drugs are becoming increasingly important.

GOALS OF ANTIRETROVIRAL THERAPY (ART)

The ARV drugs cannot eradicate the HIV infection from body, because a pool of latently infected CD4 cells is established during the earliest stages of HIV infection and persists life long. The **primary goals** of antiretroviral therapy are maximal and durable reduction in plasma viral levels and restoration of immunological functions aimed at improvement in quality of life and prologation of life as well. The reduction in viral load leads to reduction in risk of sexual transmission[2].

BASIC PRINCIPLES OF ANTIRETROVIRAL THERAPY

A continuous high level of replication of HIV takes place in the body right from the early stages of infection. At least 10^{10} viral particles are produced and destroyed each day. The HIV destroys CD4 cells, while body produces more CD4 cells. This balance is maintained for some years after which the rate of CD4 destruction becomes more than that of CD4 production. This progressive immune system damage results in susceptibility to different opportunistic infections (OI), malignancies, neurological diseases, wasting and, ultimately, death[3,4].

The most effective way to achieve and maintain durable suppression of HIV replication is the simultaneous initiation of a combination of at least three

drugs from different classes of ARV drugs. Some important factors that must be kept in mind while starting ART are:

1. To assess the severity of disease according to the baseline CD4 cell count and viral load, if possible.
2. The patients 'willingness' and 'readiness' to begin therapy;
3. The patients' education regarding pill burden, dosing frequency, food and fluid considerations, adverse effects, adherence issues and drug interactions;
4. Co-morbid conditions such as tuberculosis, liver disease, depression or mental illness, cardiovascular disease, drug dependency, pregnancy, and family planning status.

The various issues concerning ART are as below:

- When to start treatment?
- Which and how many agents to use? Choice of optimal regimen?
- How to monitor the therapy?
- How long to give therapy?
- When to change therapy and to what?
- Drug interactions involving antiretroviral therapy.

WHEN TO START TREATMENT?

There has been a continuous debate over the years about the timing of initiation of antiretroviral therapy. Various arguments have been given for and against starting ART in the early stage of infection. The 'early' therapy has advantages in terms of easy achievement of viral control, lower risk of resistance with optimal viral suppression and decreased risk of HIV transmission[5]. The 'delayed therapy' avoids negative effect on quality of life of an asymptomatic individual, preserves future drug options, but may be associated with difficulty in suppressing viral replication and irreversible immune system depletion[6]. The recommendations on starting treatment are based on symptoms, CD4 cell counts, and viral load, if possible[7,8].

Various guidelines have been issued from time to time by different expert groups constituted by Department of Health and Human Services (DHHS), USA; International AIDS Society, British HIV Association (BHIVA), Association of Physicians of India etc. The recommendation of starting ART as per guidelines released by Department of Health and Human Services (DHHS), USA in October 2006 recommend that[9]:

- Antiretroviral therapy (ART) should be given to all patients with history of AIDS defining illness or severe symptoms of HIV infection regardless of CD4 cell count,
- ART is also recommended for asymptomatic patient with CD4 count <200 cells/cmm.
- Asymptomatic patient with CD4 count of 200–350 cells/cmm should be offered treatment.
- For asymptomatic patient with CD4 count >350 cells/cmm and plasma viral load >100,000 copies/ml, the most experienced clinicians defer therapy, but some may consider initiating treatment.
- Therapy should be deferred for patients with CD4 cells >350 cells/ cmm and plasma HIV RNA <100,000 copies/ml.

These guidelines are summarised at Table 1[9].

WHO has also issued guidelines for initiating ART in resource limited settings. These guidelines are divided into two categories depending on whether CD4 count facilities are available or not. The threshold for initiating therapy is CD4 count <200 cells/mm^3 or clinical stage IV. The WHO recommendations are summarised in Table 2[10].

It has been proved that the patients with AIDS have higher rates of mortality if not treated with ART[11]. The ART is effective even in patients with advanced immunosuppression (CD4<50/mm^3) and should be offered though the rate of IRIS is higher at this stage[12]. Some Indian data is now available showing that Indian HIV infected patients with CD4 count <200/mm^3 had 19 times higher mortality as compared to those with CD4 count >350 mm^3[3,13]. Hence, all patients with an AIDS defining illness or severe symptoms suggestive of HIV must get ART irrespective of CD4 count or viral load. However, patients with certain non AIDS defining illness like OHL oral hairy leukoplakia and oral candidiasis have a rapid progression and therapy is indicated when CD4 count falls to less than 350/mm^3[3,14]. It is also seen that certain AIDS defining illness like cryptosporidiosis and PML respond only to ART due to immune reconstitution induced by HAART[15,16].

The risk of progression to AIDS in patients with CD4>350/mm^3 is low and ART should not be offered to asymptomatic patients with CD4>350/mm^3. The decision to initiate ART between CD4 counts of 200 to 350 in asymptomatic individuals is debatable. However, it is recommended that ART should be considered in patients with CD4 count less than 250 cells/mm^3[17]. This value should be confirmed by a repeat test four weeks after initial test. This is based on observation that there is a 20% normal variation in CD4 count. In the gray area of CD4 count, 250–350 cells/mm^3, ART is recommended for patients who have:

Table 1: Indications for initiating antiretroviral therapy for the chronically HIV – I infected patients (DHHS Guidelines) – October 2006

Clinical category	*CD4 cell count*	*Plasma HIV RNA*	*Recommendation*
AIDS-defining illness or severe symptoms*	Any value	Any value	Treat
Asymptomatic	CD4 cells < 200/mm^3	Any value	Treat
Asymptomatic	CD4 cells > 200/mm^3 but ≤ 350/mm^3	Any value	Treatment should be offered following full discussion of pros and cons with each patient
Asymptomatic	CD4 cells > 350/mm^3	≥ 100,000	Most clinicians recommend deferring therapy, but some clinicians will treat.
Asymptomatic	CD4 cells > 350/mm^3	< 100,000	Defer therapy

- AIDS-defining illness per Centers for Disease Control, 1993. Severe symptoms include unexplained fever or diarrhea > 2-4 weeks, oral candidiasis, or > 10% unexplained weight loss.

Table 2: When to start antiretroviral therapy–WHO guidelines

WHO Clinical Staging	*CD4 Testing not available*	*CD4 Testing Available*
1	Do not treat [A-III]	Treat if CD4 count is below 200 cells/mm^{3a} [A-III]
2	Do not treat^b [B-III)]	
3	Treat [A-III]	Consider treatment if CD4 count is below 350 cells/mm^{3acd} and initiate ART before CD4 count drops below 200 cells/mm^{3e} [B-III]
4	Treat [A-III]	Treat irrespective of CD4 cell count^a [A-III]

a CD4 cell count advisable to assist with determining need for immediate therapy for situations such as pulmonary TB and severe bacterial infections, which may occur at any CD4 level.

b A total lymphocyte count of 1200/mm^3 or less can be substituted for the CD4 count when the latter is unavailable and mild HIV disease exists it is not useful in asymptomatic patients. Thus, in the absence of CD4 cell counts and TLCs, patients with WHO adult clinical stage 2 should not be treated.

c The initiation of ART is recommended in all HIV-infected pregnant women with WHO clinical stage 3 disease and CD4 counts below 350 cells/mm^3.

d The initiation of ART is recommended for all HIV-infected patients with CD4 counts below 350 cells/mm^3 and pulmonary TB or severe bacterial infection.

e The precise CD4 cell level above 200/mm^3 at which ARV treatment should be started has not been established.

1. Rapid decline in CD4 count >100 cells/year;
2. Plasma viral load >100,000 copies/ml;
3. Patients with non-Hodgkin's lymphoma hepatitis C co-infection and HIV associated nephropathy.
4. Those with pulmonary TB, severe bacterial infection and pregnant woman.

WHAT TO START WITH?

The antiretroviral drugs act on various stages of life cycle of HIV in the body and work by interrupting the process of viral replication. Theoretically, these drugs can 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.

Currently available agents target the virus mainly by inhibiting the enzyme reverse transcriptase nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PIs) and preventing fusion of virus with CD4 cells (Fusion Inhibitors).

These drugs are listed in Table 3 and the profile of individual drugs, their doses, adverse effects and special consideration are given in Table 4[9].

To date, most clinical experience on use of combination therapy (Highly active antiretroviral therapy,

Table 3: Classes of drugs available

Nucleoside reverse transcriptase inhibitors (NRTI)	*Non-nucleoside reverse trans-criptase inhibitors (NNRTI)*	*Protease inhibitors (PI)*
Zidovudine (AZT)/ZDV*	Nevirapine*(NVP)	Saquinavir*(SQV)
Stavudine (d4T)*		Ritonavir*(RTV)
Lamivudine (3TC)*	Efavirenz*(EFV)	Nelfinavir*(NFV)
Didanosine (ddl)*	Delavirdine(DLV)	Amprenavir(APV)
Zalcitabine (ddC)*		Indinavir*(INV)
Abacavir*(ABC)	**Fusion Inhibitors (FI)**	Lopinavir/ Ritonavir (LPV)*
Emtricitabine(FTC)	Enfuviritide(T-20)	Foseamprenavir-(FPV)
(NtRTI)		Atazanavir(ATV)*
Tenofavir(TDF)*		Tipranavir(TPV)

* Available in India

HAART) in treatment-naïve individuals has been based on three different types of combination regimens, namely: *NNRTI – based* (2 NRTI + 1 NNRTI), *PI – based* (2 NRTI + 1 or 2 PI) and *triple NRTI-based* regimens[18-,20]. Table 5 compares the advantages and disadvantages of different combination of drugs that are used commonly for ARV therapy.

The therapy has to be individualised on a case to case basis taking into consideration various factors like tolerability, adverse effect profile, convenience, likelihood of adherence, affordability, concomitant drug use (e.g. rifampicin), mental illness, cardiac status and other co-existing illness etc. Table 6 illustrates the most common drug combination used currently for adults and adolescents (except for pregnant women or women who want to conceive or those who are not using effective contraception).

The present recommendation is to initiate therapy with an NNRTI based regimen (first line therapy). The efficacy of NNRTI based regimen has been shown to be equivalent to PI based regimen in a number of trials like Atlantic study[21], Combine study[22], Dupont study[23] and Focus trial[24]. NNRTI based regimen is associated with fewer toxicities and spare PIs for future use (second line therapy). But, NNRTIs have a low genetic barrier for resistance, and even a single mutation can confer cross resistance across the entire class[25].

Nevirapine is NNRTI backbone for most of first line regimens except for patients with TB co-infection, background liver disease and hepatitis B and C co-infection. A 14 day lead in dose of NVP of 200 mg once daily should be given to all patients before increasing to full dose of 200 mg twice a day as NVP may be associated with severe hypersensitivity skin reaction in some cases.

Efavirenz is the only NNRTI which can be used concomitantly with rifampicin making it a very valuable drug for HIV-TB co-infection. However, it should be used in caution in women of child-bearing age (not on adequate contraception) and those with existing depression and mental illness. The CNS disturbances associated with EFV are usually self-limiting and disappear in 2-4 weeks.

A large randomised study (2NN) has compared NVP and EFV based regimen and found them to have equal efficiency with slightly higher adverse events profile in NVP group[26]. The choice between two can be based on coexisting illnesses and toxicity issues.

As far as two neucloside backbone is concerned, a number of studies have shown that ZDV or Tenofovir plus LMV backbone based regimen are as effective as d4T + LMV based regimen[27] and both can be used as first line choice. However, recently, there have been a number of reports of adverse events like irreversible lipoatrophy, significant peripheral neuropathy and lactic acidosis with stavudine based regimen. The DHHS guidelines[9] have moved stavudine from "preferred " to "alternative" drug and it should generally be used for patients with anemia where zidovudine cannot be used.

The 2006 ART guidelines by Association of Physicians of India[17] have recommended that therapy can be initiated with stavudine plus lamivudine backbone in patients with anemia (Hb<8g/dl) and then switch to zidovudine plus lamuvudine based regimen at 12–24 weeks when hemoglobin improves. However, no randomised controlled studies have been undertaken to assess this strategy. Tenofovir (NtRTI) is another drug that has been shown to have comparable efficacy with zidovudine, has a good safety profile and has a once daily convenience[28]. It is recommended that fixed dose combinations (FDC) of ZDV + LMV + NVP or d4T+ LMV + NVP should be used with a view to reduce pill count, dosage frequency and improve adherence. This has been shown to be quite effective in a large observation cohort from India[29] and data from first year of implementation of National ART program in India[30].

Triple NRTI Regimen

Various clinical trials have shown that triple NRTI regimens are less potent virologically than NNRTI- or PI-based regimens. Hence, these regimens should only be used as an alternative to an NNRTI-based or a PI-based regimen in treatment-naïve patients where there is evidence that the other options may be less desirable due to concerns over toxicities, drug interactions, or regimen complexity. Moreover, a triple NRTI combination containing "tenofovir, abacavir and lamivudine

Table 4: Antiretroviral drugs profiles

Drug	*Dose*	*Special considerations*	*Adverse effects*
Zidovudine(AZT) (ZDV)	300 mg bd	With food	Anemia, neutropenia, GI intolerance, insomnia, myopathy
Lamivudine (3TC)	150 mg bd	With food	Minimal toxicity
Didanosine (ddI)	<60 kg: 250 mg od >60 kg: 400 mg od	Empty Stomach (1/2 hr prior or 2 hrs after meals)	Pancreatitis, peripheral neuropathy,nausea, diarrhea
Stavudine (d4T)	<60 kg:30 mg bd >60 kg:40 mg bd	With Food	Pancreatitis, peripheral neuropathy, lipoatrophylactic acidosis with hepatic steatosis (rare)
Abacavir (ABC)	300 mg bd	With food	Hypersensitivity reaction (can be fatal) fever, rash, fatigue, nausea, vomiting, anorexia
Zalcitabine (ddC)	0.75 mg tds	Without regard to food	Neuropathy, stomatitis, lactic acidosis.
Emtricitabine (FTC)	200 mg od	Without regard to food	Minimal toxicity
Efavirenz (EFV)	600 mg od	Bed time administration to avoid CNS symptoms	CNS Symptoms: dizziness, somnolence, insomnia, confusion, hallucinations, agitation elevated transaminase levels,skin rash
Nevirapine (NVP)	200 mg od x 14 days, then 200 mg bd	With or without food	Skin rash, Stevens-Johnson syndrome elevated aminotransferases, hepatitis, life-threatening hepatic toxicity
Nelfinavir (NFV)	750 mg tds	With food	Diarrhea, hyperglycaemia, fat redistribution and lipid abnormalities
Saquinavir (Soft Gel Cap) (SQV)	1200 mg tds	With fatty meals	Nausea, vomiting, elevated transaminase enzymes, hyperglycaemia, fat redistribution and lipid abnormalities
Indinavir (IND)	800 mg tds	1 hr before or 2 hrs after meal ,lot of fluid intake	Nephrolithiasis, GI intolerance, hyperglycemia, fat redistribution and lipid abnormalities, thrombocytopenia, alopecia
Ritonavir* (RTV)	600 mg bd (when used as sole PI)	Now used only as boosted PI with food	GI intolerance, paresthesia, hepatitis and pancreatitis, hyperglycemia, fat redistribution and lipid abnormalities
Lopinavir + ritonavir(LPV/r)	400 mg/100 mg bd 533 mg +133 mg bd when combined with EFV/NVP	With food	GI intolerance, nausea, vomiting, elevated transaminase, hyperglycemia, fat redistribution and lipid abnormalities
Atazanvir (ATV)	400 mg OD	Without regard to meal	Indirect hyperbilirubinaemia, jaundice
Amprenavir (APV)	>50 kg-1200 mg bd <50 kg: 20 mg/kg BD	With or without meal avoid high fat meal	GI intolerance, rash, oral paresthesia, elevation of transaminases hyperglycemia
T-20 (Enfuvirtide)	Single use vial 108 mg. reconstitute with 1.1 ml water	90 mg (1ml) S/C BD	Local injection site reaction, hypersensitivity, pneumonia
Saquinavir (hard gel cap) (SQV – HGC)	With ritonavir – 400 mg + Saquinavir 400 mg BD	Not recommended as a sole PI	GI intolerance, headache, elevation of transaminases lipid abnormalities
Tenofovir (TDF)	300 mg	300 mg od	Lactic acidosis, hepatomegaly

*Ritonavir is recommended for use in combination with indinavir, lopinavir and saquinavir as a booster and not as single PI.

'or' tenofovir, didanosine and lamivudine" should not be used as sole antiretroviral regimen at any time for treatment-naïve or experienced patients.

Follow-up of Patients on ART

The broad guidelines on follow-up on patients on ART are depicted in Table 7.

However, the ART guidelines issued by API[17] recommend a determination of plasma viral load at six months after starting ART to determine the efficacy of ARV regimen. This will help in assessing potency of regimen as well as adherence to regimen. A plasma viral load can identify failure earlier than CD4 count clinical signs and reduces the accumulation of resistant mutations.

Table 5: Advantages and disadvantages of class-sparing regimens used in HIV-1 therapy (modified from DHHS Guidelines)

Regimen	*Possible advantages*	*Possible disadvantages*
PI-based HAART regimen (NNRTI-sparing)	Clinical, virologic,and immunologic efficacy well-documented Targets HIV at two steps of viral replication (RT and PI) Preserves NNRTIs for use in treatment failure Avoids NNRTI-associated side effects Resistance requires multiple mutations Resistance primes for cross-resistance with other PIs	Some regimens are difficult to use and adhere to Long-term side effects often include lipodystrophy:, hyperlipidemia, and insulin resistance Mild to severe inhibition of cytochrome P450 leading to interaction with other drugs
NNRTI-based HAART regimen (PI-sparing)	Virologic, and immunologic efficacy well-documented Spares PI-related side effects Easier to use and adhere to, compared with PIs Fewer drug interactions compared with PIs Preserves PIs for use in treatment failure	Resistance conferred by a single or limited number of mutations Resistance usually leads to cross-resistance across entire NNRTI class
Triple NRTI regimen (NNRTI- and PI-sparing**)**	Generally easier to use and adhere to compared with PIs No cytochrome P450 interaction Preserves both PI and NNRTI classes for use in treatment failure, Sparing of PI and NNRTI side effects	Virologic efficacy inferior to PI/NNRTI-based regimen No longer recommended

Table 6: Recommended combination antiretroviral regimens

A combination antiretroviral regimen in treatment-naïve patients generally contains 1 NNRTI + 2 NRTIs or a single or ritonavit-boosted PI + 2 NRTI. Selection of a regimen for an antiretroviral-naïve patient should be individualised based on virologic efficacy, toxicities, pill burden, dosing frequency, drug-drug interaction potential and co-morbid conditions. Components listed below are designated as preferred when clinical trial data suggest optimal and durable efficacy with acceptable tolerability and ease of use. Alternative components are those that clinical trial show efficacy but that have disadvantages, such as antiviral activity or toxicities, compared with the preferred agent. In some cases, for an individual patient, a component listed as alternative may actually be the preferred component. Clinicians initiating antiretroviral regimens in the HIV-1 infected pregnant patient should refer to "*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women Maternal Health and Invervention to Reduce Perinatal HIV-1 Transmission in the United States"* as http:/aidsinfo.nih.gov/guidelines

To Construct an Antiretroviral Regimen, Select 1 Component from Column A + 1 from Column B

	Column A (NNRTI or PI Options-in alphabetical order)			**Column B (Dual-NRTI Options-in alphabetical order)**
Preferred components	NNRTI- Efavirenz[1] (AII)	or	PI- atazanavir + ritonavir (AIII) fosamprenavir + ritonavir (**2x/day**) (AII) lopinavir/ritonavir[2] (**2x/day**) (AII) (co-formulated)	Tenofovir/emtricitabine[3] (co-formulated) (AII); or zidovudine/lamivudine[3] (co-formulated) (AII)
Alternative to preferred components	NNRTI- Evirapine[4] (BII)	or	PI-atazanvir[5] (BII) fosamprenavir (BII) fosamprenavir + ritonavir (lx/day) (BII) lopinavir/ritonavir (lx/day) (BII) (co-formulated)	Abacavir/lamivudine[3] (co-formulated) (BII) didanosine + (emtricitabine or lamivudine) (BII)
Other possible options			Please see Table 8	Please see Table 8

[1]Efavirenz is not recommended for use in the 1st trimester of pregnancy or in sexually active women with child-bearing potential who are not using effective contraception

[2]The pivotal study that led to the recommendation of lopinavir/ ritonavir as a preferred PI component was based on twice-daily dosing. A smaller study has shown similar efficacy with once-daily do but also showed a higher incidence of moderate to severe dirrhea with the once-daily regimen (16% vs. 5%)

[3]Emtricitabine may be used in place of lamvudine and vice versa

[4]Nevirapine should not be initiated in women with CD_4^+ T cell count > 250 cells/mm^3 or in men with CD_4^+ T cell count > 400 cells/mm^3 because of increased risk of symptomatic hepatic events in these patients

[5]Atazanavir must be boosted with ritonavir if used in combination with tenofovir.

Table 7: Follow-up of patients on ART

	1 Month	*3 Months*	*6 Months*	*Every 6 months thereafter*
Clinical* (monthly)	Yes	Yes	Yes	Yes
CD4 counts	No	No	Yes	Yes
LFT's	Yes	No	Yes	Yes
CBC	Yes (AZT)	No	Yes	Yes
Other chemistry		As clinically indicated		

Adherence to ART

The adherence to ART is one of the most crucial determinant of success of ART on long-term basis[31]. The adherence rate of 95% or more are crucial for patients to achieve desirable suppression of viral replication as depicted in Figure 1 below. The adherence is determined by patients self report, pill count, appointments kept and refills obtained. The use of fixed dose combinations is an important part in improving adherence to ART. It is very important to adequately counsel the patients on adherence issues prior to start of therapy. Never start therapy on first visit, the patient needs to be adequately "prepared" to take it regularly on long-term basis. The counselling must continue on every visit thereafter. One of the family members should be involved in treatment protocol and patient should be encouraged to join positive networks/visit drop in centers to interact with peer educators.

Drug Interactions

Potential drug-drug interactions should be taken into consideration while selecting an antiretroviral regimen and review of drug interaction potential should be undertaken when any new drug is to be added to an existing antiretroviral combination. A list of significant drug interactions with different antiretroviral agents should be available at ART clinic for ready reference.

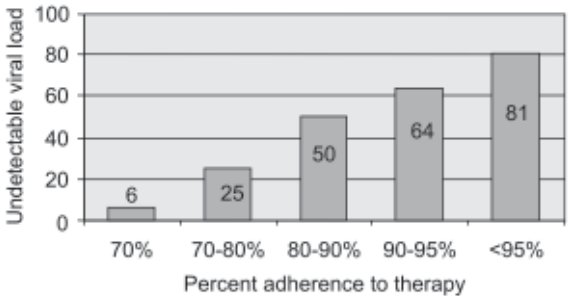

Fig. 1: Depicting the value of adherence

Most drug interactions with antiretrovirals are mediated through inhibition or induction of hepatic drug metabolism. All PIs and NNRTIs are metabolized in the liver by the cytochrome P450 (CYP) system, particularly by the CYP3A4 isoenzyme. The list of drugs that may have significant interactions with PIs and/or NNRTIs is extensive and continuously expanding. Some examples of these drugs include medications that are commonly prescribed for HIV patients such as lipid-lowering agents (the "statins"), benzodiazepines, calcium channel blockers, immunosuppressants (such as cyclosporine, and tacrolimus), neuroleptics, sildenafil, ergotamine, rifamycins, azole antifungals, macrolides, oral contraceptive and methadone.

All PIs are substrates and inhibitors of CYP3A4, with ritonavir having the most pronounced effect and saquinavir having the least potent inhibitory effect. The NNRTIs are also substrates of CYP3A4, and can be an inducer (nevirapine), an inhibitor (delavirdine), or a mixed inducer and inhibitor (efavirenz). Thus, these antiretroviral agents can interact with each other and with other drugs commonly prescribed for other concomitant diseases.

Co-administration of PIs or NNRTIs with a potent CYP3A4 inducer, on the other hand, may lead to sub-optimal drug concentrations and reduced therapeutic effects of the antiretroviral agents. These drug combinations should be avoided. If this is not possible, close monitoring of plasma HIV-RNA with or without antiretroviral dosage adjustment and/or therapeutic drug monitoring may be warranted. For example, the rifamycins (rifampicin, and, to a lesser extent rifabutin) are CYP 3A4 inducers that can significantly reduce plasma concentrations of most PIs and NNRTIs. As rifabutin is a less potent-inducer, it is generally considered a reasonable alternative to rifampicin for the treatment of tuberculosis when it is used with a PI- or NNRTI-based regimen despite the wider experience with rifampicin when used for this indication.

Changing Therapy

The reasons for changing an ART regimen include adverse effects, inconvenient regimens such as dosing/number of pills that may compromise adherence, occurrence of active tuberculosis and pregnancy and treatment failure.

The decision to change regimen should be based on clinical history, physical examination, routine and relevant laboratory investigations, CD4 counts and changes in count. An assessment of adherence to medications should be made and remaining treatment

options considered. Potential of initial viral resistance, drug interaction and diet also need to be considered.

a. Change due to Adverse Effects/Intolerance

In a patient who experiences adverse effects or is intolerant to an otherwise successful regimen, substitution of the offending drug is reasonable. An example would be metabolic adverse effects of a PI that can be replaced by an NNRTI. For serious adverse effects, such as abacavir hypersensitivity reactions and nevirapine related hepatic failure, rechallenge should not be attempted as this may lead to toxicity and death.

b. Change due to Treatment Failure

Treatment failure can be defined as clinical failure, immunologic failure and/or virologic failure. *Clinical failure* is defined as occurrence or re-occurrence of HIV related events (after at least three months on an antiretroviral regimen), excluding immune reconstitution syndrome. *Immunologic failure* can be defined as 'failure to increase the CD4 cell count by 25–50 cells/cmm above the baseline count over the first year of therapy, or a decrease to below the baseline CD4 count on therapy. *Virologic failure can* be defined as failure to achieve HIV RNA <400 copies/ml after 24 weeks or <50 copies/ml after 48 weeks or a rebound increase in viral load after initial suppression[32].

The entire regimen should be changed from a first to a second line combination regimen in the case of treatment failure. A single drug should not be added or changed to a failing regimen**.** The new second-line regimen will need to use drugs, which retain activity against the patient's virus strain and ideally include at least three new drugs, in order to increase the likelihood of treatment success. Table 8 depicts the second-line regimens one could consider in adolescents and adults for each of the first-line regimens identified.

Nucleoside analogue cross-resistance is an increasing concern. When ZDV/3TC is used in the first-line regimen, nucleoside cross-resistance may compromise the potency of d4T/ddI in the second-line regimen, in particular, in the presence of long-standing virologic treatment failure. In this regard, ABC/ddI might also be considered as the nucleoside backbone for a second-line regimen if the first line regimen did not include ABC. However, high-level ZDV/3TC resistance also confers diminished susceptibility to ABC.

The near complete cross resistance between EFZ and NVP means that a switch between these two agents in the setting of treatment failure is not advisable. In case of PIs, cross resistance among these agents is also common. A possible exception to this exists when NFV is the first PI employed. Therefore, in the case of treatment failure on a PI-based regimen, it is recommended that the PI be switched to an NNRTI.

Table 8: Recommended second-line regimens in adults and adolescents

First line regimens	*Second-line regimens for treatment failure Alternative second-line regimen for treatment failure*	
ZDV/3TC plus NVP or EFZ	RTV-enhanced PI + d4T/ddI	-RTV-enhanced PI + ABC/ddI -NFV + ABC/ddI or d4T/ddI
ZDV/3TC/ABC	NNRTI + LPV/r +/- d4T/ddI	RTV-enhanced PI + d4T/ddI
ZDV/3TC/RTV-enhanced PI or NFV	NNRTI + d4T/ddI	NNRTI + ABC/ddI

Given the diminished potential of almost any second line nucleoside component, a ritonavir (RTV/r) enhanced PI component [indinavir (IDV)/r, lopinavir (LPV)/r, saquinavir (SQV)/r)] is preferred to nelfinavir (NFV) in second line regimens because of its potency. NFV can be considered as an alternative for the PI component if a RTV-enhanced PI is not available or if there is a clinical contraindication to its use.

Antiretroviral Therapy in Special Situations

Some of the situations that demand special consideration include adolescents, women, pregnancy, breastfeeding mother, those with hepatitis B and C and tuberculosis co-infection. Of all these, special mention has to be made of tuberculosis, as it is commonest opportunistic infections in HIV-infected people in South-East Asia.

Due to the high prevalence of tuberculosis (TB) among HIV-infected individuals living in the South-East Asia Region, many patients who are candidates for ART will have active TB also. In addition, patients already receiving ART may develop clinical TB. Effective treatment and control of TB is a central priority when developing treatment strategies for co-infected patients. The management of HIV and TB co-infection is complicated because some antiretroviral agents produce unacceptable drug interactions with anti-tubercular agents and/or can increase toxicity of TB treatment. Tuberculosis treatment following the DOTS strategy should be initiated promptly in diagnosed cases of TB. The standard four drug regimen for six months is

advocated for all except for those with CNS involvement or those with slow response. These group of patients should be treated for nine months to one year[33].

The two major issues in the clinical management of patients with HIV and TB are when to start ART and which regimen to use. Initiation of ART for TB patients at high risk for HIV disease progression and mortality is recommended, i.e. a CD4 count <200 cells/mm^3, or extrapulmonary TB. For patients who develop TB with CD4 counts in the 50-200 cells/mm^3 range or, in the absence of CD4 testing, have total lymphocyte counts <1200 cells/mm^3, ART should be started after the first two months of TB therapy, because the toxicity of TB treatment is greatest during this period. In the subset of patients with very low CD4 cell counts (<50 cells/mm^3) or those with other severe HIV disease, ART should be started as soon as TB therapy is tolerated (Table 9). These group of patients should be specially monitored for development of IRIS.

The first line treatment options include ZDV/3TC or d4T/3TC plus either EFV or ABC. All other NNRTIs and PIs have significant interactions with rifampicin as discussed earlier and rifabutin is not available in India. EFV is the preferred drug as its potential to aggravate the hepatotoxicity of TB treatment appears less than with NVP. The dose of EFV need to be increased to 800 mg/day when used in combination with rifampicin.

The fixed dose combination of ZDV/3TC/ABC has no drug interactions with anti-tubercular therapy and does not require dose adjustments. However, the hypersensitivity reaction associated with ABC overlaps clinically with the immune reconstitution syndrome seen with tuberculosis. Therefore, ARV treatment could prematurely and unnecessarily be discontinued in patients with TB who initiate an ARV regimen containing ABC.

Patients already receiving ART when they develop TB should adjust the regimen to be compatible with TB treatment (EFV based). Following completion of antitubercular therapy, the ART regimen can be continued or changed depending upon the clinical and immunologic status of the patient and affordability of drugs (EFV being more expensive than NVP).

Table 9: Antiretroviral therapy for individuals with tuberculosis co-infection

Situation	*Recommendations*
Pulmonary TB and CD4 count <50/mm^3 or extrapulmonary TB	Start TB therapy. Start one of these regimens as soon as TB therapy is tolerated: • ZDV/3TC/EFZ • ZDV/3TC/SQV/r • ZDV/3TC/NVP
Pulmonary TB and CD4 50-200/mm^3 or total lymphocyte count <1200/mm^3	Start TB therapy. Start one of these regimens after 2 months of TB therapy: • ZDV/3TC/EFZ • ZDV/3TC/SQV/r • ZDV/3TC/NVP
Pulmonary TB and CD4 >200/mm^3 or total lymphocyte count >1200/mm^3	Treat TB. Monitor CD4 counts if available. Start ART according to Standard Guidelines

What should not be done in ART

- It is important to remember that ART should be started in a fully motivated patient. It should be a triple drug combination therapy;
- The ART should not be started without the capacity to diagnose, treat or prevent opportunistic infections, without capacity to meet patient's other needs such as sufficient nutritional support, adequate home care etc. and without minimum laboratory monitoring facilities like Hb., CHC, Liver Function Test etc.
- Continuing ART despite serious side effects; if treatment is not stopped or changed there may be irreversible damage.

CONCLUSION

Antiretroviral therapy (ART) has been proven to share impressive results in suppressing viral replication, delaying the progression of disease and has changed the management of HIV disease dramatically. The issues of adherence, toxicity, emerging resistance and cost of second line drugs are becoming increasingly important. The HIV care is rapidly evolving and is becoming increasingly complex. The future may bring better medicines, better strategies but the correct usage of these agents, their timings of initiation and proper monitoring is of utmost importance if we want these drugs to remain effective. The therapy is no doubt panacea for those already infected, but HIV prevention messages and probably AIDS vaccines are the keys to halting the progression of the epidemic of this dreaded disease.

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