Antiretroviral therapy: Need for a long-term view

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Antiretroviral therapy (ART) is the mainstay of management of HIV infection. World health organization and UNAIDS are aiming for "universal access to ART for all by 2010".[1] The dramatic decline in annual AIDS-related mortality has largely been attributed to the use of highly active antiretroviral therapy (HAART). Several effective antiretroviral agents are available and many more are in the pipeline [Table 1]. However, injudicious use of ART may be harmful to patients as well as society at large. It is therefore essential that the treating physician has a clear set of goals to guide him/her. This includes achieving not just maximal viral load suppression or qualitative and quantitative immune reconstitution leading to improved quality of life but also reducing human immunodeficiency virus (HIV) transmission. Moreover, all this needs to be done through rational sequencing of drugs in a fashion that achieves the above mentioned clinical, virologic, and immunologic goals while maintaining treatment options, limiting drug toxicity and facilitating adherence.

INITIATING ART[2]

This decision should be based on CD4 cell count, symptoms, and viral load. The CD4 count is the most important indicator for initiating treatment according to guidelines, and all agree that treatment is indicated for all patients with a CD4 count < 200 cells/mm^3. Symptomatic HIV infection is an indication for ART, irrespective of the CD4 counts. Whether to initiate therapy in the CD4 stratum between 200-350 cells/mm^3 in an asymptomatic patient is a controversial issue. ART should probably be started within this range depending on the symptoms, viral load, CD4 slope, patient preference, and associated co-morbidities.

The pretreatment evaluation should include a complete history and physical examination, fundus examination, complete blood count, biochemistry profile, lipid profile, CD4/CD8 T cell count/ratio, plasma HIV-1 RNA measurement (viral load) and supplementary tests including VDRL, Mantoux test, chest X-ray and serology for hepatitis C and B.[3] In India, the cost factor may preclude performance of all the above investigations, so a judicious decision is required. The supplementary tests are done if there is suspicion of underlying opportunistic infections so as to treat them before starting ART as also to predict possible immune reconstitution inflammatory syndrome (IRIS).

ADHERENCE TO ART

Before starting ART, it is imperative that the patient has a fair idea that therapy is long-term i.e., life-long; and that compliance with the drug regimen is most important for good virologic response. At least 95% adherence is required for durable and optimal viral suppression. Strategies to improve adherence have

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Table 1: Antiretroviral agents for human immunodeficiency virus infection

Drugs with intracellular MOAs†				Drugs with extracellular MOAs
NRTIs*	NNRTIs**	NtRTIs***	PIs****	Fusion inhibitor
Zidovudine (AZT, ZDV)	Nevirapine (NVP)	Tenofovir disoproxil	Saquinavir (SQV)	Enfuvirtide (ENF, T20)
Stavudine (d4T)	Delavirdine (DLV)	fumarate (TDF)	Indinavir (IDV)	
Lamivudine (3TC)	Efavirenz (EFV)		Ritonavir (RTV)	
Zalcitabine (ddC)			Nelfinavir (NFV)	
Didanosine (ddI)			Amprenavir (APV)	
Abacavir (ABC)			Fosamprenavir (FPV)	
Emtricitabine (FTC)			Atazanavir (ATV)	
			Tipranavir (TPV)	
			Darunavir (DRV)	
			Boosted Lopinavir (LPV/r)	

†Mechanism of actions (MOAs), *****Nucleoside analogs reverse transcriptase inhibitors (NRTIs), **Nonnucleoside analogs reverse transcriptase, inhibitors (NNRTIs), ***Nucleotide inhibitors reverse transcriptase inhibitors (NtRTIs), ****Protease inhibitors (PIs)

been adequately detailed elsewhere.[4]

FIRST-LINE REGIMENS

The initial regimen is the most important regimen because it is associated with the greatest probability of achieving prolonged viral suppression. In resource-limited settings like ours, nucleoside analogs reverse transcriptase inhibitors (NRTI) / non-nucleoside analogs reverse transcriptase inhibitors (NNRTI) triple combinations form the backbone of ART[5] [Figure 1]. Cost is an important determinant of this decision, as are host factors such as pregnancy, tuberculosis (TB), Hepatitis B/C virus (HBV/HCV) co-infection, and HIV-2 infection. A 3TC-containing regime is preferred in HBV co-infection, while EFV is the preferred molecule in TB, albeit at a higher dose to compensate for the low serum levels due to enzyme induction by rifampicin. However, these regimens are extremely effective and enable the clinician to reserve PIs for second-line regimens. A second advantage is the availability of fixed drug combinations of these molecules, which lead to enhanced patient compliance and adherence. Factors that influence the probability of prolonged viral suppression with any regimen include potency, adherence, baseline viral load, viral load nadir and rapidity of viral load response. Prior exposure to antiretroviral agents may also affect the response.

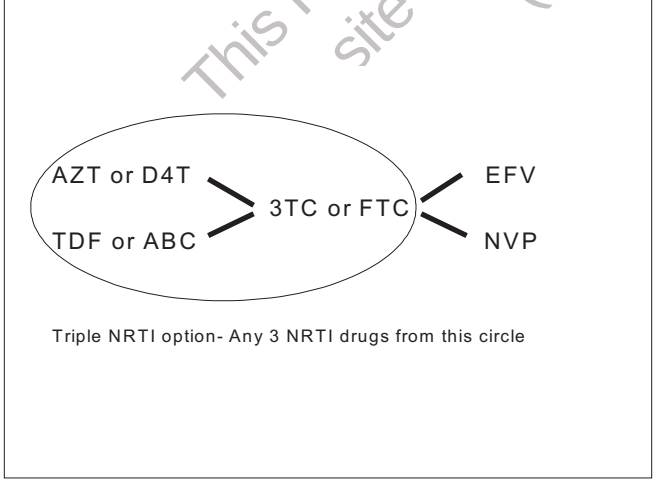

Figure 1: First-line ARV drugs for adults and adolescents First-line 2NRTI/NNRTI combinations (recommended). Triple NRTI approach is used only when NNRTI as a component is not advisable.
Adapted from http://www.who.int/hiv/pub/guidelines

ART DRUG TOXICITY

The major class toxicities of NRTIs are bone marrow suppression and mitochondrial toxicity (lactic acidosis, steatohepatitis, peripheral neuropathy, insulin resistance and lipodystrophy). While NNRTIs are associated with skin rash and hepatitis, PIs cause gastrointestinal intolerance and lipid metabolism anomalies. The major individual toxicities include bone marrow suppression (ZDV), pancreatitis (ddI), hypersensitivity (ABC), hepatic necrosis (NVP), neuropsychiatric complaints (EFV) and nephrolithiasis (IDV). Hyperlipidemias have emerged as an important concern with HAART, due to the potential for premature atherosclerosis and coronary artery disease. Highest risk has been observed with RTV and boosted PI, nil with ATV, and d4T > EFV > NVP.

DURG INTERACTIONS:[3,6]

NNRTIs, except DLV, are cytochrome P450 3A4 (CYP3A4) inducers while PIs (except TPV) are enzyme inhibitors; the result is a plethora of drug interactions.

An advantage of the CYP3A4 inhibition by PIs has been utilized in ritonavir (RTV) boosting of other PI molecules. This has led to decreased pill burden and a lower spectrum of adverse effects. The RTV-boosted PIs are the drugs of choice in second-line therapy. An important consideration in the Indian scenario is administration of rifampicin with NNRTIs. EFV is the preferred molecule in these cases.

Drugs contraindicated for use along with PIs and NNRTIs include astemizole and terfenadine, pimozide, St. John's wort (*Hypericum perforatum*), and the statins, namely simvastatin and lovastatin. Some drug interactions lead to dose modifications of certain drugs such as the azole antifungals, oral contraceptives, antimycobacterials, anticonvulsants etc. Several detailed commentaries on drug interactions of ART are available.[7-10]

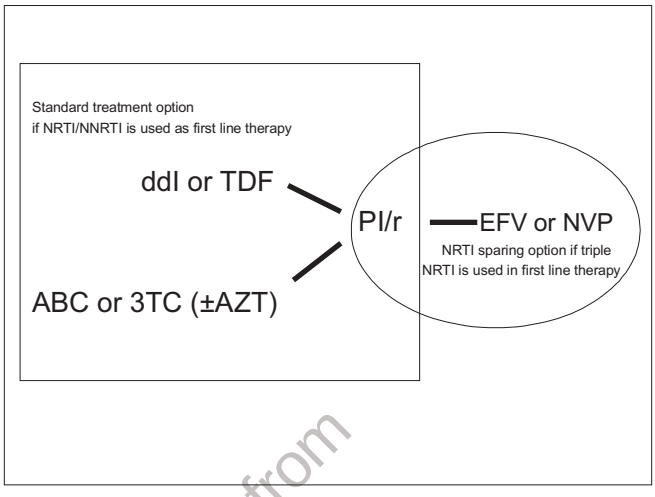

Figure 2: Second-line strategies to be considered in adults and adolescents who experience failure on the first-line regimens outlined in Figure 1
Adapted from http://www.who.int/hiv/pub/guidelines

TREATMENT FAILURE

Treatment failure is defined using the same variables that define the goals of antiretroviral therapy. Virologic failure is viral load (VL) > 200 c/mL or a sustained VL > 50 c/mL, after 24 weeks of therapy. Immunologic failure is arbitrarily defined as failure of the CD4 count to rise by 25-50 cells/mm^3 in the first year after HAART. Clinical failure is defined as the occurrence of an AIDS-defining opportunistic complication after three months of HAART, when immune reconstitution inflammatory syndrome (IRIS) has been excluded.

Causes of treatment failure are many. They include non-adherance or partial adherence, subtherapeutic drug levels, wrong choice of ART and selection of mutant strains leading to drug resistance.

SECOND-LINE REGIMENS[11,12]

Figure 2 presents the rationale behind selection of the second-line regimen.

HIV-2 INFECTION

There are certain genomic differences between HIV-1 and -2, which preclude the use of NNRTIs in treatment. However, NRTIs are as effective as in HIV-1, but the efficacy of PI is variable. IDV may be less active against HIV-2, while SQV, RTV, LPV /r and NFV appear to have comparable activity. These issues should be kept in mind before deciding any regime for HIV-2 infection.

NEED FOR A LONG-TERM VIEW

To conclude, ART provides a lifeline to those infected by the virus. Judicious use of these drugs is essential to ensure delayed development of resistance, and durable viral suppression. It is essential to define treatment goals prior to starting ART in the HIV infected and to select the most appropriate tools to achieve these goals [Table 2].

In resource-poor settings, ART drug regimens have

Table 2: Goals of human immunodeficiency virus therapy and tools to achieve goals

Goals	Tools
• Maximal and durable suppression of viral load	• Maximize adherence
• Restoration and/ or preservation of immunologic function	• Rational sequencing of therapy
• Improvement of quality of life	• Preservation of future treatment options
• Reduction of HIV-related morbidity and mortality	• Use of resistance testing in selected clinical settings

(www.aidsinfo.nih.gov/guidelines)

often not been chosen with long-term treatment as the first priority. It is now time to take a different view, especially in settings where, in the foreseeable future, drug options will still be limited. It is mandatory to make the right choices from the very beginning of treatment. An initial choice of the cheapest combination will come at a high cost later on. Although price considerations remain important, regimen choices should be driven mainly by data demonstrating durability of therapy, which is determined by antiviral potency, a high barrier against the development of viral resistance, and good short- and long-term tolerability. In combination with adherence support, this will lead to near universal treatment success, allowing for a reversal of the downward spiral of socioeconomic development that HIV / AIDS has caused in resource-poor settings.

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