Sequencing HIV/AIDS Therapies

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The turn of 20th Century has changed the dreadful HIV disease into a chronic manageable infection. More than 18 antiretroviral drugs have been approved by FDA and are currently being used to treat large number of HIV/AIDS cases. The drug therapy has led to improvement in the quality of life, significant reduction in mortality and dramatic change in the morbidity. The drug therapy has also raised many issues and some dilemmas and many more challenges.

The course of the HIV disease spans over a period of 15 to 25 or more years. The HIV infected case during this period needs a continuous psychosocial support, medical care and therapy support.

The backbone of the therapy remains to be counselling. Counselling aims at risk reduction by modifying the behaviour. A patient needs to be counselled for nutritional support as well as health maintenance measures.

In the early asymptomatic stages of the HIV disease, cases can be supported with antioxidants and micronutrients. There is an ample evidence to indicate the excess of free radicals as the HIV disease progresses. Low serum B12 levels have been reported in 15-20% of cases. Glutathione deficiency is common in HIV infected individuals and is associated with impaired T cell function and impaired survival.

Hence, the HIV infected case with high CD4 counts (>500 cells) can be supported with antioxidants, n-acetylcysteine to replenish glutathiones, B12, and other micronutrients.

During the intermediate immune depletion stage, an individual suffers various minor opportunistic infections, which are to be treated promptly.

As the HIV infection persists over a period of 15-25 years, one has to decide the optimum stage in the course of HIV disease to start anti-retroviral therapy.

When the antiretroviral drug therapy has to be initiated it is essential to consider the viral factors and the patient factors.

The HIV virus has -

1. Very high replicative rates, at least 10^{16} virions produced per day.
2. Very high mutability - The HIV-1 RT (reverse transcriptase) lacks the proof reading capability. The mutation rate is high 1 in 10^4 to 1 in 10^5 nucleotide mutations per replicative cycle or about one mutation per newly produced viral genome.
3. Very high plasticity - The proteins targeted by ARV drugs can still function on despite the presence of many mutations.

The patient factors - poor adherence, compliance, drug toxicity, pharmacokinetic drug interactions and pill burden, all limit the success of therapy in day-to-day practice.

Considering viral and patient factors, the sequencing HIV therapies become crucial.

Sequencing is the process of selecting the right drugs or drug combinations for a patient throughout his/her lifetime.

The main objectives of sequencing are:

1. To avoid / minimise drug toxicity.
2. To prolong the suppression of HIV
3. To preserve as many treatment options available

Highly active antiretroviral therapy was promising viral suppression to undetectable levels over a prolonged period. However, in a metaanalysis of 21 treatment groups from randomised clinical studies, only 46% of cases were able to suppress the plasma HIV RNA to <50 copies/ml at 48 weeks. It is estimated that 20-50% of patients have viral breakthrough within the first year of triple drug therapy.

In developing countries many more adverse factors such as illiteracy, poverty, malnutrition, non-availability and non-affordability of many drugs, poor nutrition and concomitant presence of OIs and tuberculosis, non-accountability of clinical practitioners, non-availability of prescription auditing, subsequent monitoring with expensive biochemical parameters, the sequencing of ARV therapy becomes Herculean task.

Therefore certain guidelines have been evolved

WHO guidelines state that-

1. All symptomatic cases, patients with HIV disease stage IV must be offered ARV.
2. All patients although asymptomatic at present but CD4 less than 200/ml must be offered ARV.

Therapeutic response being better at a higher CD4 count of about 300, patients can be offered treatment at a CD4 value of

Table 1 : When to start therapy?

Patient Characteristics	DHHS (USA)	IAS (USA)	BHIVA (UK)
Symptomatic	+	+	+
CD4 count (cells/µl)	< 350	< 350	< 350
Viral load (HIV RNA copies/ml)	> 55,000	> 30,000	> 55,000

Table 2 : The DHHS guidelines for ARV therapy

Antiretroviral Agents

Column A	Column B
Strongly Recommended	
Efavirenz	Didanosine + Lamivudine
Indinavir	Stavudine + Didanosine
Nelfinavir	Stavudine + Lamivudine
Ritonavir + Indinavir	Zidovudine + Didanosine
Ritonavir + Lopinavir	Zidovudine + Lamivudine
Ritonavir + Saquinavir	
1 Drug from Column A + 1 Combination from Column B = Triple Regimen.	
Recommended as Alternatives	
Abacavir	Zidovudine + Zalcitabine
Amprenavir	
Delavirdine	
Nelfinavir + Saquinavir – SGC	
Nevirapine	
Ritonavir	
Saquinavir - SGC	

300 or less. The ARV therapy can be deferred in asymptomatic cases with CD4 > 300.

The counselling concepts are new to the developing world, but therapy counselling forms an essential component of management. A patient and his family must be offered therapy counselling and treatment should begin only when they are mentally, psychologically and socially prepared to accept and adhere to the therapy.

Goals of ARV therapy:

1. To suppress viral replication
2. To increase the immune status indicated by rise in CD4 counts
3. To delay the clinical progression
4. To prolong the survival
5. To delay the emergence of drug resistance

WHEN TO START THERAPY?

See Table 1

ARV therapy is most effective the first time it is prescribed. It must aim at maximal viral suppression.

In Indian context, two additional factors limit the choice of first-line therapy:

1. The cost of therapy
2. Presence of anemia
3. Concomitant tuberculosis

Table 3 : Selection of HAART

PI based HAART, NNRTI Sparing	Targets RT & Pr, Clinical, Virologic Immunological efficacy well documented. Resistance requires multiple mutations
Long term side effects	Lipodystrophy, Insulin Resistance, ↑ Lipids
NNRTI based, PI Sparing	Sparing PI side effect Easier to use Clinical end points unknown. Resistance cof. by single mutation
Triple NRTI	Spares PI NNRTI side effects No cross-resistance Easier to use Clinical endpoints unknown.

ART therapy is most effective the first time is prescribed. The likelihood of achieving maximal virological suppression decreases with each subsequent treatment regimen.

The selection of HAART is based on various factors as shown summarily in Table 3.

The least expensive combination therapy at present is Stavudine + Lamivudine + Nevirapine. The second choice is Zidovudine + Lamivudine + Neverapine. Presence of severe anemia in large number of cases limits the use of Zidovudine.

First line therapy:

A. 2 NRTI + NNRTI
   - ❖ Stavudine + Lamivudine + Neverapine — Least expensive less potent
   - ❖ Zidovudine + Lamivudine + Neverapine
   - ❖ Stavudine + ddI + Efavirenz — Expensive, more potent
   - ❖ Zidovudine + ddI + Efavirenz

   To start with NVP has to be given 1 tab once a day for 14 days as a lead-on therapy for first 2 weeks. The patient has to be monitored for rise in liver enzymes and skin rash. Nearly 15 to 18% of Indian cases experience the skin rash. Severity of skin rash necessitates mission of NVP with substitution with another NNRTI name EFV that is expensive.

B. 2 NRTI + 1PI

   Sequencing protease inhibitors must give a consideration not only to side effects, toxicity but also to cross-resistance to other PIs

SEQUENCING THE PIs

Virological failure on nelfinavir (NFV) is associated with selection of a D30N mutation in about 2/3 cases. This selection reduces the susceptibility to nelfinavir but does not have a cross resistance to other PIs. The susceptibility to other PIs is maintained. But one-third of cases on NFV develop the L90M mutation, which causes broad PI cross-resistance. In such circumstances, NFV needs to be replaced by dual or phamaco-enhancing PI combination or the therapy has to be switched over to another class of drugs i.e. NNRTI. Cases on NFV showing early failure need to be salvaged on the basis of drug resistance studies, which are not yet available in this country.

Another PI namely Amprenavir selects 150V in most instances, which is very specific. It does not have a cross-resistance to other PIs therefore early failure on amprenavir can be managed by switching over to other PIs.

The use of ritonavir as pharmacoenhancer has revolutionized the therapy. (The combination of Lopenavir + baby dose or booster dose ritonavir).

This combination of Lopenavir/r has an extremely high genetic barrier. The resistance to this pharmacoenhancing therapy is recognized after atleast 11 PI mutations have accumulated.

Thus 2NRTI + Lopenavir/r therapy is a highly potent combination with longer duration of viral suppression and delayed emergence of drug resistance.

The Lopenavir/r can be used as a first-line therapy with considerable durability or can remain in reserve as a salvage therapy when other combinations like 2NRTI + 1NNRTI or 2NRTI + 1PI fails.

A small dose of ritonavir acting as a phamacoenhancer or booster to other PIs has raised the serum concentration of saquinavir, indinavir to 7 - 20 folds.

These ritonavir boosted PIs are increasingly been used in combination with 2 NRTIs for potent and prolonged duration as the emergence of resistance is delayed.

SEQUENCING NNRTI

It was believed that NNRTI as a group had overlapping resistance profile. But the recent evidence reveals that for EFV, the K103N mutation is almost always selected when therapy is failed. But for NVP the selection is mainly at Y181C mutation and hence in cases of NVP resistance with Y181C mutation EFV still remains active. Patients failing NVP can be rescued by EFV therapy. However, it may also be noted that, the evidence has recently emerged that patients on concomitant zidovudine and NVP favour to select K103N mutation, thus limiting the use of EFV as rescue drug.

All these studies emphasize the genetic sequencing before initiating the second-line therapy.

SEQUENCING NRTI

The recent evidences are making the NRTI sequencing more complex as ZDV mutations may arise using other NRTIs but phenotypic assays do not show a significant increase in the Stavudine or Didanosine resistance.

As a rule ZDV mutations compromise to some extent the response to all the remaining drugs in this class, therefore Stavudine should be preferred to ZDV in initiating the therapy.

In India the other constraint is a cost factor. Therefore, the most preferred first-line therapy is Stavudine + Lamivudine + Nevirapine.

SALVAGE THERAPY

When the patient fails the first-line therapy, the second-line therapy is instituted. Failure to second-line treatment precludes salvage therapy. In such circumstances, it is mandatory that a clinician takes the detailed drug history of the past, details of adherence to therapy and possibility and feasibility of directly observed therapy.

Ideally, before planning a salvage therapy, one must have a genotypic resistance assay.

When changing regimens, patient should be treated with atleast three new drugs to which no or minimal resistance is anticipated.