Introduction
Human Immunodeficiency Virus type 1 (HIV-1) is a retrovirus that infects human cells bearing
the CD4+ surface marker and causes, usually over many years, gradual loss of immune system
function. A hallmark of this process is the depletion of CD4+ lymphocytes and this and other complex
immune alterations predispose to the opportunistic infections and neoplasm characterizing Acquired
Immunodeficiency Syndrome (AIDS).1
Ever since the first case of AIDS was identified in 1981, there has been intense research in order to
understand the intricacies of HIV pathogenic mechanisms and natural course of the disease, as well as
to find out the safe and effective therapy.
The strategies of the management may differ in different countries according to their social and
economic structure but it starts as soon as the patient is detected to be HIV positive. Management
includes following points - diagnosis of HIV, counselling, investigations, management of opportunistic
infections (prophylaxis and treatment) and anti-retroviral therapy.
Anti Retroviral Therapy (ART) has transformed HIV infection from inevitably fatal disease into a
chronic condition manageable over a course of decades.2 The clinical effectiveness of antiretroviral
therapy has improved markedly over the last few years. Since 1996, there have been dramatic falls
in the incidence of new AIDS cases and AIDS associated deaths in the developed world. Although
the long-term clinical efficacy of the current antiretroviral treatment regimens remains uncertain, the
biological rationale for maintaining a clinical response has been established. Reservoirs of HIV in
latently infected resting T lymphocytes and other long-lived cell populations make it unlikely that HIV
can be eradicated by antiretroviral therapy alone. Strategies to sustain suppression of viral replication
in the long term will be necessary.3 The cost of ART has widened the gap between rich and poor in
developed and developing nations.

Anti Retroviral Therapy in HIV/AIDS
There are several potential targets for antiretroviral drugs in the viral replication cycle. (Table1)3 Three
classes of antiretroviral drugs are currently used in combination for the treatment of HIV infection,
which target the activity of two viral enzymes. New therapeutic agents are constantly being evaluated.

### Antiretroviral Drugs

1. **Nucleoside analogue reverse transcriptase inhibitors (NRTI’s)** – These constrain HIV replication by incorporation with the elongating strand of DNA, causing chain termination. (Table 2)

2. **Protease inhibitors (Pi’s)** – These are very potent group of drugs that block the action of the viral protease required for protein processing late in the viral cycle. All drugs have important interactions with the other medications, and concomitant medications should be reviewed carefully. (Table 3)

3. **Non-nucleoside reverse transcriptase inhibitors (NNRTI’s)** – These inhibit HIV by binding non-competitively to the transcriptase. Because onset of action is rapid, they may have a role in post exposure prophylaxis. (Table 4)

4. **Nucleotide analogs** – These inhibit HIV reverse transcriptase without reliance on the initial intracellular phosphorylation step, which is a required step for intracellular activation of nucleoside analogs. The nucleotide analogs may possess broader activity than nucleosides against both resting and activated cells. e.g. Tenofovir disoproxil fumarate (PMPA prodrug).\(^1\)

### When to Start ART?
The initiation of ART much depends on surrogate markers like CD4 count and HIV-RNA load. Plasma
Table 3: Protease Inhibitors (PI’s)

<table>
<thead>
<tr>
<th>PI’s</th>
<th>Base</th>
<th>Frequency</th>
<th>Daily pill burden</th>
<th>Dietary restrictions</th>
<th>Major side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>1200 mg (soft gel)</td>
<td>TDS</td>
<td>18 Capsules</td>
<td>With food</td>
<td>Nausea, diarrhea, abdominal pain, headache</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>600 mg</td>
<td>BD</td>
<td>12 Capsules</td>
<td>After food</td>
<td>Taste perversion, nausea, diarrhea, perioral tingling</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>750mg or 1250 mg</td>
<td>TDS BD</td>
<td>9 Tablets</td>
<td>With food</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Indinavir</td>
<td>800 mg</td>
<td>TDS</td>
<td>6 Capsules</td>
<td>Empty stomach</td>
<td>Nephrolithiasis, hyperbilirubinemia</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>1200 mg</td>
<td>BD</td>
<td>16 Capsules</td>
<td>None</td>
<td>Nausea, diarrhea, rash, perioral tingling</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>400 mg (with ritonavir)</td>
<td>—</td>
<td>—</td>
<td>With food</td>
<td>Diarrhea, hyperlipidemia</td>
</tr>
</tbody>
</table>

Table 4: Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI’s)

<table>
<thead>
<tr>
<th>NNRTI’s</th>
<th>Base</th>
<th>Frequency</th>
<th>Daily pill burden</th>
<th>Dietary restrictions</th>
<th>Major side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine (NVP)</td>
<td>200 mg</td>
<td>(OD for 2 initial weeks) BD</td>
<td>2 tablets</td>
<td>None</td>
<td>Rash, hepatitis</td>
</tr>
<tr>
<td>Delavirdine (DLV)</td>
<td>400 mg</td>
<td>TDS</td>
<td>12 tablets</td>
<td>None</td>
<td>Rash, headache</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>600 mg</td>
<td>3 HS (at night)</td>
<td>3 capsules</td>
<td>None</td>
<td>Dysphoria (dizziness, somnolence, abnormal dreams)</td>
</tr>
</tbody>
</table>

Viral load represents the result of steady state of viral replication and viral clearance. The same is around $10^{10}$ particles per day and number of virions produced increases as size of viral particle increases. Patients with high baseline virus load tends to progress more rapidly than lower load. Also ability of ART to suppress viral load to undetectable levels depend on initial viral load (here some newer drugs or >3 drugs may be effective). There are three groups in which one may think of initiating ART. (Table 5) The advantages and disadvantages of using ART in each group are described as below:

Primary HIV infection: Some workers favour initiation of ART as early as possible that is in primary infection stage. They follow “hit hard and early”. The arguments in favour are:

- Narrow genetic diversity of HIV.
- Mostly viruses are in macrophage/monocyte lineage.
- Non-syncitium forming virus
  a) Immune response is best (higher CD4)
  b) HIV ability is limited.
  c) Viral particles are small.

But most do not favour the initiation of ART at this stage.

- Complete eradication of HIV with ART is unlikely due to presence of long-lived cell infected with HIV.
- The treatment is to be continued indefinitely (>20 years).
Latent reservoir resting CD4 cells have long half-life of 43 months and it is extremely difficult to eradicate them (may take >60 years). Asymptomatic HIV infection: The recommendations for initiation of ART in asymptomatic HIV infection vary according to different guidelines. The basis underlying the guidelines are based on certain issues which are argued as follows:

**Arguments for:**
- HIV is an infectious disease and should be treated as such.
- Maximal suppression of viral replication leads to reduction of viral burden and decrease the risk of evolution of resistant virus.
- Prevention of immune deficiency and delays progression to AIDS and death.
- Possible greater potential for immune reconstitution.
- Less risk of side effects in patients whose general state of health is excellent.
- Possible decreased risk of viral transmission.

**Arguments against:**
- Adverse drug effects, problem with adherence, effects on lifestyle and psychology.
- Earlier development of drug resistance.
- Possible transmission of drug resistant virus.
- Limited future choices of antiretroviral agents if resistant occurs.
- Long term toxicity - some of them is currently unknown/ill defined.
- Unknown duration of efficiency of current ART.

Which Drugs to Start?
Currently monotherapy or two drugs regimen is not recommended. The gold standard is triple drug therapy (HAART). The various combinations used are: -

- 2NRTI+1PI, 2NRTI+2PI, 2NRTI+1NNRTI, 3NRTI, NRTI+PI+NNRTI.

Advantages of PI regimen: Potent, extensive experience, long-term durability, known drug to drug interaction, known toxicity profile, effective at all levels of HIV-RNA. (so this combination is first choice)

Disadvantage of PI: Complex so less adherence, cross resistance so may limit future PI regimens, long term toxicity, metabolic side effects, lipodystrophy, high cost.

Advantages of NNRTI: Durable suppression reported, lower cost, lower pill burden.
Disadvantages of NNRTI: Low genetic barrier- resistance is a problem.

3NRTI (advantages): Used when PI is deferred. But toxicity is more.²

Limitations of ART
• The prolonged use of antiretrovirals has been associated with long-term toxicities whose pathogenesis at this time is only partially understood.
• The therapy is not curative. Current antiretroviral regimens do not eradicate HIV from latent, long lasting cellular reservoirs.
• Not all patients respond to the antiretroviral therapy. (Only 60% respond)
• Treatment has to be taken life long or for very long duration and role of adherence is very important to prevent development of resistance.
• Multiple drug combinations lead to increased complexity, increased risk of toxicity and ultimately less adherence, which in turn lead to development of drug resistant strains of virus leading inevitably to failure of the regimen.
• Cost of the therapy is another important issue for a developing country like ours where not all patients can afford the ART.

Structured Treatment Interruption (STI) in Patients with Multidrug Resistant Human Immunodeficiency Virus

Interruption of antiretroviral treatment is increasingly being used for treatment failure and to manage the toxic effects of therapy. Although treatment interruption may lead to a decline in the CD4 cell count and an increase in the viral load, it has also being associated with the reemergence and predominance of a more sensitive (wild-type) viral population in patients with multidrug resistant HIV.⁸ Some studies have suggested that this change in the pattern of resistance may be associated with a better virological response when treatment is reinitiated.⁹ The break appears to boost the performance of the cytotoxic T lymphocytes (CTL) immune response strong enough to contain the virus. But some doctors fear a stop-start approach could lead to the virus developing resistance to anti-HIV drugs. Although the evidence so far looks promising, researchers are urging caution.

Future Agents in Pipeline

For the reasons of poor tolerability, suboptimal antiviral potency, and long-term drug toxicity, it is important that new antiretroviral agents and therapeutic strategies are developed and evaluated. New formulations of current drugs which improve tolerability and reduce pill burden will help to improve adherence in patients. New protease and reverse transcriptase inhibitors which in vitro appear to be effective against viral isolates which are resistant to different drugs are currently undergoing clinical trials. A recent trial with immunogen (Remune, inactivated HIV-1 core) alongwith the ART in patients with primary drug failure has shown positive results.¹⁰ Whether these agents will prove to be clinically effective will be important in treating those patients who have previously failed combination therapies. New classes of drugs are also being developed. Fusion inhibitors which block the activity of the GP41 viral transmembrane protein are in Phase III clinical trials and are likely to be the first new class of drug to reach the bedside. As well as specific drugs that inhibit targets in the viral replication cycle, immunotherapeutic approaches are also being assessed. Treatment with cycles of the cytokine interleukin 2 results in substantial increase in CD4 counts but has little effect on plasma viral load levels.² Interleukin 2 may also improve immune responses to HIV and a large randomized international trial is under way to assess its efficacy in combination with effective antiretroviral combination regimens. Therapeutic vaccines are also under evaluation, which might improve specific immune responses and assist immunological control of HIV replication. Their clinical effectiveness remains uncertain. Few areas of medicine have seen such dramatic changes in treatment, with a resulting reduction in morbidity and mortality, as there has been in the management of HIV infection. It is very likely that
therapeutic options will continue to improve, although the long-term efficacy of treatment over many years still remains uncertain.\textsuperscript{3}

Conclusion
The management of patients with HIV disease starts the day he is tested positive for HIV. The patients need intensive counselling for moral support and also to prevent the spread of infection to others. The patients should be abridged of the fact that a lot can be done to reduce the morbidity and to some extent the mortality even if they can’t afford ART. Despite major advances in ART, we are still far from ideal treatment of HIV infection. We need drugs that are safer, more effective, easier to administer, active against all strains of HIV viruses and with affordable price. It is sad truth that eradication does not appear to be feasible with most potent regimen. We, in India, also need to address the problem of unscrupulous, unwanted and incomplete ART, which may obviously prove more, damaging than helping our patients. Large numbers of HIV/AIDS patients are taking two-drug regimen in India, which is neither desirable nor recommended, and this practice should be discouraged. While cost factor remains the main deterrent to the continuing the compliance of the treatment, we must judge individually in each patient whether to start or not to start ART.

References
10. Kahn Jo, Cherng DW, Mayer K et al. Evaluation of HIV 1 immunogen, an immunologic marker administered to patients infected with HIV having 300-549/ cu mm CD4 cell counts: a randomized controlled trial. JAMA 2000; 284: 2193-2202.