Art of Initiation of Antiretroviral Therapy (in ARV Naive Patients)

JK Maniar*

The first cases of HIV infection were reported in 1981 and today, more than 30 years later: there are approximately 34 million people currently living with HIV and nearly 30 million people have died of AIDS-related causes since the beginning of the epidemic. The prevalence of the disease varies greatly across nations, with the highest disease burden in sub-Saharan Africa. South and South-east Asia, including India, account for an estimated 4 million living with HIV in 2011. 1 The number of persons living with HIV in India in 2008-2009 was estimated to be 2.4 million, with significant variation in prevalence across states.2

There is wide spectrum of opportunistic infections/ events occur during natural history of HIV infection, tuberculosis continues to be the commonest infection, others: oral / esophageal candidiasis, infective diarrhea / secretary diarrhea, herpes zoster, pneumocystis jiroveci pneumonia (PCP), neuro-toxoplamosis, cryptococcal meningitis, pruritic papular eruptions, seborrhoic dermatitis, reactivation of herpes simplex virus (HSV) and others.

Many people present late with advanced HIV infection viz absolute CD4 count less than 350 and / or with AIDS defining illness at the time of HIV diagnosis3. One of the major causes of death inspite of initiation antiretroviral therapy is late presentation. Late presenters : mostly symptomatic, fairly sick with multiple opportunistic infections / events, higher mortality rate, high chances of immuno-reconstitution inflammatory syndrome (IRIS) and antiretroviral therapy must be initiated

Combination ART, first introduced in 1996, has led to dramatic reductions in morbidity and mortality, and access has increased in recent years, rising from less than half a million people on treatment in 2003 to 8 million people in 2011, a 63% increase in the number of people on treatment since 2009. More than half (54%) of the 14.8 million people who were eligible for treatment were receiving it in 2011.3,4 There are people living with HIV (PLWH) who are eligible for anti-retroviral therapy (ART) and almost sixty percent have access to ART (Figure 1). It is needless to mention that ART has significant effect in reducing morbidity and mortality amongst PLWH, also there is reduction in incidence of new infection.

The goals of ART are:5
1. Virological goal; viral load reduction < 40 copies as long as possible.
2. Immunological goal; Immune reconstitution ; elevation of CD4 count
3. Clinical goal; reduction in morbidity and mortality, increase in life span, improvement in quality of life.
4. Theraputic goal: Sequencing of drugs to achieve clinical, virological and immunological goals.

Art of Initiation of Antiretroviral Therapy (in ARV Naive Patients)

JK Maniar*

The first cases of HIV infection were reported in 1981 and today, more than 30 years later: there are approximately 34 million people currently living with HIV and nearly 30 million people have died of AIDS-related causes since the beginning of the epidemic. The prevalence of the disease varies greatly across nations, with the highest disease burden in sub-Saharan Africa. South and South-east Asia, including India, account for an estimated 4 million living with HIV in 2011. The number of persons living with HIV in India in 2008-2009 was estimated to be 2.4 million, with significant variation in prevalence across states.

There is wide spectrum of opportunistic infections/ events occur during natural history of HIV infection, tuberculosis continues to be the commonest infection, others: oral / esophageal candidiasis, infective diarrhea / secretary diarrhea, herpes zoster, pneumocystis jiroveci pneumonia (PCP), neuro-toxoplamosis, cryptococcal meningitis, pruritic papular eruptions, seborrhoic dermatitis, reactivation of herpes simplex virus (HSV) and others.

Many people present late with advanced HIV infection viz absolute CD4 count less than 350 and / or with AIDS defining illness at the time of HIV diagnosis. One of the major causes of death inspite of initiation antiretroviral therapy is late presentation. Late presenters : mostly symptomatic, fairly sick with multiple opportunistic infections / events, higher mortality rate, high chances of immuno-reconstitution inflammatory syndrome (IRIS) and antiretroviral therapy must be initiated

Combination ART, first introduced in 1996, has led to dramatic reductions in morbidity and mortality, and access has increased in recent years, rising from less than half a million people on treatment in 2003 to 8 million people in 2011, a 63% increase in the number of people on treatment since 2009. More than half (54%) of the 14.8 million people who were eligible for treatment were receiving it in 2011.3,4 There are people living with HIV (PLWH) who are eligible for anti-retroviral therapy (ART) and almost sixty percent have access to ART (Figure 1). It is needless to mention that ART has significant effect in reducing morbidity and mortality amongst PLWH, also there is reduction in incidence of new infection.

The goals of ART are:
1. Virological goal; viral load reduction < 40 copies as long as possible.
2. Immunological goal; Immune reconstitution ; elevation of CD4 count
3. Clinical goal; reduction in morbidity and mortality, increase in life span, improvement in quality of life.
4. Theraputic goal: Sequencing of drugs to achieve clinical, virological and immunological goals.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>AIDS or HIV-Related Symptoms</th>
<th>CD4+ Cell Count &lt; 200/mm³</th>
<th>CD4+ Cell Count 200-350/mm³</th>
<th>CD4+ Cell Count 350-500/mm³</th>
<th>CD4+ Cell Count &gt; 500 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHHS 2012[DHHS 2012]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>International AIDS Society-USA 2010[Thompson 2010]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Consider</td>
</tr>
<tr>
<td>British HIV Association 2012[<a href="http://www.bhiva.org">http://www.bhiva.org</a>]</td>
<td>Yes’</td>
<td>Yes</td>
<td>Yes</td>
<td>Clinical trial</td>
<td>Clinical trial</td>
</tr>
<tr>
<td>European AIDS Clinical Society 2011[EACS 2011]</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Consider</td>
<td>Defer</td>
</tr>
<tr>
<td>World Health Organization 2011[WHO 2011; WHO 2012]</td>
<td>Yes’</td>
<td>Yes</td>
<td>No’</td>
<td>Not addressed’</td>
<td></td>
</tr>
</tbody>
</table>

With the exception of an HIV-positive partner in a serodiscordant relationship, who should be offered antiretroviral therapy at CD4+ counts > 350 cells/mm³ to prevent transmission to the uninfected partner.
5. Epidemiological goal; reduction of HIV transmission.

Therefore benefits of ART are; decreasing viral load, increasing CD4 counts, decreasing incidence of opportunistic infections, preventing diseases progression, improving quality of life, prolonging survival and prevention of HIV transmission.4-6

There are multiple guidelines for ART implementations and these are periodically updated (Table 1).

There are significant variations in initiation and monitoring of ART amongst private versus public set up for ART treatment which directly influences the outcome.

There are multiple problems of ART implementation viz.

- Currently ART initiation in public setup at absolute CD4 count < 350 while in private setup at 350-500.
- Cost in private setup vs free ART in public setup.
- Limited number of trained HIV physicians.
- Toxicity / adverse events.
- Adherence issues.
- ART failure / sequencing therapy.

Recovery of absolute CD4 count depends on the value of baseline CD4 count at the time of initiation of ART, if the absolute value is <100 then the recovery over even a period of one year of ART may be poor.10 Globally it is observed that both in developed as well as developing countries the absolute CD4 count at time of presentation is less than <300 cell (Figure 2). Therefore responses to ART is best monitored by estimation of HIV-1 viral load at 12, and 24 week, which normally achieve below detectable level. It is desirable to initiate in ART naive patients with single tablet (comprising of Tenofovir + Emtricitabine /lamivudine + Efavirenz) at bed time, this ensures better compliance and can be given along with anti-tuberculosis therapy or even in HIV and HBV co-infected patients.11,12
and 60% at a population level, and reduces TB recurrences rate by 50%-60%. Recent WHO guidelines recommend initiation of ART between 2 and 8 weeks subsequent to initiation of TB therapy for individuals with CD4 count < 200 mm⁻³. IRIS reported in 11-45% of patients who receive ART within 6 weeks of starting TB treatment. Several reports show high rate of morbidity and mortality in the first month of TB treatment in patients with CD4 count <100 cells/mm⁻³ at baseline.⁷,¹⁰

**HIV-2 Infection**¹⁹-²¹

West African countries are epicentre for HIV-2 infection. Less than 1% of HIV infection is caused by HIV-2, it was first detected in 1990 in India. HIV-2 has longer asymptomatic phase than that of HIV-1, it is less infectious than HIV-1. Clinical spectrum of HIV-1 and HIV-2 are similar. Appropriate laboratory tests viz. Western blot test for HIV-2, or more precisely HIV-1 / HIV-2 differentiating immunoassay help to confirm the diagnosis. Despite slow rates of progression mortality rates of HIV-1 and HIV-2 infection are similar. For initiation of ART almost similar indications as for HIV-1 are applied. NRTIs (Nucleoside analog reverse transcriptase inhibitors) are active. HIV-2 is intrinsically resistant to NNRTIs (Non nucleoside analog reverse transcriptase inhibitors) and Enfuvirtide. Only selected PIs (Protease inhibitors) are active (LPV/r, SQV/r, IDV/r and DRV/r).

In this issue of JAPI, Goel et al²² have shared their experience of ART in patients from eastern UP and Bihar. The important finding is that patients put on ART during early stages of disease have a long survival. This applies even to those patients with serious infections who survive initial days of ART. They do better with high survival rates. This emphasizes the need for the good outreach of ART programme and need for early initiation of ART (Figure 5).

Lessons learnt from fifteen years of ART:

- **a.** ART controls HIV viremia, enhances immune function, and prolongs survival.
- **b.** ART prevents HIV transmission.
- **c.** Current ART is potent, tolerable, convenient and increasingly available.
- **d.** Future challenges are; toxicities, drug resistance, cost and the fact that ART does not cure HIV.
- **e.** Patient initiating ART should be willing, able to commit to lifelong treatment, should understand the benefits and risks of therapy, and the importance of adherence.

**Acknowledgement**

For valuable contribution from Dr. Vinod E. Nambudiri, Brigham and Women’s Hospital Department of Medicine, Boston, USA.

**References**

13. DHHS guidelines; www.aidsinfo.nih.gov/guidelines
14. HIV drug interactions; www.hiv-druginteractions.org/