

## CURRENT THERAPY OF HIV/AIDS

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**Abstract:** HIV/AIDS is a global epidemic which has increased to an alarming proportion. Though not curable, it is a preventable and treatable disease and availability of highly active antiretroviral has dramatically improved the management of HIV/AIDS and various scientific organizations including Association of Physicians of India have developed guidelines for management of HIV/AIDS. At least a three drug regimen is recommended of which 2 NRTI plus INNRTI is the most widely used regimen in India. Dual NRTI plus boosted PI combination is reserved as a second line regimen. However Management of coinfection with TB is still a difficult task as is management of ART failure patients. The key to success in the fight against HIV/AIDS is proper knowledge about HIV, availability of ART and adherence to treatment.

### INTRODUCTION

Human immunodeficiency virus (HIV)/ Acquired immunodeficiency syndrome (AIDS) is a medical as well as a social problem of the new era which is similar to small pox of the earlier century. It is a disease caused by infection with HIV virus which belongs to the family Retroviridae and the subfamily of Lentiviruses. There are two serotypes however the most common cause of HIV disease through out the world, is HIV-1, which comprises of several subtypes with different geographic distributions. Zoonotic transmission is thought to have led to the appearance of this nuisance in humans. The hallmark of HIV/AIDS is profound immunodeficiency resulting mainly from a deficiency of helper T lymphocytes. The clinical consequences of HIV infection encompass a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease. HIV infection is known to lead to AIDS over time. Majority of individuals with HIV infection, if not treated progress of AIDS within an average of 7 to 10 years<sup>1</sup>.

### EPIDEMIOLOGY

The first documented human HIV-1 infection dates back to 1959<sup>2</sup>. However the virus got its present name in 1986 by the International Committee on Virus Nomenclature and Taxonomy<sup>3</sup>. HIV is a pandemic with an estimated 38.6 million people living with HIV infection worldwide<sup>4</sup>. With a toll of more than 25 million deaths, AIDS ranks fourth among the world's top killers of mankind<sup>3</sup>. India is considered to be the second largest population of HIV/AIDS with an estimated 5.13 million HIV infected individuals. Of these 39% are women and 58% live in rural areas. About one third of the total AIDS cases in India are among people younger than 30 years of age. A total of 111 districts in 18 states are considered high prevalence districts and the mode of transmission is primarily heterosexual except in the northern eastern states bordering the 'golden triangle' of injected drug abuse<sup>5</sup>.

### THERAPY FOR HIV/AIDS

Suppression of HIV replication below the limits of detection is the primary objective of therapy. It results in prolongation of life as well as improvement in the quality of life in patients with HIV infection. Combination antiretroviral therapy (ART), or Highly

Active Antiretroviral Therapy (HAART), is the cornerstone of management of such patients. Though the antiretroviral therapy has been limited to the developed nations, however with the continuous efforts to overcome the barriers, it is now being made available on a limited basis in the less developed parts of the world also.

Therapy of HIV/AIDS is complicated and various rules have been formulated to aid the physicians. Broadly, the existing antiretroviral (ARV) drugs for therapy of HIV infection falls in to three categories: those that inhibit the viral reverse transcriptase enzyme, those that inhibit the viral protease enzyme, and those that interfere with viral entry. **Nucleoside Reverse Transcriptase Inhibitors (NRTI)** include zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and emtricitabine. Nucleotide Reverse Transcriptase Inhibitor includes tenofovir. **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTS)**.include efavirenz, nevirapine and delavirdine. **Protease inhibitors (PI)** include saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, atazanavir, tipranavir and a fixed dose combination (FDC) of lopinavir / ritonavir. Enfuvirtide is the only drug approved in the class of fusion inhibitors.

Guidelines development group recommends that the first line regimen for adults and adolescents should contain at least three ARV drugs usually two NRTI plus one NNRTI or a PI. The preferred NRTI backbone is composed of Zidovudine or Tenofovir combined with either Lamivudine or Emtricitabine. Finally efavirenz (alternatively nevirapine) or lopinavir / ritonavir (alternatively saquinavir / ritonavir ) should be added. A combination of zidovudine, lamivudine, and efavirenz has been found to be superior in efficacy to other antiretroviral regimens for initiation of therapy in treatment naïve patients<sup>6</sup>. Following successful induction, the therapy should not be modified in an attempt to reduce the number of drugs. Reducing ART from three drug regimen to two drug regimen has been shown to increase the risk of resistance and virological failure<sup>7</sup>.

### WHEN TO INITIATE HAART

When to initiate the therapy is the most important question in HIV therapy. The decision to initiate HAART should be made on an individual basis after weighing the risk of disease progression, ART related adverse effects, cost of therapy, patient readiness and development of resistance<sup>8</sup>. WHO recommends ART for all patients with CD4 cell counts below 200 / mm<sup>3</sup> and all patients who are symptomatic with an AIDS defining illness (WHO clinical

staging) irrespective of CD4 cell counts. Therapy is also recommended in patients with some non-AIDS defining illness and CD4 cell counts  $<350/\text{mm}^3$ . The optimum time to initiate ART with a CD4 cell count of 200-350/ $\text{mm}^3$  is unknown<sup>9</sup>. Patients with CD4 cell counts in this range require regular clinical and immunological evaluation. However, ART may be considered in asymptomatic patients with CD4 cell counts between 250-350/ $\text{mm}^3$  if a decline in CD4 count is more than 100 cells/year or plasma viral load  $>100,000$  copies /ml or patient is on immunomodulators<sup>8</sup>. For most patients 350/ $\text{mm}^3$ , therapy should be deferred.

### ADHERENCE TO ART

Most important determinant of successful ART is adherence to ARV drugs since low adherence leads to rapid selection of drug resistant virus and hence treatment failure. More than 95% adherence to ART is desirable to maximize the benefits and avoid resistance<sup>10</sup>. Some of the suggested strategies to improve adherence include careful screening for patient readiness at the start of the therapy, emphasis on adherence at the start as well as during treatment, demonstration of drug schedules, buying monthly packs and follow up before supplies exhaust, using user friendly regimens, anticipating and efficiently treating adverse effects, identifying and managing condition like depression, involving a family member if the patient agrees, fittings ART in to patient's life style, regularly assessing adherence, using co-blisters packs and fixed dose combinations like Atripla, the only triple drug FDC for HIV/AIDS (containing emtricitabine, efavirenz and tenofovir disoproxil fumarate) which has been recently approved by US-FDA though not yet available in India. Other strategy to address the issue of adherence to life long ART is structured treatment interruptions<sup>2</sup>. If successful the strategy could limit the drug toxicities, improve compliance and reduce the cost of therapy. However results of clinical trials are mixed. SMART trial was terminated due to increased morbidity and mortality in the treatment interruption arm<sup>11</sup> but another recent trial in 403 patients suggested that an 8 week off and on intermittent therapy is safe over 96 weeks<sup>12</sup>.

### ART FAILURE AND SECOND LINE THERAPY

Treatment failure could be clinical (new or recurrent WHO stage 4 condition), immunological (fall of CD4 cell counts to pretreatment values or below; or 50% fall from on-treatment peak values; or persistent tCD4 cell counts below 100/ $\text{mm}^3$ ) or virological (plasma viral load above 100,000 copies /ml)<sup>9</sup>. It is not currently clear that which criteria are optimal WHO recommends that the regimen should be changed completely in case of ART failure. New regimen should ideally include at least three active drugs, one of them drawn from at least one new class. However there are limited options to offer to the patients with ARV drug resistance. The PI class is thus reserved for second line treatment and ritonavir boosted PI, forms the core of the

second line regimen preferably supported by two new NRTI. Alternatively, efavirenz or nevirapine may be used along with a PI/r and didanosine as a NRTI sparing option<sup>9</sup>.

In case of multiple regimen failure, the therapy becomes even more difficult. Preferably three but at least two fully active agents are required to start a new regimen after previous ART failure. If at least two such drugs cannot be identified, maintaining the current regimen should be considered until new drugs become available.<sup>13</sup> When choosing a new regimen, maintenance of NRTI particularly lamivudine and emtricitabine confers benefits even resistance is present. However NNRTI or double boosted PI should be avoided. Enfuvirtide should be reserved as a last resort drug<sup>13</sup>.

### HIV AND CHILDREN

Pediatric HIV is important for three reasons. *Firstly*, data suggests that half life of intracellular HIV proviral DNA is longer in infected children compared to adults (14 vs. 5-10 months respectively)<sup>14</sup>. *Secondly*, HIV disease progression is more rapid in children as compared to adults; this progression is inversely related with age<sup>15</sup>. *Thirdly*, ART in children is based mainly on clinical trials done in adults and very few studies have been done in children. Reducing mother to child transmission (MTCT) is the most effective way to reduce/prevent pediatric HIV/AIDS. Prevention of MTCT mainly relies on zidovudine prophylaxis in mother and the newborn. However once a child is diagnosed as having HIV infection while on zidovudine prophylaxis, zidovudine should be stopped and HAART should be considered.

*Guidelines* for the same are being refined as new data from clinical trials is becoming available. The recommendations for starting ART in children differ with age<sup>16</sup>. Percentage CD4 positive (%CD4+) values vary less with age and hence are more valuable in children under 5 years of age<sup>16</sup>. WHO recommends a CD4-guided initiation of ART for WHO pediatric stages 1 and 2. The threshold CD4 levels are  $<25\%$  for infants  $<11$  months,  $<20\%$  for children aged 12-35 months, or  $<15\%$  for children aged 3 years and above. Infants under 6 months of age are a special concern since they are at a higher risk of death or progression to AIDS. Whereas for children aged 5 years and above the same cut off value as in adults, i.e. 200 cells/ $\text{mm}^3$ , can be used<sup>16</sup>.

The *recommended treatment regimens* are the same for children as for adults. The preferred option when choosing a first line regimen for infants and children is two NRTI plus one NNRTI. NRTI/NNRTI based regimen has the advantages of being efficacious, less expensive, having lower pill burden, not requiring cold chain and preserving PI/NRTI based regimen as future treatment option. The preferred NNRTI is efavirenz for age more than 3 years and nevirapine for age less than 3 years (due to availability of liquid formulation). The preferred dual NRTI is (zidovudine or stavudine) plus (lamivudine or emtricitabine) For PI/NRTI based regimens, the preferred PI is lopinavir/ritonavir

combination or alternatively nelfinavir for children more than 2 years age. Triple NRTI regimens may also be used in children under special circumstances like significant drug interactions, HIV and tuberculosis (TB) co-infection, pregnant adolescent girls with CD4 absolute cell count  $>250/\text{mm}^3$  and documented poor adherence. The preferred combination is zidovudine or stavudine plus lamivudine plus abacavir<sup>16</sup>.

### **HIV AND WOMEN OF CHILD BEARING POTENTIAL OR PREGNANT WOMEN**

The choice of ART for women of child bearing potential depends on the possibility that ARV drugs may be required during the early first trimester also. The drug of concern is efavirenz. In women for whom effective contraception can be assured, EFV is a good option. However for patients who are not receiving adequate contraception, efavirenz should not be used due to risk of teratogenicity. ARV drugs especially PI may interact with hepatic microsomal enzymes leading to decreased levels of estradiol and potential risk of failure of oral contraceptives. Hence additional contraceptive methods should be made use of in order to avoid pregnancy in women receiving PI or NNRTI<sup>9</sup>.

Pregnancy is not a contraindication for ART. The indications for therapy and drug selection are similar to that in non pregnant patients. However, the threshold values of CD4 cell count need to be adjusted to account for a physiological decrease that is associated with pregnancy itself<sup>17</sup>. It is desirable to initiate ART after first trimester so as to minimize the risk of teratogenicity. However, benefits of ART outweigh the potential fetal risks and once started therapy should be continued postpartum.

The choice of ARV drugs in pregnancy is complicated by several factors like health of the woman effect of ARV drugs on pregnant woman and her infant, long term consequences on the child exposed to ARV drugs in utero and efficacy of ARV drugs for prevention of MTCT<sup>9</sup>. Zidovudine and lamivudine are the preferred NRTI. Alternatively stavudine, abacavir and didanosine may also be used. However, stavudine and didanosine combination should not be used. Nevirapine is preferred over efavirenz as NNRTI component due to the teratogenic effects of the latter. However, nevirapine induced hepatotoxicity is more common in women with CD4 cell counts  $> 350/\text{mm}^3$ . In such a case triple NRTI (zidovudine + lamivudine + abacavir or tenofovir) may be used in place of NRTI/NNRTI; PI based therapy is kept as second line regimen; the preferred PI for second line ART in pregnancy include saquinavir/ritonavir and nelfinavir<sup>9</sup>.

### **HIV & TUBERCULOSIS COINFECTION**

Tuberculosis is one of the earliest opportunistic diseases to develop amongst persons infected with HIV. A compromised immune system due to HIV increase the vulnerability of a person to TB, the risk of progression from TB infection to TB disease and leads to re-activation of latent TB. A HIV positive individual is six times (50-60% lifetime risk) more likely to develop TB

disease once infected with tubercle bacilli, as compared to an HIV negative person, who has a 10% lifetime risk. WHO has estimated a prevalence of 5.2% of HIV in adult TB patients in India<sup>18</sup>. In addition, there is increasing concern that HIV-1 will enhance the spread of multi drug resistant TB. The problem is further worsened by the fact that access to HAART is particularly limited in areas where both the diseases are highly prevalent.

WHO recommends that ART be given to all HIV positive patients with extra pulmonary TB (stage 4) and pulmonary TB (stage 3), unless the CD4 cell count is above  $350/\text{mm}^3$ . ART reduces both case fatality rates and the incidence of TB and recurrent TB<sup>9</sup>. As per WHO, development of TB in HIV patients already on ART does not imply a treatment failure unless it is supported by development of other non-TB stage 3 or 4 events and the ART regimen should be adjusted for co-administration with rifampicin-containing regimens<sup>9</sup>.

For patients with TB in whom HIV is diagnosed, there is also limited data present till date to guide the treatment<sup>20</sup>. High case fatality rates during the first two months of TB treatment in patients with HIV support the early use of ART. On the other hand consideration of pill burden, drug drug interactions, additive toxicity and occurrence of immune reconstitution inflammatory syndrome (IRIS) in 7-36% patients in whom ART and antituberculosis treatments started simultaneously support the late initiation of ART (20-21). Currently four trials (CAMELA, START, AACTG A 5221 and TB HAART WHO/TDR sponsored trial) are going on to address the dilemma of when to initiate the HAART in patients with HIV and TB coinfection<sup>20</sup>.

Until the results of such studies are available, the priority is to start anti tuberculosis treatment. WHO recommends that in persons with CD4 cell counts below  $200/\text{mm}^3$ , ART should be started between two and eight weeks after the start of TB therapy when the patient has stabilized on TB treatment. For patients with CD4 cell counts above  $200/\text{mm}^3$ , ART may be delayed until after the initial intensive phase of TB treatment has been completed. In patients with CD4 cell counts above  $350/\text{mm}^3$ , ART can be delayed until after the completion of short course TB therapy, following a reassessment of the patient's eligibility for ART and evaluation of the response to TB therapy<sup>9</sup>. The preferred regimen is 2NRTI plus efavirenz. Alternatively, triple NRTI regimen may also be considered<sup>9</sup>.

### **HIV AND ALTERNATIVE SYSTEMS OF MEDICINE**

A disease similar in symptoms to AIDS has been defined in Ayurveda Rajayakshma. Whether Rajayakshma and AIDS are same is not known. But some physicians believe that the treatment for Rajayakshma may be used for HIV also. This treatment includes rasayanams to boost the immune system and 'shodana' techniques to expel toxins from the body<sup>3</sup>.

**Herbal Medicine** is another important component of complimentary and alternative medicine and many patient with

HIV/AIDS seek such therapy due to non availability or high cost of HAART, unacceptable side effects<sup>22</sup>. However a meta analysis reveals that the evidence supporting such use lacks strength and larger and well defined trails are needed. The drugs found to have some potential in treatment of HIV/AIDS include Igm-1, Chinese herbal medicine (SH), Zhongyan –4 SPV – 30 (22-23). IGM –1 may improve the symptoms of HIV / AIDS, SPV – 30 may delay the progression of disease in some patients and SP – 303 may be helpful in AIDS patients with diarrhea. In a small number of patients SH potentiated zidovudine<sup>23</sup>. However potential risk of interaction between herbal drugs like ginkgo and St. John's wort needs attention<sup>22</sup>.

In Siddha, AIDS has been called as Vetta Noi which is caused by a defect in the three humors. Three formulations (rasagandhi mezhu, amukkara churnam, and nellikai lehyam) are said to be effective for HIV –infected patients who do not have neural involvement<sup>3</sup>.

Unani medicine is distinct from other systems of medicine as it uses medications that are natural in their sources and forms. There are no reports about Unani's efforts in developing a cure for HIV infection<sup>3</sup>.

## HIV VACCINE

AIDS vaccine with only 50% efficacy and covering 30% of the population could prevent seventeen million HIV infections over fifteen years<sup>24</sup>. However recent failure of the AIDS vaccine is a deep set back to research in the AIDS Vaccine field. In the phase II test of concept trial (STEP trial), the data safety monitoring board found that the vaccine V520 did not prevent HIV infection in volunteers engaged in high risk activities and Merck has halted the trail<sup>25</sup>.

## RESPONSE TO HIV IN INDIA

Since reporting of the first case of AIDS in India in 1986, the number of HIV/AIDS cases is rising continuously. Anticipating a serious threat, National AIDS Committee was constituted in 1986 followed by launch of National AIDS Control Programme (NACP) in 1987 and establishment of National AIDS Control Organization (NACO) in 1992<sup>26</sup>. The phase I of NACP completed in 1999. The objectives of NACP – II aims to reduce the spread of HIV infection in India and to strengthen the country's capacity to respond to HIV epidemic on a long term basis. The plan of action of NACP includes surveillance, condom promotion, blood safety, strengthening of programme management, information education and communication, reduction of impact, clinical management and control of sexually transmitted disease<sup>27</sup>. However, HIV prevention and education efforts in India are complicated by social stigma. India is one of the biggest producers of cheap generic ARV drugs that are sold to many countries all over the world. Still millions of needy Indians are not getting ART because free of charge treatment is available only in selected government institutions in certain cities.

## CRITICAL ISSUES AND MAJOR CHALLENGES

The key issues regarding HIV/AIDS that face India include

prevention of MTCT, expanding the coverage of ART, ensuring the quality of drugs, strengthening the drug procurement systems, increasing the access to counseling and testing services, ensuring adherence to therapy and proving second line ART<sup>5</sup>.

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