ANTI-RETROVIRAL THERAPY OF HIV INFECTED PATIENTS

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ABSTRACT

Initiation of Highly Active Anti-Retroviral Therapy (HAART) depends on clinical or immunological criteria. Clinical criteria include the presence of opportunistic infections, categorized by the WHO as stage 3 and 4. Immunological criteria are based on CD4 cell count. The WHO guidelines have changed frequently. All patients with CD4 cell count less than 200 cells/µl and symptomatic HIV or late disease or severe recurrent HIV illnesses or patients with AIDS or tumor at any CD4 count, should start therapy. WHO guidelines in 2013 recommended initiating HAART at CD4 counts less than 500 cells/µl. HAART is usually initiated when CD4 is less than 200 cell/µl because HIV infected patients present at a late stage. Research on factors responsible for this is sorely needed so that interventions can be targeted at this group.

Keywords*: HAART, AIDS, HIV, CD4, Antiretroviral*

Highly Active Anti-Retroviral Therapy (HAART) has been available world-wide since 1996. It is a combination of three drugs which include 2 Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI) or Non-Nucleoside Analogue Reverse Transcriptase Inhibitor (NNRTI) and Protease Inhibitor (PI) (1). Anti-retroviral therapy can help people living with HIV to live longer, increase quality of life and reduce AIDS-related deaths. According to the 2011 world report, anti-retroviral therapy is enjoyed by 8 million people, which is 20 times the number in 2003. Since 1995, anti-retroviral therapy has added 14 million life-years in low and middle income countries, including 9 million in sub-Saharan Africa in 2012 (2). HAART is given to decrease the viral load in the blood. This helps to repair the damage caused by HIV. It is recommended that a basic clinical assessment be carried out before starting anti-retroviral therapy. The clinical progression in HIV patients receiving treatment is estimated by the different levels of viral load and CD4 count. Existing medical conditions such as tuberculosis, hepatitis, injecting drug user (IDU), major psychiatric illness, pregnancy and body weight are identified to determine the patient's readiness for treatment. The presence of opportunistic infections have to be considered prior to starting treatment. A person's CD4 cells count too is used to determine when to start the treatment. CD4 cell count is also a major clue in asymptomatic patients (3). Several other factors such as symptoms, possible adherence, potential toxicity and patients' concerns should be considered in this matter (4).

All patients with CD4 cell count less than 200 cells/µl and symptomatic HIV or late disease or severe recurrent HIV illnesses or patients with AIDS or tumor at any CD4 count, should start therapy (3). If CD4 measurement is unavailable, simple tools such as haemoglobin level and total lymphocyte count can be used as laboratory markers to initiate HAART in resource-poor settings (5).

The question about when to initiate treatment should take into account that anti-retroviral therapy is a lifelong treatment, with significant adherence issues, potential side effects and high cost. To measure the HAART adherence, self-reported adherence (SRA) is an accurate instrument compared to therapeutic drug monitoring (TDM) and can be reliably used in practice in resource-poor settings (6).

The information about the prognosis of HIV infection is very important to monitor the progress of the HIV/AIDS epidemic, to develop treatment guidelines, to gain a better understanding of the prior treatment of HIV infection and to plan health services in the HAART period. These data are also important for the comparisons of treatment outcomes in resource poor settings once HAART becomes more widely available in less developed countries (7). Access to HIV care and anti-retroviral therapy still remain a challenge

to control the HIV epidemic in developing countries due to the financial burdens for people living with HIV in accessing and receiving HIV care (8).

Classes of drugs

There are different classes of antiretroviral drugs classified based on different phases of the retroviral life cycle and inhibitors. Anti HIV medications are grouped into six classes and each class targets a different step in the HIV life cycle (9,10).

Class 1: Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI) inhibit the transcription back in a way incorporated into newly synthesized viral DNA and prevent further elongation.

Class 2: Non-nucleoside reverse transcriptase inhibitors (NNRTI) inhibit the reverse transcriptase directly by binding to the enzyme and disrupting its function.

Class 3: Protease inhibitors (PI) targets viral assembly by inhibiting the activity of protease, an enzyme used by HIV to bypass nascent proteins for final assembly of new virions.

Class 4: Integrase inhibitors: inhibit the integration of the enzyme, it is responsible for integration of viral DNA into the DNA of infected cells.

Class 5: Entry inhibitors (or fusion inhibitors): disrupt binding, fusion and entry of HIV-1 into host cells by blocking one of several targets.

Class 6: Maturation inhibitors: inhibit the final step in the processing of *gag* in which the virus capsid poly-protein cleaved, thereby blocking the conversion of the poly-protein to the mature capsid protein (p24), because the virus particle has a core defect, which virions released consist mainly of non-infectious particles (9).

Using a combination of medications from different classes may increase the treatment's effectiveness while decreasing the risk of drug resistance. The approved medication to treat HIV infection fact sheet lists the food and drug administration (FDA) approved anti HIV medication by class, brand names, generic and date. Some are available as a combination pill of two or more different anti HIV medications from one or more classes (9).

Initiation of anti-retroviral therapy

The most important issue in HIV treatment is the determination of the optimal time to initiate anti-retrovirals. Anti-retroviral treatment can be initiated after an appropriate time of commencement and the combination of drugs to be used are decided. It will be influenced by many factors such as prior anti-retroviral history, stage of disease, concomitant therapies and illnesses, ability to tolerate and comply/adhere to certain combinations of drugs, adverse effects of the anti-retroviral agents, affordability and the cost of the regimen.

It is very important to ensure that the patient is able to adhere to the anti-retroviral regimen that he/she is started on. The importance of reducing the development of resistant viral strains and good drug adherence in maintaining viral suppression was highlighted in previous studies. Thus antiretroviral therapy should only begin when the patient is committed to long term treatment (9). The guideline recommends that in developing countries, HIV infected adults and adolescents should start anti-retroviral therapy when one of the following conditions is present and HIV infection has been confirmed.

Generally, the decision to start anti-retroviral therapy depends on the clinical or immunological criteria. Clinical criteria are based on the presence of one or more severe opportunistic infections, categorized by the WHO as stage 3 and 4. All developed and developing country guidelines recommend starting anti-retroviral therapy if a patient presented with stage 3 or 4 though decisions based on such clinical criteria alone are generally only used in resource limited settings where laboratory capacity is limited (1). Commonly, the decision to start anti-retroviral therapy is based on immunological criteria, as defined by the level of CD4 count. According to current WHO guidelines 2013, all HIV-infected patients with a CD4 less than 500 cells/µl must be started on HAART (11).

The majority of the current HAART regimens consist of 2 NRTI + a NNRTI/PI. The first line drug which is used in initial regimens must have low side effects and high efficacy. Treatment guidelines for adult HIV-1 infected patients in the developed countries have been provided by the International AIDS Society (IAS) USA since 1996. The IAS-USA anti-retroviral guidelines therapy was developed by a panel of volunteer experts.

Resistance tests are recommended prior to initiation of treatment. This is important for urgent treatment needs and to handle high rates of baseline resistance in certain countries. Later the chosen treatment regimen can be started and adjusted further based on resistance test. In Britain, there are 11.8 per cent of moderate to high level of resistance at baseline to a combination of Efavirenz + Zidovudine + Lamivudine and 6.4 per cent for medium to high level resistance to Stavudine + Lamivudine + Nevirapine (12).

In early 2010, the European AIDS Clinical Society (EACS) guidelines stated that in HIV-infected patients with CD4 count 350 to 500 cells/µl treatment should be considered if there is a viral load of more than 100,000 copies/ml, if CD4 declines to more than 50-100 cells/µl per year, age more than 50 years, high cardiovascular risk and malignancy. For patients with CD4 having more than 500 cells/µl, anti-retroviral therapy should be deferred. Treatment can be offered in the presence of co-morbid condition or in patients seeking and are ready for anti-retroviral therapy (13).

In July 2010, the panel of the International AIDS Society (IAS) in the US recommended anti-retrovirals for all HIV-infected patients with CD4 counts up to 500 cells per microlitre and in those with 500 cells per microlitre but were losing CD4 at a rate of more than 100 cells per microlitre per year, had viral loads more than 100,000 and whose ages were more than 60 years (14).

The guidelines of when to begin anti-retroviral therapy has been changed frequently (1). A comparison of anti-retroviral therapy initiation based on WHO guidelines in 2013, 2010 and 2006 is summarized in Table 1.

Switch to second line anti-retroviral therapy

Second line HAART regimes are indicated for patients who are forced to discontinue their initial treatment regime as a consequence of treatment failure or severe toxicity. Treatment failure is defined by clinical failure, immunological failure or virological failure (11). WHO definition of clinical failure for adult and adolescents is new or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment. Immunological failure is defined as CD4 count falling to the baseline (or below) or persistent CD4 levels below 100 cell/µl. Virological failure is defined by persistently detectable viral load exceeding 1000 copies/ml (that is two consecutive viral load measurements within a three months interval, with adherence support between measurements) after at least 6 months of using ART (11).

The recommendation of WHO (2013) when to switch to second line ART is based on:

- Where available, use viral load to confirm treatment failure;
- Where routinely available, use viral load every 6 months to detect viral replication;
- A persistent viral load more than 1000 copies/ml confirms treatment failure;
- When viral load is not available, use immunological criteria to confirm clinical failure;

Anti-retroviral therapy switching criteria (11):

- Clinical failure: new or recurrent stage 4 condition (condition must be differentiated from an immune reconstitution inflammatory syndrome/IRIS; certain WHO clinical stage 3 conditions (PTB, severe bacterial infection) may be an indication of treatment failure;
- Immunological failure:
  - Fall or immunological to baseline or below;
  - 50 per cent fall from on treatment peak value;
  - Persistent CD4 level below 100 cells/µl;
- Virological failure: viral load of more than 1000 copies/ml, the optimal viral load threshold for defining viral load failure has not been determined. Values of viral load which are more than 1000 copies/ml are associated with clinical progression and a decline in the CD4 cell count. The targeted viral load strategy for failure and switching anti-retroviral therapy is displayed in Figure 1.

Table 1. *A comparison of anti-retroviral therapy initiation based on WHO guidelines in 2013, 2010 and 2006*

Target population	2013 ART guidelines	2010 ART guidelines	2006 ART guidelines
HIV + asymptomatic	≤ 500 cell/µl	≤ 350 cell/ µl	≤ 200 cells/ µl
HIV + symptomatic	WHO clinical stage 1 and 2 if CD4 ≤ 500 cell/µl (CD4 ≤ 350 cells/ µl as priority)	WHO clinical stage 2 if CD4 ≤ 350 cells/µl WHO clinical stage 3 or 4 irrespective of CD4 cell	WHO clinical stage 2 if CD4 ≤200 cells/µl WHO clinical stage 3 if CD4 not available WHO clinical stage 4 if CD4 irrespective of CD4 cell Consider treatment for WHO clinical stage 3 and CD4 cell between 200 and 350 cells/µl
HIV + pregnant	All pregnant and breastfeeding women should initiate triple ART and maintained at least for the duration of MTCT risk. Women meeting treatment eligibility criteria should continue lifelong ART	CD4 < 350 cell/ µl irrespective of CD4 cell orWHO clinical stage 3 or 4 irrespective of CD4 cell	WHO clinical stage 1 or 2 if CD4 <200 cells/µl WHO clinical stage 3 or 4 if CD4 < 350 cells/µl WHO clinical stage 4 irrespective of CD4 cell
HIV/TB co-infection	Presence of active TB disease, irrespective of CD4 cell	Presence of active TB disease, irrespective of CD4 cell	Presence of active TB disease and CD4 ≤350 cells/µl ART Initiation can be delayed if CD4 ≥200 cells/µl
HIV/HBV co-infection	Individuals co-infected with HBV with evidence of severe chronic liver disease	Individuals who require treatment for their HBV infection, irrespective of CD4 cell count	No specific recommendation

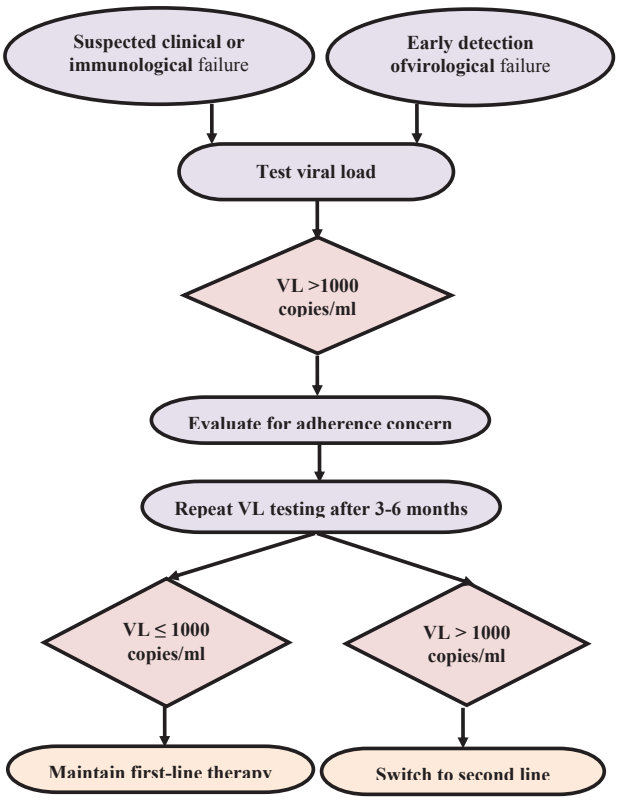

Figure 1. *Targeted viral load strategy for failure switching*

Second-line drug regimens

The 2010 WHO ART guidelines recommended that second line regimens included a boosted PI plus two NRTIs (determined by the drug used in first line therapy). Those guidelines placed a high value on using simpler second line regimes, ideally heat-stable formulations and fixed-dose combinations (one-daily formulation when possible). Since first line ART should preferably be based on an NNRTI, PI based regimens are recommended for second line therapy. Of the PI option, Atazanavir/Ritonavir (ATV/r) and Lopinavir/Ritonavir (LPV/r) are preferred. Darunavir/ Ritonavir (DRV/r) is an alternative but is currently not available as a fixed-dose combination, although one is in development. The other PIs such as Fosamprenavir/ Ritonavir (FPV/r), Indinavir/Ritonavir (IDV/r), Saquinavir/ Ritonavir (SQV/r) are not available as heat-stable fixed-dose combinations and/or associated with high pill burden and higher frequency of side effects. Second line ART regimes for adults and adolescents; if Stavudine (d4T) or Zidovudine (AZT) was used in first line, preferred second line regimes are Tenofovirdisoproxilfumarate (TDF) + Lamivudine (3TC) or Emtricitabine (FTC) + ATV/r or LPV/r. If TDF was used in first line ART, preferred second line regimen are AZT + 3TC + ATV/r or LPV/r (11).

Anti-retroviral therapy in Malaysia

In Malaysia, anti-retroviral treatment is available at all general hospitals and some district hospitals where there are specialist physicians managing medical clinics. Anti-retroviral treatment is also provided in some local university hospitals. All HIV clinics are run by physicians, who have had some training in HIV medicine.

The standard HAART Regimens (1;4) comprise one of three possible regimens:

- NRTI + NRTI + PI
- NRTI + NRTI + NNRTI
- NRTI + NRTI + PI + PI

Anti-retroviral therapy was introduced in stages in Malaysia. In 1989, AZT was available, in the early 1990's ddI and ddC were also available and in mid-1990's d4T and 3TC became available. In Malaysia, HAART was available from February 1997 with the entry of IDV but the cost of these drugs was high. In the late 1990's, a standard regimen of AZT + 3TC + IDV, would cost close to RM 2000 per month. In 2003, the MOH took the initiative to access cheaper generic anti-retroviral drugs from India. This led to the introduction of generic d4T, RTV and NVP into Malaysia. Generic drugs such as AZT, ddI and the fixed drug combination of AZT + 3TC, followed subsequently in early 2004. This led to the second big jump in anti-retroviral therapy uptake locally (4).

One of the three targets of Malaysia's Millennium Development Goals (MDG) is to achieve treatment for all HIV/AIDS patients by 2010. The Ministry of Health Malaysia reported that 9,962 people living with HIV had received anti-retroviral therapy by the end of 2009 (15). The Government of Malaysia provides first line anti-retroviral access for all HIV-infected patients without charging money at all government hospitals and clinics. From 2006, the Government of Malaysia provided anti-retroviral therapy to all HIV patients in prisons and drug rehabilitation centres. The second line anti-retroviral therapy is partly subsidized by the government (15). Malaysia will continue providing affordable access to clinical care for HIV patients through the public health system (4).

Anti-retroviral therapy programs in developing countries follow a public-health approach rather than an individualized approach. Guidelines for developed countries cover individual patient management delivered by specialist doctors prescribing from the full range of anti-retroviral drugs, supported by routine high-technology laboratory monitoring. This approach is not suitable in resource-limited settings where doctors are scarce, laboratory infrastructure is not adequate and the procurement and supply-chain management is frail. This difficulty in translating guidelines from developed to developing nations caused concerns over whether anti-retroviral therapy scale-up in poor countries is feasible, affordable and cost-effective (16).

Most HIV infected patients present at a late stage in developing countries and HAART is usually initiated when CD4 was less than 200 cell/µl, although WHO guidelines in 2013 recommend HAART initiation when CD4 is less than 500 cell/µL. Research on factors responsible for this is sorely needed so that interventions can be targeted at this group.

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