Monitoring of Antiretroviral drug therapy in HIV infected patients by Immunological and Virological Markers

ABSTRACT SUBMITTED TO

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By

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Abstract

The human immunodeficiency virus constitutes the greatest challenge to public health in modern times.

An estimated 22.5 million living with HIV or 68% of the global total are in sub-Saharan Africa. Eight countries in this region now account for almost one third of all new HIV infections and AIDS deaths globally. According to recent UNAIDS global HIV prevalence data, it has been estimated that in 2007 itself, 2.5 million newly HIV infected cases have been detected and 2.1 million people died of AIDS. In other words, an average of more than 6800 new infections (each day) and over 5700 deaths per day are attributed to HIV/AIDS

With the advent of antiretroviral drugs HIV infection however, has changed from a fatal condition to a manageable chronic illness in the developed world.

WHO declared the lack of access to ARV treatment for HIV/AIDS a "Global Health Emergency" in September, 2003 and announced that it would release an emergency plan to scale up access to ARV treatment for at least 3 million people by the end of 2005. This joint WHO/UNAIDS announcement popularly came to be known as the '3 by 5' initiative. So, keeping '3 by 5' initiatives in mind Government of India (GOI) launched free ART on 1st April 2004 for six high prevalence states namely Andhra Pradesh, Karnataka, Maharashtra, Tamil Nadu, Manipur, Nagaland and National Capital Territory of Delhi through 8 government hospitals in first phase.

Since the accessibility of ART to large number of HIV infected persons has increased due to availability of low cost generic drugs and free ART distribution by GOI, cases of development of drug resistance are also likely to increase resulting in ART failure. The other causes of ART failure are insufficient drug exposure due to poor adherence, inadequate drug absorption and pharmacokinetics or inability of the agents to penetrate reservoirs of HIV. However, one of the biggest issues among those managing of HIV disease in India is the high rate of sub-optimal adherence. This sub-optimal adherence is brought about by a combination of various factors like financial constraints, forgetfulness, drug toxicities and stigma.

Hence the monitoring of prevalence of drug resistant strains is a major public health concern especially since India is a home to the third largest HIV infected population in the world after South Africa and Nigeria. But the cost of monitoring drug resistance is very high. As antiretroviral therapy is most affordable and accessible, inexpensive laboratory tests are required to monitor the progression of disease and response to treatment in HIV infected individuals, living in resource-limited environments most heavily impacted by the epidemic.

While the level of absolute numbers of the peripheral CD4 T-cells and the Plasma viral load have eventually become the reference markers in clinical practice for monitoring HIV infected individuals, several additional parameters are still being evaluated. Immunological markers such as CD4 T-lymphocyte count, rate of fall in CD4 counts, CD8 lymphocyte counts and clinical signs and symptoms i.e. clinical markers such as oral candidiasis, hairy leukoplakia, etc plays important role in monitoring efficacy of ART.

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Apart from immunological markers, markers of viral replication i.e. virological markers such as viral load assay also play an important role in disease progression and assessment of antiretroviral treatment efficiency.

Measurement of HIV RNA in plasma is the most representative and sensitive laboratory marker currently available.

In countries like India where resources are limited we address four aspects of monitoring of ART: monitoring for therapeutic effectiveness, monitoring for drug toxicity, monitoring for adherence to medication regimens and monitoring for the emergence of resistant virus strains.

Most of the above mentioned parameters for monitoring ART have been routinely practiced in developed countries as shown by the ample data available on this subject. But due to financial and technical constraints many of these techniques are not used routinely in developing countries like India. These countries must have their own sufficient data for proper monitoring of ART, so that necessary planning/guidelines can be formulated on large scale to tackle this menace and expand lifespan of HIV positive individuals. Currently few studies have been carried out on different aspects of ART monitoring in these countries. Therefore present study was undertaken to throw more light on monitoring efficacy of various parameters in HAART. The objectives of this study were:

(1) To study the impact of Antiretroviral Therapy (ART) by using CD4 and plasma viral load.
(2) To compare the effectiveness of these markers in predicting drug efficacy.
(3) To assess ART adherence and virologic suppression among HIV infected individuals.

A total of 110 subjects (HIV positive individuals from various risk groups) were enrolled in the study during January 2004 at Advance center for AIDS and Related Diseases, NICD-Delhi / ART Clinic Lok Naik Jai Prakash Hospital New Delhi and followed up till November 2006. Pre and Post test counseling and informed consent were obtained from all individuals. In our study we had performed 3 ELISA/Rapid tests. Further, discordant samples were confirmed by Western blot or by Polymerase chain reaction (PCR), according to National HIV testing policy, formulated by National AIDS Control Organization (NACO) - Government of India. Immunological marker, namely

T - Lymphocyte subsets and a Virological marker, namely **Plasma viral load** assay were used in the study.
After 18 months only 69 subjects completed the final follow up. 59 subjects responded well to the various drug combinations. ART Treatment was failed in 10 subjects.

The present study encompasses the following findings:

(1) Significant loss of CD4 cells and drop in CD4/CD8 ratio was noticed in HIV positive (Asymptomatic & Symptomatic) subjects when compared with HIV negative healthy controls.

(2) Symptomatic subjects from various clinical stages i.e. stage-II, III, IV also showed significant decline in CD4 T-cells. It shows that clinical stages in HIV infected subjects correlate well with the CD4 level of T- cell count. Secondly, Plasma viral load was also found to clearly demarcate various stages of HIV/AIDS.

(3) Symptomatic subjects (mean: 4.5; range: 4.0-5.1) had significantly higher log 10 copies/ml of Plasma viral load in comparison to asymptomatic subjects (mean: 4.0; range: 3.9-4.5).

(4) Symptomatic subjects correlated well with symptoms and various clinical / laboratory diagnosed Opportunistic infections.

(5) Tuberculosis was the most common infection (39%) of which pulmonary tuberculosis was observed in nearly 60% of all the cases of tuberculosis. 45.6% of symptomatic subjects showed co-infection with two or more pathogens / parasites.

(6) Risk of recurrence of opportunistic infections was almost nil in patients who adhered to ART for a longer duration.

(7) Majority of subjects responded well after initiation of ART and showed on an average 55-60 cells increase in CD4 cells at follow-up and undetectable level of Plasma viral load after second follow-up.

(8) Rate of adherence > 95% was observed in 88.1% of subjects.
- Social support came out to be a good predictor for adherence.
- Higher educated individuals were found to be more adherent.
- Married subjects were more adherent than unmarried ones.
- Virologic suppression and Immunological response were found to be better observed in adherent subjects as compared to non adherent ones.
- Subjects taking Efavirenz combination (NNRTI) were more adherent due to less toxicity and side effects.

(9) 10 subjects did not respond to ART. Suggestive reasons for treatment failure might be non-adherence, poor drug tolerability, drug resistance and lack of awareness in understanding importance of ART.

(10) In all symptomatic subjects clinical symptoms found at induction into study were mostly cured after taking ART. This shows effective and positive response of ART.

(11) Appropriate education of masses in terms of knowledge regarding sexually transmitted infections, safe sexual practices, needle exchange programmes (for IDUs), etc., can definitely cut down the fresh infection of HIV.