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# SUCCESSFUL VIROLOGICAL SUPPRESSION IN THE FACE OF IMMUNOLOGICAL FAILURE AMONGST HIV SEROPOSITIVE PERSONS ON ANTIRETROVIRAL TREATMENT

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## ABSTRACT

**Background**: In the absence of viral load tests as monitoring tool for people living with HIV/AIDS on antiretroviral therapy, CD4 cell count and clinical assessment were depended upon as a monitoring tool. Our clinically healthy clients with immune failure repeatedly for two to three times were switched to second line drugs. Those clinically ill with immune failure with no other known comorbidity were also switched to second line drugs.

Studies have shown that some persons living with human immunodeficiency virus (HIV) who did normalise their immune status while on HAART, had viral suppression while others showed blunted immune response despite virologic suppression evidenced by low plasma HIV-1 RNA.[1-5] Quality improvement programme later on set up and funded by the PEPFAR US based programme in which 1,520 clients on antiretroviral therapy were randomly selected and subjected to viral load assay. We reviewed the CD4 response of our patients on HAART at baseline and at time of viral load assay, in order to identify discordant patients and thus formulate strategies for more efficient and effective antiretroviral client treatment monitoring.

**Materials and Methods**: Of the 1,520 clients who had their viral load assayed, we reviewed their CD4 count at baseline and at time of viral load assay. We also reviewed the age, gender distribution and the discordancy rate.

**Results**: We found a discordant immune response to antiretroviral therapy in 165 (10.9% of 1520) clients whose viral load were assayed. Univariate analysis showed that low CD4 counts less than 100cells/ml at baseline, less than 50% gain in CD4 count more than one year after commencement of antiretroviral therapy and time on antiretroviral therapy more than three years, with P-value of 0.035 were associated with immunological failure.

**Conclusion**: We therefore concluded that approximately 11 per cent of our clients with immune response failure had successful viral suppression.

## INTRODUCTION

Since the institution of highly active antiretroviral therapy (HAART) the setting for the management of human immunodeficiency virus (HIV) has been transformed.[1-4] Usually when a person with HIV is on HAART, the immune status recovers while morbidity and mortality are vividly diminished.[1-2] Although the person's ability to survive has appreciated but this cannot be compared to that of an healthy individual without HIV infection, since the HIV infected person will still be at risk of hepatic, cardiovascular and malignant diseases when compared with the healthy uninfected person.[1-2] It is also a well-known fact that when the HIV – 1 infected person is placed on effective therapy, there is associated immunological and clinical improvement.[1-3] It has also been observed that CD4 rebuilding is not homogenous. While some have a rapid immunological rebuilding and therefore recovery, others have either a slow, blunted or failure to recover.[3] When immunological reconstitution is related to viral suppression one finds a discordant response to HAART in some of the patients. However most of the patients on potent HAART are virally suppressed. The reason for the discordant response in some of the patients on HAART is not well known, hence our study was to determine the presence and magnitude of the discordant responses and possibly carry out a further analysis to determine the factors associated with the discordancy noted.

## MATERIALS AND METHODS

The CD4 counts of the clients were monitored at baseline and every six months for one year. Viral load as mentioned above was checked when there was fund available for viral load assay following a continuous quality improvement project that included fund for viral load for limited number of subjects. The viral load assay was carried out on subjects who had been on HAART, for at least 12 months. The number of subjects randomly selected for the viral load assay was 1520, out of the over five thousand clients that were on therapy at the time.

We obtained consent from all our clients as part of the Doctor - patient encounter exercises at enrolment, to enable us be able to analyse data obtained from client for both programme improvement and possible publication without disclosing the patients' identity. We obtained ethical clearance from the Bingham University Teaching Hospital's Health Research Ethics Committee. Data were collated both in hard copies in patient case files while the electronic copies were computed into the HIV/AIDS Programme data base. The electronic copies of the relevant data were accessed and where necessary, crosschecked with the patients' case files.

We therefore collated and analysed the viral load assays, the CD4 counts of the subjects at baseline and at CD4 at time of viral load sampling using the statistical package for social sciences version 14.
Those whose CD4 counts at time of viral load assay showed non-immune response were collated and analysed to demonstrate either immunologic failure when there was virologic suppression. We further carried out univariate and multiple regression analysis to determine the factors associated with non-immune response in clients with viral suppression. Multiple regression analysis was carried out by assessing those variables that showed some degree of association at the univariate analysis where p value was $< 0.05$.

## RESULTS

The result of 165 clients showed discordant responses to HAART and the characteristics were as follows: low or less than 50 per cent increase in CD4 count over the period of treatment and viral suppression (less than 10 copies in 127, less than 50 copies in 16, less than 100 in 5 subjects, less than 200 in 4 copies, less than 300 in 2 subjects, less than 400 in 4, less than 500 copies in 2, less than 600 in 1, less than 700 in 3 and less than 800 in 1 subject)

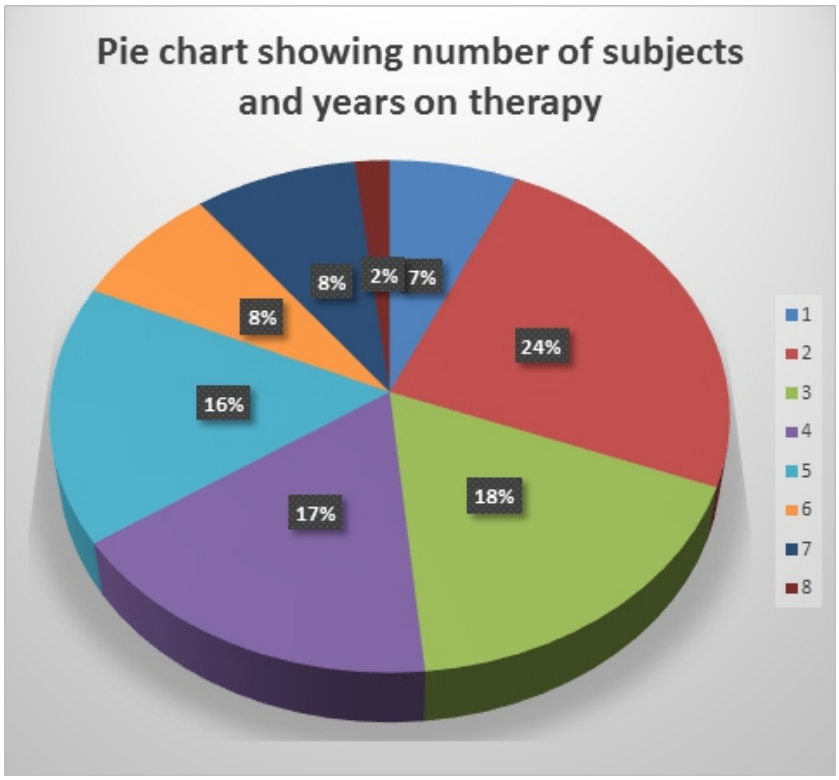
Out of 1,520 clients who had their viral load and CD4 counts assayed, we found a discordant immune response in 165 clients which was 10.9 per cent of the total number of clients whose viral load and CD4 were assayed.

The 165 clients adjudged to have failed immunologically but had their viral load suppressed, meaning that their plasma viral loads were at least below 1000 copies/ml according to WHO definition of viral suppression.

The discordant subjects were adjudged so if their CD4 result showed CD4 decline to a pre-antiretroviral therapy (baseline) CD4 values (4 subjects of 165), CD4 drop to less than 50% of peak while on therapy (111 subjects of 165) and failure to achieve more than $100c/mm^3$ increase while on therapy (50 subjects of 165).

Of the 165 with discordant response, 38 (23% of 165) were males while 127 (77% of 165) were females showing male to female ratio of 1:3. The oldest amongst the subjects was 71 years old, the mean age was 43, median age was 41 while the most occurring age was 36. There were 3 children out of the 165 study subjects. With the above results more females showed discordancy while on antiretroviral therapy. All the 165 subjects were clinically asymptomatic and with viral suppression were not eligible for second line therapy, hence they were maintained on their first line drug regimen.

After univariate analysis it was discovered that immunological failure was significantly associated with low CD4 less than 100cells/ml, less than 50% gain in CD4 count after at least one year of ART and time on ART more than three years as shown in the univariate analysis table 1 below. The multiple regression analysis showed the time on ART or duration of ART, age and lowest CD4 count ever while on treatment, predicted immunological failure for the respective subjects as shown in table 2 below.

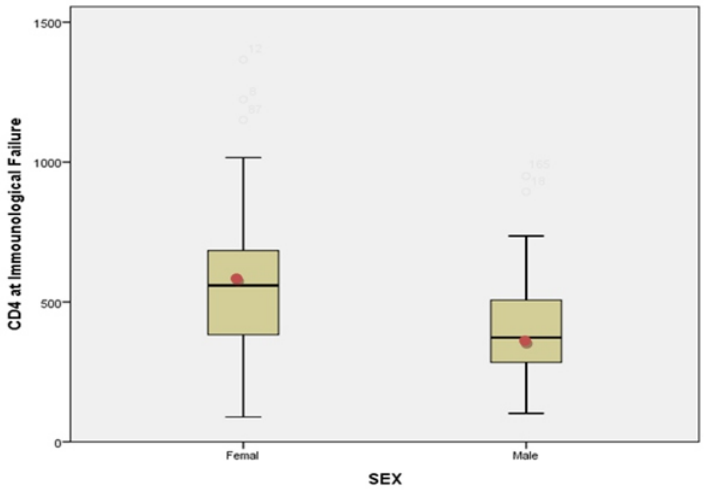



1 to 8 Equals Number of Years on Therapy

**Table 1 Showing Univariate Analysis**

| NO OF SAMPLE | NUMBER | % | MEAN | SD | P-VALUE (a=0.05) |
|---|---|---|---|---|---|
| **Gender** | | | | | |
| **Male** | 37 | 23 | - | - | - |
| **Female** | 127 | 77 | - | - | - |
| **Age (in Years)** | | | 43.06 | 11.191 | 0.001 |
| **<55** | 139 | 84.2 | | | |
| **≥55** | 26 | 15.8 | | | |
| **CD4 Count (cell/µl) from baseline of ART** | | | | | |
| **>100** | 161 | | 1.00 | .0001 | 0.10 |
| **<100** | 4 | 1.1 | 1.00 | .0001 | 0.001 |
| **Gain In CD4 Count (cell/µl) from baseline of ART** | | | | | |
| **<50%** | 165 | 100 | 8.30 | 29.559 | 0.04 |
| **>50%** | 0 | - | - | - | - |
| **Duration on ART** | | | | | |
| **<3** | 44 | | 1.1 | .0001 | 0.090 |
| **>3** | 90 | | 1.1 | .0001 | 0.035 |

Above table 1 shows the results of univariate analysis performed on 165 immunologic non-responders despite viral suppression showing immunologic failure. The table shows that low CD4 counts less than 100cells/ml at baseline with p – value < 0.001, less than 50% gain in CD4 count more than one year after commencement of antiretroviral therapy with p – value of 0.04 and time on antiretroviral therapy more than three years, with P-value of 0.035 were statistically significantly associated with immunological failure.




Comparison of CD4 count at the time of immunological failure in male and female discordant patients. Boxes represent interquartile range, horizontal line inside box is median value. Means are indicated by solid circles

**Table 2 Showing Multiple Regression Analysis**

| | *Coefficients* | *SD* | *t Stat* | *P-value* | *r2* |
|---|---|---|---|---|---|
| Intercept | 17.7181 | 4.4116 | 4.0163 | 0.0001 | 0.09 |
| SEX | 3.2400 | 2.0416 | 1.5870 | 0.1145 | |
| BASELINE CD4 | -0.0010 | 0.0047 | -0.2123 | 0.8321 | |
| CD4 CURRENT | 0.0098 | 0.0047 | 2.0547 | 0.0415 | |
| AGE | -0.2267 | 0.0746 | -3.0368 | 0.0028 | |
| Duration On ART | 0.0480 | 0.4764 | 0.1007 | 0.9199 | |

Standard deviation = SD, Coefficient of determination = $r^2$

**DISCUSSION**

Usually the commencement of HAART on HIV patients leads to rapid drop in the plasma levels of HIV – RNA with a corresponding increase in peripheral blood CD4 counts.[2,3] Nevertheless, there are patients that do not follow the pattern described above. Such patients manifest what is called discordant response. This is a situation whereby the plasma HIV – RNA level is less than the limit of detection whereas the CD4 count response is blunted. In Nigeria there are limited data on discordant responses amongst Nigerians infected with HIV and are on treatment.

This study revealed that 165 (10.9% of 1520 clients failed immunologically despite having their viral load successfully suppressed, thus showing a discordant response of approximately 11%. This was comparable with what had been reported in some other parts of the world including some developing countries. In the Antiretroviral Therapy in Lower Income Countries Collaboration (ART – LINC) study, an epidemiological network of HIV/AIDS treatment programmes in Asia, Africa and South America, the frequency of discordant responses was discovered in 15 developing countries.[2] In their study they found discordant response of 269 amounting to 14% of the study population, even though their definition of virological only response was below 500 copies/ml and thus may be responsible for the higher discordant rate when compared with our own study, another study in India showed non-immune responses of 28 (24%) out of 116 subjects in the study. The Indian study finding of 24% discordant response was much higher than what we found in our own study of 11% and this large difference may be due to difference in the sample size while we studied 1520 clients for non-immune response the Indian study focused only on those referred to them for switch to second line therapy having failed immunologically, since CD4 count was the standard for monitoring antiretroviral treatment efficacy in their own treatment sites.[2,6,8]

In resource limited settings/developing countries, clinical evaluation followed by immunological response evaluation and follow up of clients are the tools readily and widely available to physicians to

assess treatment quality and effectiveness. Viral load is available in developing countries but are not as readily and widely available as the other tools mentioned above. This has made reliance on CD4 count as a treatment efficacy measurement tool to persist, since even when HIV -RNA assay is available may take weeks to months for the result to come out and by that time patients on a failing regimen would have developed resistant viruses. On the other hand, the developed countries with lower HIV/AIDS burden do analysis for HIV genotype in search of HIV mutations related to antiretroviral resistance in HIV infected persons presenting with treatment failure.[2] Such practice has even been expanded to include HIV infected clients without previous treatment experience with the aim of providing customized therapy for treatment naïve clients thus reducing the risk of therapeutic failure.[2]

Most HIV infected persons reside in developing countries like Nigeria that is now the second largest HIV burdened nation globally after India. Limited resources and high cost of carrying out genotypic studies has led to limited access to such studies in Nigeria.

Discordant responses amongst HIV clients on heart has not been well studied, hence not much is known about the pathogenesis this atypical response to antiretroviral therapy. Available data suggests multi-factorial interaction involving viral, host and treatment related factors. Many studies discovered that genetic polymorphisms that include the Fas receptor (CD95) gene, the Fas Ligand (CD178), the Interleukin – 6 gene and the MHC genes involvement in T – cell immunity can determine whether or not a person can experience immunologic response to antiretroviral therapy.[2] Dulled CD4 response in the face of viral replication suppression has been blamed on the physiognomies of the host especially old age.[2]

In our own study younger age was associated with discordant response to antiretroviral therapy since 84.2% of our discordant response subjects were less than 55 years of age. This result in our study showing that old age is is not associated with discordant immune response is in keeping with a study in Catholic University in Rome, Italy that showed that old age was not associated with discordant immune response.[9]Another hypothesis suggest that amount of immune reconstitution depends on the activities of the thymus and that these activities decrease with age.[2] Our own research findings showed that majority of the non-responders were people below 55 years of age as already alluded to above. The modal age being 36, mean age 43 while the median age was 41 in our study. Thus, in our study younger age less than 55 years of age was significantly associated with immunological non-response and virologic response with P – value of 0.001.

Similar to other studies, our research work showed that poor CD4 cell reconstitution in the face of virological response correlated with lower baseline or pre-treatment CD4 cell count;[2,7,10,11] signifying a more widespread reduction in CD4 cells in the gut related lymphoid tissue all through primary acute HIV infection and this process may lead to slow or refractory immune rebuilding in the antiretroviral therapy period.[2,10]

Onen et al in their research work evaluated risk factors for sub-optimal CD4 recovery while on suppressive HAART and discovered that 36% of their subjects had sub-optimal response of less than 150 cells/microlitre during the first year of virologic suppression.[2] Whereas in our own study only 7% had sub-optimal immune response during the first year of antiretroviral therapy. We also discovered that duration on antiretroviral therapy greater than three years was associated with discordant response to antiretroviral therapy, similar to other published research findings.

## CONCLUSION

We conclude that discordant response was found in 10.9% of 1520 based on the WHO criteria for immunological failure and virological suppression.

We therefore recommend that in a resource limited setting, resources for viral load can be reserved for those who have failed immunologically within the first year of antiretroviral therapy. This will save some money that can be used for resistant testing for those who are virally unsuppressed. This means that though CD4 count is still important for treatment monitoring particularly in the absence of viral load testing; viral load testing remains the gold standard for monitoring treatment success and efficiency amongst HIV patients on treatment and thus recommend that in resource poor setting, viral load assay can be reserved for those clients who are failing immunologically with or without evidence of co – morbidity.

**We further recommend the following**:

Early identification of discordancy is possible by noting the factors such as the baseline CD4 count, the percentage gain in CD4 in less than 50% more than one year after commencement of antiretroviral therapy and time on antiretroviral therapy more than three years with immune failure.

Clinicians providing care for the HIV infected persons can effectively monitor their clients even in resource limited setting where CD4 count is the only monitoring tool available besides clinical assessment tools based on the findings in this study.

The national government through ministry of health should develop and incorporate into the national guideline for HIV management; a simple standard operating procedure that uses the findings in this study to guide physicians and other HIV care and treatment service providers in the early detection of discordancy in order to treat accordingly.

There is need for the evolvement of a national strategy that will take into consideration the uneven distribution of resources so as to ensure prioritization and that scarce resource are utilised where and when they are really needed.

**REFERENCES**


1. Eleanor M.P. Wilson, Irini Sereti. Immune Restoration after Antiretroviral Therapy: The Pitfalls of Hasty or Incomplete Repairs. Immunol Rev. July; 2013 254(1): 343–354.
2. Michael M. Lederman, Leonard Calabrese, Nicholas T. Funderburg, Brian Clagett, Kathy Medvik, Hector Bonilla et al. Immunologic Failure Despite Suppressive Antiretroviral Therapy Is Related to Activation and Turnover of Memory CD4 Cells. Journal of Infectious Disease October; 2011; 1217 – 1226.
3. Fernando Dronda, Santiago Moreno, Ana Moreno, Jose´ L. Casado, Marı´a J. Pe´ rez-Elı´as et al. Long-Term Outcomes among Antiretroviral- Naive Human Immunodeficiency Virus–Infected Patients with Small Increases in CD4+ Cell Counts after Successful Virologic Suppression. Clinical Infectious Diseases 2002; 35:1005–1009.
4. B. Prabhakar Asima Banu, H. B. Pavithra, P. Chandrashekhara, and Suresh Sasthri. Immunological failure despite virological suppression in HIV seropositive individuals on antiretroviral therapy. Indian J Sex Transm Dis. 2011 Jul-Dec; 32(2): 94–98.
5. Jean-Paul Viarda, Marianne Burgard, Jean-Baptiste Hubert, Laurent Aarona, Ce´cile Rabiana, Nathalie Pertuiset, et al. Impact of 5 Years of Maximally Successful Highly Active Antiretroviral Therapy on CD4 Cell Count and HIV-1 DNA level, AIDS 2004, 18:45–49.
6. David Alain Wohl. We Order Too Many CD4 Cell Counts, but Should We Really Stop? Top HIV Clinical Development; November 15, 2017
7. DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial, Lancet. 2010 Jan 9; 375(9709): 123–131.
8. Mrudula N. Dravid, Ravindra K. Khadse, Shubhangi D. Kulkami and Hitesh R. Adchitre. Two years CD4 count follow-up of rural patients on antiretroviral therapy: A study in Government Hospital, Indian J Sex Transm Dis. 2011 Jan-Jun; 32(1): 59–60.
9. Mario Tumbarello, Ricardo Rabagliati, Katleen de Gaetano Donati, Silvia Bertagnolio, Ever Montuori, Enrica Tamburrini et al. Older Age Does Not Influence CD4 Recovery in HIV – 1 Infected Persons Receiving Highly Active Anti-Retroviral Therapy. BMC Infectious Disease, Nov. 2004. Accessed online on the 10/07/2018 at http://www.biomedcentral.com/1471-2334/4/46/prepub
10. WHO - South East Asia – New Delhi. Laboratory Guidelines for enumerating CD4 T Lymphocytes in the context of HIV/AIDS, June; 2007 page 11-16.
11. Muzah BP, Takuva S, Maskew M, Delany – Moretlwe S. Risk Factors for Discordant Immune Response Among HIV Patients Initiating Antiretroviral Therapy: A Retrospective Cohort Study. S Afr J HIV Med. 2012; 13(4):168-172