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RESEARCH PAPER

Correlation of immunological failure and virological failure in a group of HIV patients on 1st line ART

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ABSTRACT

Background and objectives: *Human Immunodeficiency Virus (HIV), a Lentivirus (a subgroup of retrovirus), infects humans and causes progressive failure of the immune system that ultimately leads to AIDS (acquired immunodeficiency syndrome), a state which allows life-threatening opportunistic infections and cancers to thrive. Despite the reduction in mortality and morbidity with the introduction of highly active antiretroviral therapy (HAART), a considerable proportion of patients fail to achieve a sustained virologic response to therapy, which has led to treatment failure. National AIDS Control Organisation (NACO) has developed simple immunological, virological and clinical criteria to diagnose treatment failure. The study aimed to determine the correlation between patients with immunological failure and virological failure in a study group of people living with HIV/AIDS (PLHA) on 1st line anti-retroviral therapy (ART) after six months of treatment.* ***Methods****: A hospital-based observational study was done with data collected over one year. The study included patients above 15 years of age with treatment failure (either immunological or clinical, as defined by NACO) after six months of ART. As per definition of NACO, virological failure was defined as a plasma viral load (PVL) of >1000 copies/ml.* ***Results****: Out of 90 patients with an immunological failure, only 74 patients also had virological failure, resulting in a 17.78% discordant response. Discordance between immunological failure and virological failure was more common in patients with a low baseline CD4 count and patients on a Zidovudine-based regimen. Moreover, adherence to therapy played an essential role in the development of treatment failure.*
Conclusion*: Instead of targeted viral load testing, universal access to routine viral load testing is necessary for the early diagnosis of treatment failure with a switch to 2nd line ART and to avoid immuno-virological discordance. Adherence was observed to be an essential predictor of ART effectiveness.*

Keywords*: Treatment failure; Zidovudine; CD4 count; plasma viral load; adherence.*

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INTRODUCTION

HIV infection is a global pandemic, with cases reported from virtually every country. The HIV epidemic has occurred in waves in different regions of the world, each wave having somewhat different characteristics depending

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on the demographics of the country and region in question and the timing of the introduction of HIV into the population. The National ART programme, launched on Apr 1 2004, in eight government hospitals in six high-prevalence states, has since been scaled up, provides HAART, and monitors the PLHA population in India. The national programme provides free first-line, alternate first-line and second-line ART drugs as per eligibility criteria (NACO).

Despite the reduction in morbidity and mortality with the introduction of HAART, a considerable proportion of patients fail to achieve a sustained virologic response to therapy, which has led to treatment failure. NACO has developed simplified immunological, clinical and virologic criteria to diagnose treatment failure, as shown in **Table 1**.

Table 1 Guidelines of treatment failure (NACO 2018)

Clinical failure	New or recurrent WHO stage 4 condition after at least six months of ART.
Immunological failure	(a) Fall of CD4 count to pre-therapy baseline (or below) (b) 50% fall from on-treatment peak value, if known (c) Persistent CD4 levels below 100 cells/microliter after 6-12 months of treatment
Virological failure	Plasma viral load >1000 copies/ml

Monitoring individuals receiving ART is essential to ensure successful treatment, identify adherence problems and determine whether and which ART regimens should be switched in case of treatment failure.

Before 2010, WHO guidelines on ART recommended using clinical outcomes and CD4 count to monitor the response to ARV drugs routinely. However, the value of viral load testing as a more sensitive and earlier indicator of treatment failure is increasingly recognized. A large cohort study[1] demonstrated that WHO immunologic criteria lack sensitivity for predicting virologic failure. Another study[2] concluded that HIV-RNA monitoring is the optimal approach for monitoring ART. A study[3] at Tambaram, Chennai, reported the estimated treatment failure as 3.9% in 1300 patients on first-line therapy.

Though several studies have been reported from India and abroad, there is a shortage of such studies in this region. So, this study has been taken up to study treatment failure and the correlation between immunological failure and virological failure in patients with HIV on first-line ART.

MATERIALS AND METHODS

This institution-based observational study was conducted from Jul 1, 2019, to Jun 30, 2020. It included HIV-infected patients with treatment failure (immunological and/or clinical) to first-line ART as decided by the State AIDS Clinical Expert Panel (SACEP) attending ART Plus centre and OPD and IPD of Department of Medicine, Gauhati Medical College and Hospital, Assam.

Inclusion criteria: HIV/AIDS patients of more than 15 years of age with first-line ART treatment failure immunological and/or clinical, as defined by NACO) after six months of treatment.

Exclusion criteria: HIV-infected patients of age less than 15 years, HIV-infected patients with first-line ART duration less than six months, ART-naive patients, HIV-2 patients, patients on or failing 2nd line ART and patients unwilling to participate in the study were excluded from this study.

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The patients who fulfilled the inclusion criteria were assessed through medical history, clinical examination and laboratory parameters. The data was collected in performed proformas. The patients were selected as per SACEP (State AIDS Clinical Expert Panel). Before data collection, institutional ethics committee approval was obtained, vide reference: MC/190/2007/pt-11/MAR-2019/PG/54.

Adherence was calculated by:

$$\text{Adherence (in \%)} = \frac{\text{total number of pills the patient has actually taken}}{\text{total number of pills the patient should have taken in that time period}} \times 100$$

$$= \frac{\text{Number of pills given to the client-number of pills balance in the bottle}}{\text{number of pills the client should have taken}} \times 100$$

RESULTS

A total of 90 HIV-infected patients with treatment failure (immunological and/or clinical) to first-line ART (as decided by the SACEP meeting) attending the ART Plus centre and OPD and IPD of the Department of Medicine were included in this study.

Amongst 90 treatment failure patients, all 90 patients had an immunological failure (100%), only 8 had a clinical failure (8.89%), and only 74 had a virological failure (82.22%), as shown in **Table 2**.

Table 2 Type of failure

Type of failure	No. of patients	Percentage (%)
Immunological	90	100
Clinical	8	8.89
Virological	74	82.22

Out of 90 patients with an immunological and/or clinical failure in our study, 74 had virological failure, whereas 16 patients were virological responders, resulting in a 17.78% discordant response. The p-value is <0.001, which is statistically significant.

The details of age distribution are shown in **Table 3**. The median age seen in the discordant responders was 42 years.

Table 3 Age distribution

Age in year	Number of patients	Percentage (%)
10-20	0	0
20-30	1	6.25
30-40	4	25.00
40-50	8	50
>50	3	18.75

Amongst the total discordant responders (16), 43.75% (7) were on the Tenofovir + Lamivudine + Efavirenz (TLE) regimen, and 56.25% (9) were on the Zidovudine + Lamivudine + Nevirapine regimen (ZLN).

The baseline CD4 are shown in **Table 4**.

Table 4 Baseline CD4 (cells/mm3)

Baseline CD4 (cells/mm3)	Number of discordant patients	Percentage (%)
<100	8	50.00
100-200	5	31.25
>200	3	18.75

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Amongst the total discordant responders, 50% of patients had a baseline pre-treatment CD4 count of less than 100 cells/mm^3.

Amongst the first-line ART failure patients (immunological and clinical), the following failure rates were observed: 33.33%, 24.44% and 42.22% in the patients with adherence of >95, 90-95, and <90, respectively. Maximum failure was seen in the patients with adherence of <90%.

DISCUSSION

In our study of 90 patients with immunological failure, 17.78% had a discordant response, which was statistically significant.

Similarly, a study[4] observed a 15.4% discordant response among the immunological failure patients. Another study[5] encountered a higher frequency of 19% discordance [VL (Viral load) +/CD4-], like the present study. In two Indian studies,[3,6] discordant responses were seen in 13.5% and 21.1% of the study population referred for viral load tests based on immunological failure. The results of the above and present studies have shown a significant VL-CD4 cell count discordance in the range of 10-30%.

Amongst the discordant responders, the maximum number of patients (50%) was 40-50 years old. The median age in the discordant responders was 42 years. In a similar study,[4], VL+/ CD4- discordance was associated with increasing age (median age of 40 years), which was like the median age of the present study. Some recent studies[5,8] also reported that compared with complete responders (VL+/ CD4+), virologic-only responders were older (median age: 36 years). In an Indian study,[6] poor immunological reconstitutions despite virological response were of age < 55 years (86%), with a median age of 40 years. Although the median age was younger in the discordant group of one of the studies[3] compared to the concordant group (35 vs 39 years), all the above studies showed discordance in the median age <50.

Amongst the total discordant responders (16), 43.75% (7) were on the TLE regimen, and 56.25% (9) were on the ZLN regimen. In a similar study,[4] the discordant response was found to be associated with the use of Lamivudine / Zidovudine. The effect of nucleotide regimens may be related to bone marrow toxicities (bone marrow suppression) that may inhibit CD4 cell recovery. Thus, the patients do not achieve immune reconstitution despite the absence of active viral replication. Similarly, a study[5] found that 55.5% of virological-only responders were on an NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitor) regimen. In an Indian study,[6] 71% of virological-only responders were currently on a Zidovudine-based regimen and 29% on a stavudine-based regimen. Although there was no stavudine-based current regimen in our study, a higher discordance rate can be attributed to the Zidovudine-based regimen.

This study found maximum discordance in the patient group with a baseline pre-treatment CD4 count of less than 100 cells/mm.[3] The median CD4 count was 182. In a similar study,[4] discordant responses were associated with a baseline CD4 <50 cells/µl. The median baseline CD4 is 180, almost like the present study. In a similar Indian study,[6] 71 % of discordant patients had CD4 cells <100, and 29% had CD4 >100, highlighting low nadir pre-treatment.

CD4 is associated with discordance. The present study showed consistent results with the earlier studies, attributing low baseline CD4 count to poor immunological reconstitution despite virological response.

Adherence is the most significant patient-enabled predictor of treatment outcomes for the patients on HAART, as good adherence leads to decreased disease progression and death. WHO recommends at least 95% adherence to ART to avoid the emergence of resistant strains. Our study found maximum failure to first-line ART (immunological and/or clinical) among patients with less than 90% adherence. These findings were similar to a study[9] in which 67% of patients with failing ART were seen with 80-

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89.9% adherence, signifying the importance of adherence. In a study,[10] 21% of patients with near-perfect adherence (≥95%) failed to achieve a viral load of fewer than 400 copies/ mL. Likewise, in the present study, 33.33% of patients with near-perfect adherence failed to achieve a viral load of less than 1000 copies/ ml. These results imply that adherence is necessary for virologic control but not always sufficient. The increasing percentage of failure in the present study is due to the higher cut-off criteria for virologic failure (>1000 copies/ ml).

CONCLUSION

Statistically significant immuno-virological discordance was observed in this study. Discordance was seen more in patients with a low baseline CD4 count and those on a Zidovudine-based regimen. Adherence was observed to be an essential predictor of ART effectiveness. Instead of Targeted viral load testing, universal access to routine viral load testing is necessary for the early diagnosis of treatment failure with a switch to 2nd line ART and to avoid immuno-virological discordance. This was a single ART centre observational study, so the results may not be generalized to all. So, a further prospective study with a larger sample size must be done in the broader community and multiple ART centres to arrive at a definite conclusion.

Conflicts of interest: None declared

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Ethical clearance: Taken.

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