Virological discordance in patients on first line antiretroviral therapy with Immunological failure in Tambaram, India

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Abstract

Background: A percentage of HIV patients who fail first line ART (FLA) via immunologic (i.e. CD4 cell count) criteria may have adequate HIV suppression on viral load (discordance). We studied the prevalence and factors for this discordance when viral load testing became available in patients enrolled in an HIV treatment program in a large tertiary care hospital in India. Methodology: A cross-sectional study of HIV patients on FLA in Government Hospital of Thoracic Medicine, Tambaram with immunological failure (IF) and who were eligible for viral load testing as determined by the State AIDS Clinical Expert Panel (SACEP). Eligibility criteria for SLA include: received FLA for at least 6 months with adherence > 95% and has failed FLA immunologically or clinically (WHO) with a subsequent failed virologic response. Concordant response was defined as IF and VL > 10,000 copies/ml, discordant response as IF and a VL < 400 copies/ml; intermediate response was defined as IF and VL between 400 and 10,000 copies/ml. Various clinical and demographic factors were analyzed between discordant and concordant groups using Chi-Square and Fisher’s exact test. Results: From January to August 2008, 106 patients were referred for SACEP. Of these, 76 (71.6%) were eligible for evaluation. In those evaluated 69.7%, 21.1%, and 9.2% had a concordant, discordant and an intermediate response. The respective baseline characteristics for discordant and concordant groups were: mean age in years 35 and 39 (p-value < 0.05), 81.3% and 96.2% males (p-value > 0.05), median CD4 count of 51 and 56 cells/cubic millimeter (p-value > 0.05). Other characteristics of the discordant and concordant groups respectively were: median CD4 count at IF (68 vs. 96 cells/cubic millimeter; p-value > 0.05), median time to IF (12 vs. 15 months; p-value > 0.05), previous history of ART (6.3% vs. 37.7%; p-value < 0.05), ART substitution (50% vs. 71.7%; p-value > 0.05), clinical failure in addition to IF (12.5% vs. 37.7%; p-value < 0.05). Conclusion: In this population, 21.1% of HIV treatment patients with IF on FLA were found to have discordant virologic response to ART. Such patients may be inappropriately initiated on more costly and potentially toxic SLA.

Keywords: Virological Discordance, SACEP, ART, Immunological failure, India

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INTRODUCTION:

The estimated number of people living with HIV (PLHIV) globally was 36.7 million at the end of 2015. Nearly 18.2 million PLHIV were on Antiretroviral therapy (ART) by June 2016. The total number of PLHIV in India were 2.1 million at the end of 2015. Of which 44% adults were on ART in India. The National AIDS Control Organisation (NACO) initially started providing first line ART (FLA) in India from 1st April 2004 in eight government hospitals and the Government hospital of thoracic medicine (GHTM) was one of those centres. Effective ART generally results in immune reconstitution with increased CD4 and virologic suppression with undetectable HIV viral load (VL).

However a major concern regarding ART is when there is a discordant response between CD4 count and the viral load. There are two types of discordant responses: Immunological failure (IF) (decrease in CD4 count) despite VL suppression or immune reconstitution (increase in CD4 count) despite VL failure. Interestingly both types of discordant responses to ART are related to AIDS defining events and mortality. There is very limited data regarding discordant responses and its associated factors to FLA in India. Hence we studied the prevalence and factors associated with virological discordance in patients on FLA with immunological failure attending a tertiary Government hospital (GHTM) in Tambaram, India.

MATERIALS AND METHODS:

We conducted a cross sectional study of HIV adults on FLA with immunological failure in GHTM, Tambaram, India. State AIDS Clinical Expert Panel (SACEP) is NACO expert panel which evaluates patients who have failed FLA treatment either by immunological or clinical criteria after taking FLA for a period of 6 months with adherence >95% and decides whether to test with HIV viral load, so that confirmed failure cases can be initiated on second line ART (SLA). The treatment failure in FLA is based on immunological failure (IF) or clinical failure (CF) criteria.

Immunological failure is identified by a) Fall of CD4 count to pretherapy baseline. b) 50% fall from on treatment peak value. c) Persistent CD4 count below 100 cells/mm3. Clinical failure is defined as recurrent stage 4 illness after 6 months on FLA. The Government FLA consists of four regimens, Zidovudine/Lamivudine/Nevirapine, Stavudine/Lamivudine/Nevirapine, and Zidovudine/Lamivudine/Efavirenz and Stavudine/Lamivudine/Efavirenz.

Study Period: Jan to Oct 2008. From Jan to August 2008 nearly 106 patients were referred to SACEP, of which only 90 patients were eligible for VL test. Finally 76 patients were included in the study based on the inclusion and exclusion criteria.

Inclusion Criteria: Adult patients on FLA in GHTM and referred from other government ART centres with immunological or clinical failure and eligible for viral load testing were included in the study.

Exclusion Criteria: Patients not on FLA in Government programme and patients who have already taken SLA drugs and failed treatment were excluded. Patient not meeting the WHO (World Health Organisation) immunological or clinical failure criteria were excluded.

Relevance of the study: Since the data is quite old, we have to inform the relevance of this study pertaining to current trends. This is the first time data available regarding discordant response to FLA from whole of India. Initially when viral load testing was started for the first time in India on patients taking FLA and failing treatment, NACO selected only 2 centres to do viral load testing and to provide second line ART, one in JJ Hospitals Mumbai and other one is Government hospital of thoracic medicine, Tambaram in whole of India. So this data is very important first hand data available regarding discordant response to first line ART from our country, India and that too from GHTM which is a centre of excellence for HIV treatment.

Even now in government programme we still use the Zidovudine and Nevirapine and all other drugs mentioned in this study as alternative first line regimen, and also many patients are still continuing to take the first line regimens mentioned in our study. Even now NACO follows the viral load testing as gold standards for detecting confirmed treatment failure in patients on FLA.

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The WHO criteria for immunological failure mentioned in our study is still the same and being followed now in India.

**Working Definitions for different responses:**

**Concordant response group or (Virological failure):** NACO guidelines defines viral load > 10,000 copies/ml as virologic failure. Patients with immunological failure or clinical failure, and VL > 10,000 copies/ml were categorized as confirmed treatment failure cases and concordance response group.

**Discordant response group:** The patients with IF or CF, with VL < 400 copies/ml were categorized under discordant response group.

**Intermediate response group:** Patients with IF or CF and VL 400 to 10000 copies/ml were categorized as intermediate response group. Patients in this intermediate response group were excluded from analysis as it was not clear if these were just one time viral blips or whether they would progress to virologic failure as defined by NACO.

**Data collected:** Baseline demographics, baseline haemoglobin, haemoglobin value at the time of failure, baseline CD4 counts, CD4 counts at the time of failure, viral load, ART regimens, ART substitutions, clinical failure, previous history of Anti tuberculous therapy (ATT), were collected from hospital information system and patients treatment card.

**Ethical Clearance:** Ethical clearance was obtained from Institutional Review board and Institutional Ethical committee of GHTM. Written consent was obtained from all study participants.

**Statistical Analysis:** The data collected were entered into excel sheet and analysed using SPSS (Statistical Package for Social Sciences) version 14. The frequency tables for all collected variables were computed. Clinical and demographic factors between discordant and concordant groups were analyzed using Chi-Square and Fisher’s exact test.

**RESULTS:**

**Baseline characteristics:** 90.8% of the study population were males with a median age of 37 (Inter-quartile range 32 to 40). Other baseline characteristics like median baseline CD4 counts, median CD4 counts at the time of failure, percentage of CF, previous history of ART in private clinics before entering into government ART programme, previous history of ATT, substitution of ART, different ART regimens at time of initiation and at the time of failure are shown in tables 1, 2, 3 and 4.

**Table 1 Baseline Characteristics N=76**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Inter-quartile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age in Years</td>
<td>37</td>
</tr>
<tr>
<td>Median CD4 counts at baseline</td>
<td>48</td>
</tr>
<tr>
<td>Median CD4 counts at failure</td>
<td>91.5</td>
</tr>
</tbody>
</table>

**Table 2 Baseline Characteristics N=76**

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%)</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>69 (90.8)</td>
<td>81.9 - 96.2</td>
</tr>
<tr>
<td>Clinical Failure</td>
<td>22 (28.9)</td>
<td>19.1 - 40.5</td>
</tr>
<tr>
<td>Previous history of ART</td>
<td>21 (27.6)</td>
<td>18.0 - 39.1</td>
</tr>
<tr>
<td>Previous history of ATT</td>
<td>61 (80.3)</td>
<td>69.5 - 88.5</td>
</tr>
<tr>
<td>Substitution of ART</td>
<td>47 (61.8)</td>
<td>50.0 - 72.8</td>
</tr>
</tbody>
</table>

ART: Antiretroviral therapy; ATT: Anti tuberculosis therapy; N: Numbers; (%): Percentage
Table 3 Baseline characteristics N= 76

<table>
<thead>
<tr>
<th>FLA Regimens</th>
<th>Initial Regimen</th>
<th>95% CI</th>
<th>Regimen at the time of failure</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>AZT/3TC/NVP</td>
<td>40 (52.6)</td>
<td>40.8 – 64.2</td>
<td>36 (47.4)</td>
<td>35.8 – 59.2</td>
</tr>
<tr>
<td>AZT/3TC/EFV</td>
<td>1 (1.3)</td>
<td>0.0 – 7.1</td>
<td>3 (3.9)</td>
<td>0.8 – 11</td>
</tr>
<tr>
<td>D4T/3TC/NVP</td>
<td>25 (32.9)</td>
<td>22.5 – 44.6</td>
<td>24 (31.6)</td>
<td>21.4 – 43.3</td>
</tr>
<tr>
<td>D4T/3TC/EFV</td>
<td>10 (13.2)</td>
<td>6.5 – 22.9</td>
<td>13 (17.1)</td>
<td>9.4 – 27.5</td>
</tr>
</tbody>
</table>

FLA: First line antiretroviral therapy; N: Numbers; (%): Percentage; CI: Confidence Limits
AZT: Zidovudine ; 3TC: Lamivudine ; NVP: Nevirapine ; EFV: Efavirenz ; D4T: Stavudine

Table 4 Variables analysed between Concordant and Discordant group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Discordant Group</th>
<th>Concordant Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years</td>
<td>32</td>
<td>38</td>
<td>0.033*</td>
</tr>
<tr>
<td>Median CD4 count at baseline(cells/mL)</td>
<td>51</td>
<td>56</td>
<td>0.814</td>
</tr>
<tr>
<td>Median CD4 count at failure(cells/mL)</td>
<td>68</td>
<td>96</td>
<td>0.929</td>
</tr>
<tr>
<td>Clinical failure in addition to IF</td>
<td>12.50%</td>
<td>37.70%</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Median time to IF in months</td>
<td>12</td>
<td>15</td>
<td>0.19</td>
</tr>
<tr>
<td>Previous history of ART</td>
<td>6.30%</td>
<td>37.70%</td>
<td>0.037*</td>
</tr>
<tr>
<td>Substitution of ART</td>
<td>50%</td>
<td>71.70%</td>
<td>0.19</td>
</tr>
<tr>
<td>Previous history of ATT</td>
<td>68.80%</td>
<td>84.90%</td>
<td>0.279</td>
</tr>
<tr>
<td>Mean baseline haemoglobin (mg/dl)</td>
<td>11.02</td>
<td>11.15</td>
<td>0.813</td>
</tr>
<tr>
<td>Mean haemoglobin at failure (mg/dl)</td>
<td>11.51</td>
<td>11.56</td>
<td>0.922</td>
</tr>
</tbody>
</table>

VL: Viral Load; (%): percentage; IF: Immunological failure; *: Significant P-Value <0.05

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Nearly 28.9% of the study population had CF in addition to IF. 27.6% of our study population had been on FLA in private clinics before entering into government programme (Table 2). From table 3 you can see the majority of the patients (52.6%) were initiated on Zidovudine based regimen and 47.4% experienced IF while on zidovudine based regimen.

**Discordant Response:**
From figure 1 we can see the virological profile of patients who have failed immunologically. 69.7% of the study population showed concordant VL failure indicating confirmed treatment failure. However, nearly 21.1% of immunologically failed patients showed discordant viral response upon VL testing. 9.2% showed intermediate response (VL between 400 – 10000 copies/ml). Interestingly, 12.5% of patients with clinical failure and IF actually had undetectable VLs (discordant) (Table 4). The median time to IF was slightly shorter in discordant group when compared with concordant group (12 vs 15 months), but this was not statistically significant (Table 4). We also analysed the median CD4 counts at the time of initiation of FLA and at the time of IF (Fig 2). The median CD4 counts at the time of IF was slightly less in discordant group when compared with concordant group (68 vs 96), but it was not statistically significant.

We also compared the WHO clinical staging of FLA patients at the time of IF. We found that WHO stage 2 illness was much more prevalent in discordant group when compared with concordant group (50% vs 7.5%). The WHO stage 4 illness was more in discordant group when compared with discordant group (12.5% vs 37.7%) (Fig 3). The findings were statistically significant.

**DISCUSSION:**
Our study showed nearly 21.1% of patients with immunological failure on FLA had a discordant viral response and 69.7% showed a concordant response. Since the NACO definition of virological failure at the time of study period was VL > 10,000 copies/ml there was an intermediate group. The intermediate group of 9.2% (VL > 400 to 10,000 copies/ml) would now be categorized under the discordant response group.

The discordant response of 21.1% was comparable with another study done by Prabhakar et al in a similar settings in India, which found a discordant percentage of 24% (virologic only responders). On the other hand a study done by Antiretroviral Therapy in Lower Income Countries Collaboration (ART-LINC) 12, an epidemiological network of HIV/AIDS treatment programmes in Africa, Asia and South America, has reported on a frequency of virologic only response around 19%. Several studies have reported lower prevalence of discordant response of 8 to 16% 4,6,13-17. While certain other studies have been nearly comparable to our study with a discordant prevalence between 17 to 21% 12,18. Few studies 19,23 have also shown a high prevalence of above 24% 13.

The wide differences in prevalence of discordance can be attributed to several factors including different criteria for immunological response, virologic suppression, sample size, variation in time to failure, ethnic background and importantly different types of ART regimens 13.

Our study showed the discordant group were slightly younger (Table 4) when compared with virologic failure group (median age 32 vs 38). On the contrary few studies 6,21 have attributed discordance to older age.

Clinical failure in addition to IF was also significantly associated with concordance response (Table 4). It is quite natural to expect WHO stage 4 illnesses in discordant group, as they have failed both immunologically and virologically, subsequently leading on to development of clinical failure. Many studies 4,6,17 have shown that opportunistic infections, AIDS defining illness and mortality was associated with discordant group. Even our study showed inspite of good viral suppression nearly 12.5% and 25% of the study population had WHO Stage 4 and stage 3 illness in addition to IF. Our study also showed that more of WHO stage 2 illness was noted in discordant group when compared with concordant group (50% vs 7.5%) (Fig 3). This probably means, if these discordant groups are followed, there is a possibility of future developments of more stage 4 illness.

Our study showed that there was no significant difference in baseline CD4 counts in discordant and discordant groups (Fig 2). Also no significant difference in CD4 counts at the time of immunological failure in discordant and discordant groups. While several other studies 20,21,23,28 have
attributed discordant response to low baseline CD4 counts.

CONCLUSIONS:
We found that 21.1% of patients with IF with or without clinical failure had a discordant virological response (VL< 400 copies/ml). Our study also showed that 12.5% of patients with both IF and CF were virologic responders (VL< 400 copies/ml). The risk factors for discordant group were identified as younger median age, and presence of more WHO stage 2 illness. The predictors of concordance group were previous history of ART in private clinic before entering into government programmes, and clinical failure. Since the median time duration to immunological failure in concordance group was 15 months, we strongly recommend routine VL testing at the end of 12 months for all patients on FLA to detect treatment failure early. We also recommend the global HIV related authorities to implement uniform guidelines for immunological and virological response, so that the wide difference attributed to the prevalence of discordance can be assessed and decided whether it is a true difference in prevalence. These discordant groups need to be carefully monitored for opportunistic infections and more studies are needed as to ways to improve the immunologic response in these patients.

Limitations: As it is a pilot research project about a pilot programme, the sample size is small. All the patients with immunological failure could not get VL testing due to certain inclusion criteria formed by SACEP. Patients with virological failure and WHO stage 2 illness could not be studied as all the study participants were only immunologically failed cases.

Next Step: The clinical outcomes and mortality related outcomes of discordant groups needs to be studied further.

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DECLARATIONS:
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Conflict of interest: None

Authors Contribution: Dr. Ganesh S.A carried out the study design, data collection and wrote the manuscript. Dr Rajasekaran S, Dr Jyoti Somani, Nadol P, Dr Manoharan G and Dr Raja K carried out study design, and reviewed the manuscript. Mr Ezhil R carried out the data management and statistical analysis.

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