Original Article

Immunovirological discordance among people living with human immunodeficiency virus at a center in Western India: A retrospective study

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Abstract

Background and Objectives: Treatment of people living with human immunodeficiency virus (HIV) (PLHIV) is monitored using plasma HIV viral load levels and CD4 counts. Patients with either immunological nonresponse (virological suppression achieved) or virological nonresponse (immune reconstitution achieved) are termed as having a discordant response. These patients are at higher risk for acquired immunodeficiency syndrome (AIDS)-related infections/diseases/neoplasms, non-AIDS-related illnesses (cardiovascular, neurological, renal, hepatic diseases), and all-cause death. This study was conducted to assess the prevalence of immunovirological discordance among PLHIV after completion of at least 1 year of combination antiretroviral therapy (cART) at an antiretroviral therapy (ART) plus center in India and analyze contributory factors. **Methods:** The study was a retrospective study of PLHIV receiving cART at the ART plus clinic in Western India from January 18 to December 21. Four hundred and ninety-six patients were studied based on sample size calculated and assessed for CD4 and viral load response at 0, 6, and 12 months of ART. **Results:** Of the 496 patients, 48 patients (9.7%) had immunovirological discordance. Out of them, 36 patients (75%) had a virological response (immunological nonresponse) and 12 (25%) patients had an immunological response (virological nonresponse). The factors contributing to immunological nonresponse were as follows – low baseline CD4 levels (<100 cells) (36.1%), adherence <95% (33.3%), presence of opportunistic infections (16.6%), and failure on first-line therapy (11.1%). Other factors noted included higher baseline viral load (2.7%), chronic kidney disease (5.5%), and chronic hepatitis B virus co-infection (5.5%). Virological nonresponse was associated with poor adherence to therapy <95% (33%) and failure of first-line regimen (33%). Opportunistic infections were noted among 33% of patients and 8.3% of patients were found to have higher baseline viral load. **Interpretation and Conclusion:** Immunovirological discordance is an important factor influencing response to cART and is associated with many complications such as AIDS and non-AIDS-related events and even death. Improved adherence and timely identification and management of opportunistic infections are measures that are beneficial in reducing the incidence of immunovirological discordance.

Key words: Antiretroviral therapy, human immunodeficiency virus, immunological failure, immunovirological discordance, virological failure

Introduction

Over the last two decades, the survival of patients infected with human immunodeficiency virus (HIV) has significantly improved with slower progression toward acquired immunodeficiency syndrome (AIDS).[1] Since the implementation of the latest treatment guidelines in 2014, which recommend starting combination antiretroviral therapy (cART) for all patients irrespective of CD4 count,[2,3] treatment has become more accessible to HIV patients and has resulted in the improvement of their overall quality of life. This response is associated with an increase in CD4 T-cell count and a decrease in viral load.[4,5] Viral load and CD4 T-cell counts are the most used parameters to assess response to treatment.[6] CD4 cell counts are the most important indicator of immune function. Viral load level is an indicator of virological response.

Access this article online

Quick Response Code:

Website: www.ijstd.org

DOI: 10.4103/ijstd.ijstd_121_22

How to cite this article: Kacker M, Vashisht R, Menon AS. Immunovirological discordance among people living with human immunodeficiency virus at a center in Western India: A retrospective study. Indian J Sex Transm Dis 2023;44:15-9.

Submitted: 13-Dec-2022 **Revised:** 27-Jan-2023
Accepted: 28-Jan-2023 **Published:** 06-Jun-2023

Despite the implementation of timely treatment, care of concurrent infections, and frequent monitoring of immunological and virological responses, there is a subset of patients who are unable to achieve the desired response, either immunological or virological, or immunovirological. Patients with either immunological nonresponse (virological suppression achieved) or virological nonresponse (immune reconstitution achieved) are termed as having a discordant response. Immunovirological discordance occurs when there is either an inadequate immune response and adequate virological response or an inadequate virological response in the presence of an adequate immune response. These patients are at higher risk for AIDS-related infections/diseases/neoplasms, non-AIDS-related illnesses (cardiovascular, neurological, renal, hepatic diseases), and all-cause death.[7] Factors associated with immunovirological discordance have been studied in a few countries in the past. These factors include low baseline CD4 levels, poor adherence, co-infections, duration of cART, and male sex preponderance. However, criteria used for the assessment of both immunological and virological responses have not been uniformly used in all the studies and hence there has been a variation in the global prevalence of immunovirological discordant response.[8]

Data on the incidence of immunovirological discordance are scarce in India, and there are gaps in knowledge about the incidence among the Indian sub-population. This study was carried out at an antiretroviral therapy (ART) plus center in Western India to identify the prevalence of immunovirological discordance among people living with HIV (PLHIV) receiving cART and identify possible factors contributing to the discordance.

Methods

Aims

Primary aim

The primary aim of this study was to assess the prevalence of immunovirological discordance among PLHIV after completion of at least 1 year of cART at an ART plus center in India, a record-based study.

Secondary aim

The secondary aim of this study was to describe the distribution of selected factors concerning immunovirological discordance.

Study design

The study was a retrospective study of PLHIV receiving cART at the ART plus clinic in Western India from January 18 to December 21.

Sample size

There are about 5500 patients on active follow-up at the clinic. The sample size was calculated to estimate a 95% confidence interval for the prevalence of immunovirological discordance after at least 1 year of treatment for HIV with a 3% absolute error margin. The sample size worked out to be 496 assuming that the prevalence is 15%.[6,8] [Figure 1].

Inclusion criteria

i. All patients diagnosed with HIV infection and on cART for at least 1 year
ii. Minimum 3 CD4 levels (0, 6, and 12 months) with at least one viral load value (at 6–12 months) were included in the study.

Exclusion criteria

Patients on immunomodulators, chemotherapy, or any other drugs affecting the immune system were excluded from the study.

Data collection

The following parameters were collected: age, gender, residence, education, occupation, viral load levels, CD4 counts, ART regimens with dates, duration of cART, opportunistic infections with dates, comorbidities, and treatment adherence.

Definitions

The criteria used for defining immunovirological discordance were adapted from the National AIDS Control Organisation (NACO) guidelines.[9]

Virological response

Plasma viral load levels 6 months after initiation of ART <1000 copies/ml.

Immunological response

The CD4 count of the patients should increase after initiation of cART. This increase is usually 50–100 cells/mm^3 within 6–12 months of the initiation of the cART in ARV naïve patients, who are adherent to their treatment.

Immunological failure: National acquired immunodeficiency syndrome control organisation definitions of immunological failure (any one of the following three)

- A return to or fall below the pretherapy (baseline) CD4 at least after 6 months of therapy
- A 50% decline from the on-treatment peak value (if known)
- A persistent CD4 count of fewer than 100 cells/mm^3 after 12 months of therapy.

Virological failure

Detectable viral load count of 1000 or more copies/ml (in targeted or routine viral load monitoring) at least 6 months after ART with >95% of treatment adherence, for each of the last 3 months.

Noncompliance

Adherence to the recommended regimen <95% is termed as noncompliance.

Results

Characteristics of patients

Of the 496 patients selected as part of the sample size, 48 patients (9.7%) had immunovirological discordance. Thirty-six patients (75%) had immunological nonresponse and 12 (25%) patients had virological nonresponse, 24 (50%) were male, 23 (47.9%) were female, and 1 (2.1%) were transgender. Among males, 6 (12.5%) had virological nonresponse and 18 (37.5%) had immunological nonresponse. Among females, 6 (12.5%) had virological nonresponse, and 17 (35.4%) had immunological nonresponse. The only transgender patient had immunological nonresponse [Table 1].

Among the discordant patients, 5 (10.48%) patients were in the age group of 5–20 years, 20 (41.66%) were in the age group of 21–40 years, and 19 (39.5%) belonged to the age group of 41–60 years and 4 (8.33%) patients were in the age group of more than 60 years. The median age was 38.14 years.

The educational levels among the discordant patients varied from illiterate to college graduates. Eight (16.67%) out of 48 discordant patients were college graduates, 11 (22.91%) were illiterate, 16 (33.33%) had received primary, and 13 (27.1%) had received secondary level school education.

Most patients among the discordant cases, 42 (87.5%) out of 48, were on first-line cART regimens and only 6 (12.5%) were on second-line regimens.

Table 1: Characteristics of discordant population

Characteristic	Frequency (%)
Age (years)	
6-20	5 (10.48)
21-40	20 (41.66)
41-60	19 (39.5)
>60	4 (8.33)
Gender	
Male	24 (50)
Female	23 (47.9)
Transgender	1 (2.1)
Immunological nonresponse	
Males	18 (37.5)
Females	17 (35.4)
Transgender	1 (2.1)
Total	36 (75)
Virological nonresponse	
Males	6 (12.5)
Females	6 (12.5)
Total	12 (25)
Opportunistic infections/chronic disease/co-infection	
Tuberculosis	5 (10.4)
Syphilis	1 (2.1)
Chronic HBV infection	2 (4.2)
Chronic kidney disease	2 (4.2)
Adherence (%)	
>95	34 (70.8)
<95	14 (29.2)
Mean baseline CD4 value (cells/mm^3)	
Immunological nonresponse	219
Virological nonresponse	306
Mean duration of follow-up (years)	
Immunological nonresponse	2.99
Virological nonresponse	3.26
Baseline ART regimen	
TDF + 3TC + EFV/DTG	43 (89.5)
AZT + 3TC + NVP	2 (4.2)
ABC + 3 TC + EFV/DTG	2 (4.2)
AZT + 3TC + ATV/R	1 (2.1)

HBV=Hepatitis B virus; ART=Antiretroviral therapy

Thirty-four (70.8%) out of 48 patients had good adherence (>95%) and 14 (29.2%) out of 48 had adherence <95% to cART.

Six (12.5%) out of 48 patients had opportunistic infections/co-infections in the form of tuberculosis (TB) and syphilis, whereas 2 (4.16%) patients had chronic kidney disease and chronic hepatitis B virus (HBV) infection each, which could have influenced their response to cART.

The baseline CD4 level among patients with immunological nonresponse was 219 cells/mm^3 and 306 cells/mm^3 among patients with virological nonresponse. The mean follow-up on cART was 2.99 years for patients with immunological nonresponse and 3.26 years for patients with virological nonresponse.

Almost 90% of our patients were on tenofovir disoproxil fumarate-based first-line cART along with efavirenz/dolutegravir as per the current WHO recommendations.

During the study period, we also followed up on these discordant subjects and found that 9 (18.75%) out of 48 patients improved subsequently at the end of 24–36 months of treatment. All these patients belonged to the immunological nonresponse category, and none of the virologically unsuppressed patients showed any signs of recovery beyond 12 months. Thirty-three (68.75%) out of 48 patients continued to be discordant beyond 12 months, and 6 (12.5%) patients had just completed 12 months of cART during the study period.

Factors associated with immunological nonresponse

Among the factors contributing to immunological nonresponse, the most prevalent factors were the following – low baseline CD4 levels (<100 cells) at the time of starting cART (36.1%), adherence <95% (33.3%), presence of opportunistic infections (16.6%), and failure on first-line therapy (11.1%). In as many as 41.6% of patients, the cause of discordance was not known [Table 2].

Factors associated with immunological nonresponse

Virological nonresponse was found to be associated with many factors, the most common factors being, poor adherence to therapy <95% (33%), and failure of first-line regimen (33%). In 33.3% of cases, the cause of discordance was not known [Table 3].

Discussion

The establishment of immunovirological discordance is dependent on the criteria used to define immunological and virological failure. Other factors influencing its prevalence include the total duration of treatment, choice of the first-line treatment, and the stage of disease at which treatment was initiated. Initiation of treatment irrespective of CD4 count was recommended only after 2014, and thus in most previous studies assessing the incidence of discordance, a subset of patients receiving deferred treatment was invariably included. These factors are critical determinants of response to therapy and thus impact the results of any study. The current study included all patients receiving treatment immediately upon diagnosis. The overall prevalence of immunovirological discordance among patients in our study was 9.7%, comparable to studies in Northern Ethiopia (11.5%)[10] and Brazil (9%),[11] but lower than studies in Nigeria (33%).[12]

In our study, the prevalence of immunological nonresponse was 7.25%. In an Indian study of 2011,[13] which used similar criteria for immunological failure, the incidence of immunological nonresponse was 13.59%. Incidence was lower in studies from Europe (12%, 15%),[14,15] South Africa (24%),[16] and Nigeria (22.6%)[11] and higher than a study in Ethiopia (2.7%).[12] The variation in prevalence can be explained by the different cutoffs used to define immunological failure.

Our study showed that the prevalence of virological nonresponse was 2.41%, which is lower than studies from Ethiopia (8.8%)[10] and Nigeria (17%).[11] The difference is due to different cutoffs used to define virological failure.

Our study demonstrated that both males (50%) and females (47.9%) were equally affected by immunovirological discordant responses. In studies in Ethiopia,[10] Nigeria,[12] and Rwanda,[17] the male gender has been independently associated with a higher risk for immunological nonresponse.

Low baseline CD4 was found in 36.1% of patients with immunological nonresponse which is similar to many other studies.[10,13,18] In a study among female sex workers in Africa, a discordant response was associated with a higher CD4$^+$ T-cell count above 200 cells/μl at ART initiation.[19] Tuboi *et al.*[20] and Moore *et al.*[21] reported that increases in

Table 2: Immunovirological discordant responses and their associated factors

Characteristic	Proportion (%)
Factors associated with immunological nonresponse	
Low baseline CD4 levels	13 (36.1)
Adherence <95%	12 (33.33)
Opportunistic infections	6 (16.66)
Failure of first-line therapy	4 (11.1)
Chronic disease	2 (5.5)
Co-infection	2 (5.5)
Unknown	15 (41.6)
Factors associated with virological nonresponse	
Adherence <95%	4 (33)
Failure of first-line therapy	4 (33)
Opportunistic infections	4 (33)
Baseline high viral load	1 (8.3)
Unknown	4 (33.3)

Table 3: Summary of overall treatment response in sample population

Response	Immunological response	Immunological nonresponse	Total
Virological response	442	36	478
Virological nonresponse	12	6	18
Total	454	42	
Grand total			496

CD4 cell count after initiation of therapy might be greater in individuals with lower $CD4^+$ T-cell count at therapy initiation. Some studies also found no correlation between baseline CD4 cell count and discordance.[17] Association of lower baseline CD4 count with immunological nonresponse is possible due to many explanations such as impaired bone marrow hematopoietic function and decreased proliferative capacity, lower thymic output, dysfunction in some cytokine expressions, and CD4 cell destructions.[22-24,28]

The incidence of TB co-infection among immunological nonresponders was 16.6% which was in concurrence with studies in Ethiopia[10,25] and Korea.[26] A possible explanation would be that TB infection impairs cellular immune responses through *Mycobacterium tuberculosis*-induced apoptosis of $CD4^+$ cells which subsequently leads to the depletion of $CD4^+$ cells and results in poor immunological recovery despite viral suppression.[27]

5.5% of patients with immunological nonresponse had HBV co-infection. HBV co-infection was among the factors associated with a higher risk of immunological nonresponse in a study in Northern Ethiopia.[10]

In our study, lesser than 95% adherence was associated with higher rates of both immunological and virological discordant responses. This was further evident from the fact that 25% of patients with immunological discordant responses did experience recovery from discordance at the end of 36 months of follow-up. Similar outcomes were observed from studies in Ethiopia,[10] Nigeria,[11] and Thailand.[29]

Among patients with virological nonresponse, TB was the most common opportunistic infection (16.6%). In a study in Ethiopia, TB co-infection was also associated with virological discordant responses.[25] In another study in Northern Ethiopia, age at or below 35 years at highly active ART initiation, male gender, type of regimen given,

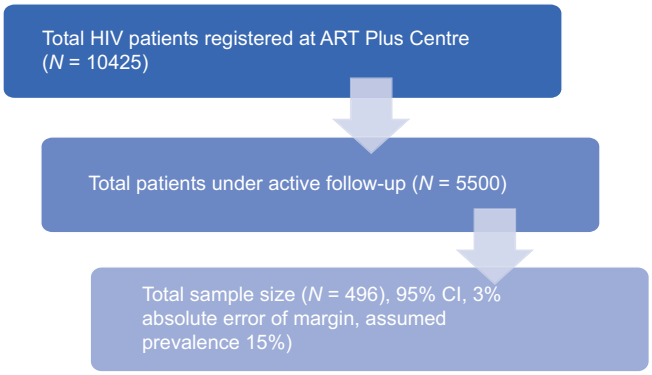

Figure 1: Workflow of the study. ART: Antiretroviral therapy, CI: Confidence interval

and good treatment adherence were associated risk factors for virological discordant response.[10]

Discordant responses are associated with an increased incidence of AIDS events such as Oncogene-induced senescence and cancers. Further, there is an associated risk of increased incidence of non-AIDS events such as stroke, liver failure, renal failure, endocarditis, meningitis, and all-cause death.[7,21] It is thus important to identify discordant responses, not only to reduce the incidence of complications as mentioned above but also to avoid unnecessary switches to second-line therapy.

During the study, the authors were able to assess the response to interventions such as stepped-up adherence and timely management of opportunistic infections, and as a result, 18.75% of total discordant and 25% of patients with immunological nonresponse experienced reversal, i.e., had an immunological recovery when observed for up to 36 months. There was no change in the status of patients who had virological nonresponse. This finding was a valuable input and could be a vital tool for improvement in response to cART, limiting the occurrence of discordance and reducing the risks associated with discordance.

The current study, to the best of the knowledge of the authors, is the first study from India, to study the prevalence of immunovirological discordant responses independently and analyze the factors independently associated with each response. The criteria used to define failure and establish discordance were adapted from NACO guidelines applicable to the period of the study.

The current study has a limitation that it included a lesser duration of follow-up as compared to previous similar studies. Further, this is only a single-center study, and more studies on the subject are required to be able to derive better conclusions.

Conclusions

Immunovirological discordance is an important factor influencing response to cART and is associated with many complications such as AIDS and non-AIDS-related events and even death. Early identification of causative factors and possible correction is as important as continuing cART itself. Even though risk factors associated with discordance have been studied in this study, the exact mechanisms associated with these risk factors can be an area of further research. Risk factors such as low baseline CD4 counts or high baseline viral load levels are consequential to delay in diagnosis or delay in commencement of cART. Suitable measures for early diagnosis and starting

treatment are advisable. Improved adherence and timely identification and management of opportunistic infections are measures that are beneficial in reducing the incidence of immunovirological discordance.

Acknowledgment

We would like to thank the staff of the ART center for their support in conducting this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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