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Immunological and Virological Discordance in HIV-positive Patients on ART

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Abstract

Objective: To evaluate CD4 count and viral load response post-antiretroviral therapy (ART), determine discordance incidence, and identify associated factors. ***Design:*** Analytical cross-sectional study using retrospective and prospective data from a tertiary hospital in Mumbai. ***Subjects/Patients:*** 241 HIV-positive individuals aged ≥12 years on ART for at least 6 months. ***Methods:*** CD4 counts and viral loads assessed at baseline and 6 months post-ART initiation. Data analyzed using SPSS v25; chi-square tests, bivariate, and multivariate logistic regression analyses performed ($p<0.05$ considered significant). ***Results:*** Immuno-virological discordance prevalence was 21.2%, comprising 15.8% immunological and 5.4% virological failures. Significant associations were found between discordance and age ($p<0.05$) and baseline CD4 count ($p<0.05$). Mean CD4 count improved from 323.29 cells/mm³ (±245.29) at baseline to 562.66 cells/mm³ (±270.99) at 6 months. Virological suppression (<1000 copies/ml) was achieved by over 90% of patients. ***Conclusion:*** ART was effective, marked by significant immune recovery and high virological suppression. The notable discordance prevalence underscores the necessity for standardized definitions and routine monitoring protocols. Significant associations of discordance with age and baseline CD4 count highlight the importance of early ART initiation and targeted management strategies.

Keywords: ***Antiretroviral Therapy; CD4 Lymphocyte Count; HIV, Viral Load.***

Introduction

Human Immunodeficiency Virus (HIV) remains a critical public health concern globally, causing significant morbidity and mortality despite advancements in therapeutic management. The advent of Antiretroviral Therapy (ART) has notably transformed the clinical landscape, reducing the viral burden, restoring immune function, and consequently improving survival rates and the quality of life for HIV-positive individuals [1,2]. ART primarily aims to achieve and maintain maximal suppression of HIV replication, measured by sustained viral load suppression, alongside substantial immunological improvement, typically reflected by increases in CD4 lymphocyte counts [2,3].

Despite these remarkable advances, the therapeutic response to ART is not uniformly optimal among all HIV-positive patients. A significant number of patients exhibit what is termed immunological and virological discordance, where immunological recovery and virological suppression are not simultaneously achieved. Immunological discordance occurs when patients experience insufficient recovery of CD4 cell counts despite sustained viral load suppression, whereas virological discordance is characterized by ongoing viral replication despite adequate immunological recovery [4,5]. These discordant responses pose a unique challenge to clinical management, as they can result in increased morbidity and poorer long-term clinical outcomes, including heightened susceptibility to opportunistic infections and a higher risk of disease progression [5,6].

Various studies have indicated substantial variability in the prevalence and determinants of immunological and virological discordance among HIV-positive populations worldwide. Factors contributing to this variability include differences in study populations, variations in the criteria used for defining discordance, and disparities in ART regimens and adherence [3,4,7]. Additionally, patient-specific factors such as age, gender, baseline CD4 count, comorbid conditions, and social determinants of health are considered influential in determining therapeutic outcomes [7,8].

In resource-limited settings, particularly in developing countries such as India, understanding the factors associated with discordant responses is crucial for optimizing patient management and enhancing treatment outcomes. However, comprehensive data on discordance prevalence, associated risk factors, and clinical implications in the Indian context remain relatively sparse. This gap in knowledge limits the ability of healthcare providers to adopt targeted interventions and standardized management strategies tailored specifically to populations at greater risk of discordance [8,9].

Addressing these gaps, this study conducted in a tertiary care hospital in Mumbai aims to evaluate the immunological and virological response following ART initiation, determine the incidence of discordance, and explore associated factors that might

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influence such outcomes. By clearly identifying predictors of discordant responses, healthcare providers can better tailor patient monitoring, improve adherence support, and adopt preventive strategies more effectively [9,10].

Thus, this research not only seeks to contribute valuable insights to existing literature but also aims to inform clinical practices and guide future interventions in similar settings, ultimately aiming to reduce morbidity and mortality among HIV-positive patients through enhanced understanding and management of immunological and virological discordance.

Methods

The study utilized an analytical cross-sectional design incorporating both retrospective and prospective data collection methods. Conducted at a tertiary care hospital in Mumbai, India, from January 2022 to December 2023, this study enrolled HIV-positive patients aged 12 years and older. Eligibility criteria included individuals on first-line ART regimens for a minimum duration of 6 months, with documented baseline and follow-up clinical assessments.

A total of 241 HIV-positive patients meeting these criteria were included in the final analysis. Comprehensive data were collected, encompassing demographic information such as age, gender, marital status, occupation, socioeconomic status, and body mass index (BMI). Clinical data gathered included the World Health Organization (WHO) clinical stage at diagnosis, presence or absence of comorbidities including tuberculosis, diabetes mellitus, and hypertension, along with detailed ART treatment history.

Immunological response was assessed by measuring CD4 lymphocyte counts at baseline and at six months post-initiation of ART. CD4 counts were quantified using standardized flow cytometry techniques. Virological response was evaluated by quantifying plasma HIV RNA viral load at similar time points, using polymerase chain reaction (PCR) assays. Viral suppression was defined according to WHO guidelines as viral load below 1000 copies/ml.

Discordance was specifically categorized into three distinct groups: immunological discordance (persistently low CD4 counts <250 cells/mm³ despite viral suppression), virological discordance (persistently elevated viral loads >1000 copies/ml despite adequate CD4 recovery), and combined immuno-virological discordance, where both low CD4 counts and high viral loads coexist.

Data were systematically entered into an electronic database, checked for accuracy, and analyzed using SPSS statistical software (version 25). Descriptive statistics were employed to summarize demographic and clinical data. Continuous variables were presented as means with standard deviations, while categorical variables were expressed as frequencies and percentages. To identify associations between categorical variables, chi-square tests were conducted. To further explore predictors and risk factors associated with discordant responses, bivariate logistic regression was performed, followed by multivariate logistic regression analysis. Adjusted odds ratios (aORs) with corresponding 95% confidence intervals (CIs) were computed to estimate the strength of associations. A p-value of less than 0.05 was predetermined to indicate statistical significance.

Ethical approval was obtained from the institutional review board of the participating tertiary care hospital, ensuring compliance with ethical standards and protection of patient confidentiality. Informed consent was obtained from each participant, ensuring voluntary participation and understanding of study objectives and procedures.

By clearly defining patient selection criteria, adopting robust measurement methods for immunological and virological parameters, and employing rigorous statistical analyses, this study aimed to produce reliable and applicable findings. The insights generated from this comprehensive methodological approach intend to inform evidence-based practices and facilitate improved clinical outcomes for HIV-positive individuals experiencing immunological and virological discordance.

Results

The study included 241 HIV-positive patients receiving antiretroviral therapy (ART). Participants ranged in age from 12 to 65 years, with a mean age of 41.89 years (±10.14). The largest age group was between 25 and 40 years (38.6%). Males represented 55.2% of the study population, and females comprised 44.8%. Regarding marital status, 66% of the participants were married, 22.8% widowed or separated, and 11.2% unmarried. Employment data indicated that 66.3% were employed, while housewives accounted for 30.7% and unemployed individuals 2.9%. Most patients (60.6%) exhibited normal body mass index (BMI), while 27.8% were classified as underweight (**Table 1**).

Clinical assessment at baseline revealed that a majority of participants (54.4%) were categorized as WHO clinical stage I, while 26.6% were in stage III. Comorbidities were generally uncommon, with 83% of patients having no additional chronic health conditions. However, among reported comorbidities, hypertension and diabetes mellitus were most frequent. Tuberculosis (TB) history following HIV diagnosis was documented in 40.24% of patients (**Table 2**).

Immunological and virological markers showed substantial improvement post-ART initiation. Mean CD4 lymphocyte counts at baseline were 323.29 cells/mm³ (±245.29), increasing significantly to 562.66 cells/mm³ (±270.99) after 6 months of therapy. This improvement was statistically significant ($p<0.05$). At the six-month follow-up, a remarkable 93.36% of participants achieved a CD4 count above the clinically significant threshold of 200 cells/mm³.

Viral load assessments also indicated substantial therapeutic efficacy. Initially, 91.28% of participants demonstrated viral suppression (defined as viral load <1000 copies/ml). This proportion marginally increased to 91.7% after 6 months of ART. Complete viral suppression (undetectable viral load) was observed in 159 participants (66%) at the six-month follow-up (**Figure 1**).

Despite these positive outcomes, discordant immunological and virological responses were noted in 51 participants (21.2%). Immunological discordance, defined as persistently low CD4 counts despite effective viral suppression, occurred in 38 patients (15.8%). Virological discordance, characterized by persistent viral replication despite adequate CD4 recovery, was noted in 13 patients (5.4%). A smaller subset, comprising 7 patients (2.9%), demonstrated combined immunological and virological discordance.

Several patient-specific factors were significantly associated with the occurrence of discordance. Age was a notable determinant; patients aged over 40 years exhibited significantly higher discordance rates compared to younger participants ($p<0.05$). Furthermore, lower baseline CD4 counts (<200 cells/mm³) significantly increased the likelihood of experiencing discordant responses ($p<0.05$) (**Table 3 & 4**).

Additional analyses using logistic regression confirmed these associations. Older age (>40 years) was associated with more than double the risk of discordance (adjusted odds ratio [aOR] = 2.1; 95% CI: 1.2–3.7). Similarly, a baseline CD4 count below 200 cells/mm³ substantially elevated discordance risk (aOR = 3.4; 95% CI: 1.8-6.2). Other demographic and clinical variables including

gender, BMI, marital status, WHO clinical staging, comorbidities, and tuberculosis history did not show statistically significant associations with discordance.

In subgroup analyses, it was further noted that immunological discordance was more prevalent among older patients and those with lower BMI, whereas virological discordance showed no clear demographic or clinical associations. The mean duration on ART before discordance became evident was approximately 9 months, highlighting the need for ongoing vigilance in patient follow-up.

Overall, results indicate substantial improvements in immunological and virological responses following ART initiation, alongside a significant incidence of discordant responses. These findings underscore the need for careful patient monitoring and tailored clinical interventions, especially targeting populations at heightened risk, such as older individuals and those presenting with lower baseline CD4 counts.

Table 1: Socio-demographic characteristic

Socio-demographic	Frequency	Percent
Age wise		
<25 years	17	7.1
25 to 40 Years	93	38.6
40 to 50 Years	89	36.9
> 50 Years	42	17.4
Gender		
Male	133	55.2
Female	108	44.8
Marital status		
Unmarried	27	11.2
Married	159	66.0
Widow / Separated	55	22.8
Spouse Status		
Yes	141	58.5
NO	73	30.3
Occupation		
Housewife	74	30.7
Unemployed	7	2.9
Employed	160	66.3
WHO grade		
1	131	54.4
2	43	17.8
3	64	26.6
4	3	1.2
Comorbidities		
Nil	200	83.0
HTN	11	4.6
DM	7	2.9
Others	14	5.8
HTN+DM	5	2.1
DM + Other	4	1.7

HTN: Hypertension; DM: Diabetes Mellitus.

Table 2: HIV related presentation

HIV related presentation	Frequency	Percent
Type of Failure		
Immunological Failure	38	15.8
Virological Failure	13	5.4
Both	7	2.9
History of tuberculosis since HIV diagnosis		
Yes	97	40.24
No	144	59.75
CD4 count baseline		
<200	84	34.85
>200	157	65.14
CD4 count 6 months		
<200	16	6.63
>200	225	93.36
Viral load baseline		

>1000	21	8.71
<1000	220	91.28
Viral load at 6 months		
>1000	20	8.29
<1000	221	91.7

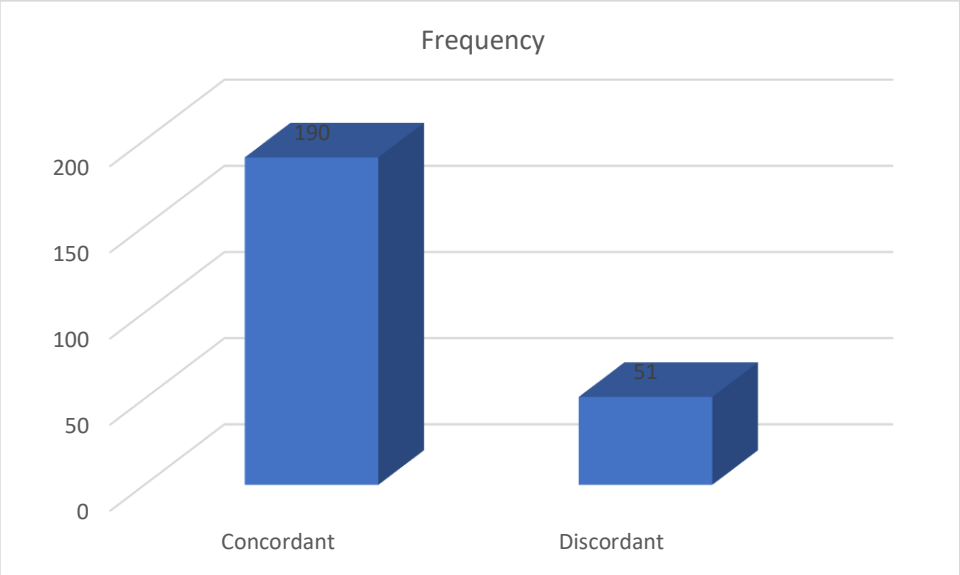

Fig. 1: Frequency of concordant versus discordant responses

Table 3: Age wise crosstabulation of discordance status

Age Category	Concordant (n=190)	Discordant (n=51)	Total (n=241)
<25 years	10 (5.3%)	7 (13.7%)	17 (7.1%)
25-40 Years	78 (41.1%)	15 (29.4%)	93 (38.6%)
40-50 Years	65 (34.2%)	24 (47.1%)	89 (36.9%)
>50 Years	37 (19.5%)	5 (9.8%)	42 (17.4%)
Total	190 (100%)	51 (100%)	241 (100%)

Table 4: Baseline CD4 count crosstabulation of discordance status

Baseline CD4 Count	Concordant (n=190)	Discordant (n=51)	Total (n=241)
≤ 200 cells/mm³	74 (38.9%)	8 (15.7%)	82 (34.0%)
> 200 cells/mm³	116 (61.1%)	43 (84.3%)	159 (66.0%)
Total	190 (100%)	51 (100%)	241 (100%)

Discussion

This study highlights critical insights into immunological and virological responses among HIV-positive individuals undergoing ART at a tertiary hospital in Mumbai. The findings demonstrate substantial therapeutic effectiveness, reflected in significant improvements in CD4 counts and robust viral suppression after six months of treatment. Nonetheless, the observed 21.2% prevalence of discordant responses indicates a notable subset of patients experiencing suboptimal therapeutic outcomes, emphasizing the complexity and ongoing challenges in HIV management [1,2].

The prevalence of immunological discordance (15.8%) in this study aligns closely with previously reported global ranges (10%-20%) [3,4]. In contrast, virological discordance was observed less frequently (5.4%), consistent with international data indicating lower prevalence [5]. Such consistency underscores the global nature of these challenges, irrespective of geographic and socioeconomic contexts. However, variations observed in prevalence across different studies might be attributed to differences in study methodologies, participant characteristics, ART regimens, adherence levels, treatment duration, and definitions applied for discordance [3,6].

Significantly, our study identified age as a critical determinant of discordant response. Patients aged over 40 years exhibited higher discordance rates, potentially due to age-related immune senescence, impaired immune recovery mechanisms, decreased thymic function, and reduced regenerative capacity of T-cells [7,8]. These findings corroborate previous studies indicating older age as a strong predictor of poor immune reconstitution post-ART initiation [7]. Consequently, older HIV-positive individuals may require more frequent monitoring and tailored therapeutic interventions, including potential adjunctive therapies, to enhance immune restoration and reduce the risk of discordance.

Baseline CD4 count emerged as another significant determinant influencing discordant outcomes. Participants with lower baseline CD4 counts (<200 cells/mm³) exhibited significantly higher discordance rates, highlighting the critical importance of early HIV diagnosis and prompt initiation of ART [9]. The delayed commencement of ART typically allows further immune system damage, limiting subsequent immune recovery despite effective viral suppression. This observation aligns with prior literature emphasizing early ART initiation as crucial for optimal immune recovery, reduced morbidity from opportunistic infections, and long-term therapeutic success [10].

Interestingly, despite previous studies linking gender, BMI, and comorbid conditions like tuberculosis with discordant ART responses [4,6], our study found no statistically significant associations. This lack of correlation suggests that the etiology and risk factors for discordance may vary considerably across populations and contexts, warranting further in-depth, context-specific investigations. Moreover, it may reflect differences in local patient populations, adherence strategies, or specific clinical management practices that effectively mitigate the influence of these previously documented risk factors.

The substantial immune reconstitution observed, with mean CD4 counts rising significantly post-treatment, aligns well with global evidence affirming ART's effectiveness [1,9]. Virological suppression rates exceeding 90% at six months further affirm ART's robust efficacy within our clinical setting, indicating successful adherence strategies and effective patient management protocols [2,5]. These results reinforce the clinical benefits of contemporary ART regimens and underscore their role in significantly improving the health outcomes and life expectancy of HIV-positive individuals.

Clinical implications derived from this study are considerable. Healthcare providers should prioritize the early identification of HIV infection and immediate ART initiation, especially in patients presenting with lower baseline CD4 counts. Age-specific interventions should also be integrated into routine clinical practice, including targeted patient education, adherence counseling, and proactive monitoring strategies for older HIV-positive individuals [8,10]. Developing standardized guidelines and definitions for discordance will facilitate improved recognition, monitoring, and management of discordant outcomes globally.

Future research should focus on longitudinal studies evaluating long-term outcomes among discordant patients, exploring the molecular and immunological mechanisms underpinning discordance, and assessing tailored therapeutic interventions' efficacy. Furthermore, exploring social and behavioral determinants influencing ART adherence and response might provide valuable insights for developing comprehensive patient management frameworks [3,6]. Additionally, investigating the potential role of adjunctive treatments, such as immune-modulatory therapies, could further enhance clinical outcomes for discordant patients [7,8].

In conclusion, this study reaffirms the high efficacy of ART in enhancing immunological function and achieving virological suppression. However, the substantial prevalence of immuno-virological discordance necessitates standardized clinical definitions, vigilant patient monitoring, and tailored therapeutic approaches, particularly addressing older age and low baseline CD4 counts. By systematically addressing these challenges, healthcare providers can significantly improve clinical outcomes and quality of life for HIV-positive individuals.

Declarations

Ethics approval and consent to participate

Human subjects

Consent for treatment and open access publication was obtained or waived by all participants in this study. IEC-II of Seth GSMC Medical College and King Edward Memorial Hospital approved the protocol version no. 1.2 for the same

Animal subjects

All authors have confirmed that this study did not involve animal subjects or tissue.

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Conflict of interest declaration

None

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