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Immuno-virological discordance and its association with AIDS-defining events, non-AIDS comorbidity, and mortality in people living with HIV on antiretroviral therapy: an ambispective cohort study from North India

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Abstract

Background

A subset of people living with HIV (PLHIV) fail to regain adequate CD4 counts despite sustained viral suppression on antiretroviral therapy (ART), a pattern termed immuno-virological discordance. Its contribution to AIDS-defining events, non-AIDS comorbidity, and mortality is not well described in Indian ART cohorts. We assessed the burden of discordance and its clinical consequences at a tertiary government ART centre in North India.

Methods

We conducted an ambispective cohort study of PLHIV attending the ART centre at AIIMS, New Delhi, between January 2018 and January 2024. Adults on adherent ART for more than one year with a suppressed plasma viral load were classified as discordant (CD4 count < 250 cells/mm3) or non-discordant (CD4 count ≥ 250 cells/mm3). We compared demographic, socioeconomic, and clinical characteristics between groups using the Mann-Whitney U test for continuous variables and the chi-square or Fisher exact test for categorical variables. We defined a composite AIDS-defining event as tuberculosis or a fungal, bacterial, viral, or parasitic opportunistic infection meeting WHO stage 3/4 criteria, and a composite non-AIDS event as hypertension, type 2 diabetes, coronary artery disease, chronic kidney disease, or other organ-system disease. We estimated risk ratios (RR) with 95% confidence intervals (CI) for these composites and for all-cause mortality, and fitted a multivariable logistic regression model for predictors of discordance.

Results

Of 682 PLHIV analysed, 103 (15.1%) were discordant. Discordant patients were older (mean 43.4 vs 33.9 years, $p < 0.001$), had lower baseline CD4 counts (median 104 vs 308 cells/mm3, $p < 0.001$) and lower haemoglobin (11.4 vs 12.4 g/dL, $p < 0.001$). The composite AIDS-defining event was more common in discordant patients (50.5% vs 19.7%; RR 2.56, 95% CI 1.99–3.30), as was the composite non-AIDS event (29.1% vs 13.5%; RR 2.16, 95% CI 1.50–3.12). All-cause mortality was higher in the discordant group (8.7% vs 0.5%; RR 16.9, 95% CI 4.6–61.3). Age (adjusted odds ratio [aOR] 1.07 per year, 95% CI 1.05–1.10), lower baseline CD4 count (aOR 0.99 per cell/mm3, 95% CI 0.99-1.00), and tuberculosis (aOR 2.56, 95% CI 1.44–4.54) were independently associated with discordance.

Conclusions

Immuno-virological discordance affected around one in seven PLHIV in this North Indian cohort and was associated with a substantially higher burden of AIDS-defining events, non-AIDS comorbidity, and mortality. Older age, low baseline CD4 count, and tuberculosis co-infection identify patients who may benefit from closer monitoring after starting ART.

Background

Antiretroviral therapy (ART) has changed HIV from a fatal illness into a manageable chronic condition. In India, an estimated 24 lakh (2.4 million) people are living with HIV, with an adult prevalence of 0.21% and 62,970 new infections recorded in 2021, a 46% decline from a decade earlier [1]. The goal of ART is not only to suppress viral replication but also to restore CD4 count, since CD4 recovery is closely linked to the reduction in opportunistic infections and mortality that ART achieves.

Most patients who achieve virological suppression also recover their CD4 count over time. A minority do not. This pattern, in which the plasma viral load falls below the limit of detection but the CD4 count remains low, is termed immuno-virological discordance, or immunological non-response. Reported prevalence varies widely, from 5.6% in a Mysuru cohort [2] to 13.6% in a Bengaluru referral series [3], 9.7% in a Western Indian cohort [4], and 11.5% in Tigray, Ethiopia [5]. Large single-centre cohorts from China and Indonesia have reported broadly similar patterns, with older age and low baseline CD4 count as the most consistent predictors of non-response [6, 7], while 15–25% has been reported in some North American cohorts [8, 9]. A systematic review of 20 studies reported a pooled range of 8% to 45%, reflecting differences in the definition of discordance and in follow-up duration [10].

The clinical consequences of discordance extend beyond a laboratory abnormality. Persistent immune activation, microbial translocation, and unresolved co-infections are thought to drive continued CD4 depletion despite viral suppression, and this has been

linked to a higher risk of both AIDS-defining events and non-AIDS morbidity. In the EuroSIDA cohort, discordant patients had an unadjusted risk ratio of 1.96 for serious non-AIDS events compared with CD4 responders [11], and an Italian multicentre cohort reported a similarly elevated hazard (HR 1.65) of severe non-AIDS events, driven mainly by malignancy, infection, renal, and cardiovascular diagnoses, among patients unable to raise their CD4 count above 200 cells/mm3 [12]. Similar excess risk has been reported for mortality: a Canadian cohort found discordant responses independently associated with a two-fold higher hazard of death [8], and a multicountry analysis of resource-constrained settings reported an intermediate mortality risk for discordant responders that persisted after adjustment for clinical stage and CD4 count [13].

As ART coverage expands and PLHIV survive longer, non-AIDS comorbidities have emerged as important contributors to morbidity, particularly in patients with incomplete CD4 recovery [14]. A recent meta-analysis of 43 studies and over four million PLHIV found low CD4 count, alongside conventional risk factors, independently associated with cardiovascular events [15]; ART-treated PLHIV have also been reported to carry nearly twice the odds of metabolic syndrome compared with ART-naive peers [16], and hypertension alone affects an estimated one in five PLHIV in Ethiopian cohorts [17]. Whether this pattern holds in India, where tuberculosis co-infection, late presentation, and nutritional deficits are common, has not been well studied. Existing Indian data describe the prevalence and risk factors of discordance itself [2, 3, 4] but rarely report its downstream clinical consequences, including mortality, within the same cohort.

We used ambispective cohort data from a large tertiary government ART centre in North India to address this gap. Our objective was to compare the incidence of AIDS-defining events and non-AIDS events, all-cause mortality, and sociodemographic and clinical risk factors between PLHIV with and without immuno-virological discordance.

Methods

Study design and setting

This was an ambispective (combined retrospective and prospective) cohort study conducted at the ART centre of the Department of Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, a tertiary government referral hospital. The study period was January 2018 to January 2024. Reporting follows the STROBE guidelines for cohort studies [18].

Participants

We included adults (18 years or older) with HIV-1 infection who were on adherent ART for more than one year and had provided informed consent. We excluded patients who did not consent, who were non-adherent to ART, or who had a known primary immunodeficiency disorder. Virological suppression was defined as a plasma viral load below 1000 copies/mL. Patients were classified into two groups on the basis of CD4 count at the time of assessment: Group D (discordant), with a CD4 count below 250 cells/mm3 despite viral suppression, and Group ND (non-discordant), with a CD4 count of 250 cells/mm3 or higher. Non-discordant patients were selected to be broadly comparable to discordant patients in clinical background, consistent with the ambispective, single-centre design.

Data collection

Demographic, socioeconomic, clinical, and laboratory data were abstracted from ART centre records and supplemented with prospective follow-up. Variables included age, sex, HIV transmission category, education, marital status, occupation, monthly household income, weight, height, baseline haemoglobin, baseline and latest plasma viral load, baseline and latest CD4 count, ART regimen and any regimen switch, isoniazid preventive therapy (IPT) status, baseline WHO clinical stage, and the presence of tuberculosis, fungal, bacterial, viral, or parasitic opportunistic infections, syphilis, hepatitis C co-infection, hypertension, type 2 diabetes, coronary artery disease or stroke, chronic kidney disease, and other organ-system disease. Vital status (alive, transferred out, lost to follow-up, or died) was recorded as of the last available contact.

Outcome definitions

We defined two composite clinical outcomes for this analysis. An AIDS-defining event was the presence of tuberculosis or any fungal, bacterial, viral, or parasitic opportunistic infection meeting WHO clinical stage 3 or 4 criteria [19]. A non-AIDS event was the presence of hypertension, type 2 diabetes, coronary artery disease or stroke, chronic kidney disease, or other organ-system disease (predominantly hepatobiliary). Syphilis and hepatitis C were analysed separately as co-infections. All-cause mortality was defined as a recorded status of "died" in ART centre records; cause-specific mortality was not classified.

Statistical analysis

We compared continuous variables between groups using the Mann-Whitney U test, given the non-normal distribution of most laboratory variables, and categorical variables using the chi-square test, with Fisher's exact test applied for sparse cross-tabulations (fewer than 5 expected observations in any cell). We calculated RR with 95% CI (log method) for the composite AIDS-defining event, the composite non-AIDS event, co-infection, and all-cause mortality, comparing Group D with Group ND. We fitted a multivariable logistic regression model with discordance as the outcome and age, sex, monthly income, body mass index (BMI), baseline haemoglobin, baseline CD4 count, baseline viral load, and the individual opportunistic infection and comorbidity variables as predictors, reporting adjusted odds ratios (aOR) with 95% CI. Because this model included 15 predictors against 103 discordant outcomes (approximately 6.9 events per variable, below the commonly cited threshold of 10), estimates for predictors with few affected patients in either group (bacterial infection and coronary artery disease, each affecting under 3% of the cohort) should be interpreted cautiously; their wide confidence intervals reflect this sparsity rather than a precise effect. A two-sided p-value below 0.05 was considered statistically significant throughout. Analyses were performed in Python (pandas, scipy, statsmodels); all reported results were independently cross-checked using a second statistical package (scikit-learn for the regression model) to confirm numerical stability.

Ethics

This study involved the analysis of data collected under the oversight of the Institutional Ethics Committee of AIIMS New Delhi (Reference No. AIIMSA01022/21.02.2024). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants for the prospective component of data collection.

Results

Study population

Of approximately 1800 PLHIV with virological suppression assessed at the centre over the study period, 682 met the eligibility criteria and were analysed (Fig. 1). Of these, 103 (15.1%) were classified as discordant (Group D) and 579 (84.9%) as non-discordant (Group ND).

Demographic and socioeconomic characteristics

Discordant patients were older than non-discordant patients (mean 43.4 ± 10.7 years vs 33.9 ± 10.6 years, $p < 0.001$) and were more often in the older age bands: 55% of Group D were older than 40 years, compared with 23% of Group ND. Group D also had a higher proportion of men (82.5% vs 72.2%, $p = 0.029$). HIV transmission category did not differ significantly between groups ($p = 0.233$). Education, marital status, and monthly income differed significantly: Group D had a lower proportion with college education or above (18.4% vs 31.3%, $p = 0.042$), a higher proportion currently married (83.5% vs 68.4%, $p = 0.002$), and a lower median monthly household income (INR 6000 vs 8000, $p = 0.040$). Given the marked age difference between groups, these socioeconomic differences most likely reflect the older age structure of Group D rather than an independent association with discordance; we did not adjust for these variables individually in the multivariable model beyond income, which was not independently significant after adjustment (Table 1).

Table 1
Sociodemographic characteristics of the study population, by discordance status.

Characteristic	Group D (n = 103)	Group ND (n = 579)	p-value
Age (years)	43.4 ± 10.7	33.9 ± 10.6	< 0.001
≤30 years, n (%)	12 (12)	263 (45)	
31–40 years, n (%)	31 (30)	184 (32)	
41–50 years, n (%)	30 (29)	82 (14)	
51–60 years, n (%)	26 (25)	41 (7)	
>60 years, n (%)	4 (4)	9 (2)	
Sex, n (%)			0.029
Male	85 (83)	418 (72)	
Female	18 (17)	160 (28)	
Transgender	0 (0)	1 (0.2)	
HIV transmission category, n (%)			0.233
Heterosexual	90 (87)	511 (88)	
Blood transfusion	4 (4)	7 (1)	
Mother-to-child	1 (1)	11 (2)	
MSM	2 (2)	7 (1)	
Unknown	6 (6)	31 (5)	
Injection drug use	0 (0)	12 (2)	
Education, n (%)			0.042
Illiterate	15 (15)	107 (18)	
Non-literate	1 (1)	4 (1)	
Primary school	36 (35)	153 (26)	
Secondary school	31 (30)	133 (23)	
College and above	19 (18)	181 (31)	
Marital status, n (%)			0.002
Married	86 (83)	396 (68)	
Single	11 (11)	149 (26)	
Widowed	6 (6)	18 (3)	
Divorced/separated	0 (0)	11 (2)	
Monthly household income, INR, median (range)	6000 (2000–100000)	8000 (700–300000)	0.040

Notes: SD, standard deviation; INR, Indian rupee; MSM, men who have sex with men. p-values: Mann-Whitney U test for age and income; chi-square test for categorical variables (Fisher's exact test for sex, given a sparse cell). Fisher's exact test.

Anthropometric and laboratory characteristics

Weight (55.3 vs 58.9 kg, p = 0.012) and BMI (21.4 vs 22.9 kg/m2, p = 0.002) were lower in Group D; height did not differ. Baseline haemoglobin was lower in Group D (11.4 vs 12.4 g/dL, p < 0.001). Baseline viral load category differed between groups (p < 0.001), with a higher proportion of Group D above 1000 copies/mL before suppression. Baseline CD4 count was markedly lower in Group D (median 104 vs 308 cells/mm3, p < 0.001) (Table 2, Fig. 2).

Table 2
Anthropometric, laboratory, and clinical characteristics, by discordance status.

Characteristic	Group D (n = 103)	Group ND (n = 579)	p-value
Weight, kg	55.3 ± 10.9	58.9 ± 13.3	0.012
Height, cm	160.7 ± 9.0	160.2 ± 9.4	0.655
BMI, kg/m2	21.4 ± 3.7	22.9 ± 4.7	0.002
Baseline haemoglobin, g/dL	11.4 ± 2.0	12.4 ± 1.9	< 0.001
Baseline viral load, copies/mL, median (range)	5 (5–2511840)	5 (5–1033448)	0.334
Baseline viral load category, n (%)			< 0.001
Target not detected	77 (75)	446 (77)	
5–999 copies/mL	10 (10)	102 (18)	
≥1000 copies/mL	16 (16)	31 (5)	
Baseline CD4 count, cells/mm3, median (range)	104 (19–697)	308 (9–1461)	< 0.001
WHO clinical stage at baseline, n (%)			< 0.001
Stage I	23 (22)	333 (58)	
Stage II	18 (17)	84 (15)	
Stage III	39 (38)	91 (16)	
Stage IV	23 (22)	61 (11)	

Notes: BMI, body mass index; TND, target not detected (viral load below the assay's limit of detection); WHO, World Health Organization. p-values: Mann-Whitney U test for continuous variables; chi-square test for categorical variables.

AIDS-defining events, non-AIDS events, and co-infections

A composite AIDS-defining event was present in 52 of 103 (50.5%) discordant patients compared with 114 of 579 (19.7%) non-discordant patients (RR 2.56, 95% CI 1.99–3.30). Tuberculosis was the largest individual contributor, affecting 41.7% of Group D versus 13.5% of Group ND (RR 3.10, 95% CI 2.28–4.22). A composite non-AIDS event was present in 29.1% of Group D versus 13.5% of Group ND (RR 2.16, 95% CI 1.50–3.12), driven mainly by hypertension (18.4% vs 7.9%; RR 2.32, 95% CI 1.42–3.80). Syphilis or hepatitis C co-infection was present in 11.7% of Group D versus 2.8% of Group ND (RR 4.22, 95% CI 2.06–8.65). WHO clinical stage III or IV at baseline was more frequent in Group D (60.2% vs 26.3%; RR 2.29, 95% CI 1.86–2.82) (Table 3, Fig. 3).

Table 3
AIDS-defining events, non-AIDS events, co-infection, and all-cause mortality, by discordance status.

Outcome	Group D, n/N (%)	Group ND, n/N (%)	Risk ratio (95% CI)	p-value
AIDS-defining event, composite[1]	52/103 (50.5)	114/579 (19.7)	2.56 (1.99–3.3)	< 0.001
Tuberculosis	43/103 (41.7)	78/579 (13.5)	3.1 (2.28–4.22)	< 0.001
Fungal infection	11/103 (10.7)	32/579 (5.5)	1.93 (1.01–3.71)	0.078
Bacterial infection	3/103 (2.9)	4/579 (0.7)	4.22 (0.96–18.56)	0.126
Non-AIDS event, composite[2]	30/103 (29.1)	78/579 (13.5)	2.16 (1.5–3.12)	< 0.001
Hypertension	19/103 (18.4)	46/579 (7.9)	2.32 (1.42–3.8)	0.002
Type 2 diabetes	10/103 (9.7)	49/579 (8.5)	1.15 (0.6–2.19)	0.823
Coronary artery disease	3/103 (2.9)	4/579 (0.7)	4.22 (0.96–18.56)	0.126
Chronic kidney disease	1/103 (1.0)	0/579 (0.0)	not estimable	0.329
Syphilis or HCV co-infection	12/103 (11.7)	16/579 (2.8)	4.22 (2.06–8.65)	< 0.001
WHO clinical stage III/IV at baseline	62/103 (60.2)	152/579 (26.3)	2.29 (1.86–2.82)	< 0.001
All-cause mortality	9/103 (8.7)	3/579 (0.5)	16.86 (4.64–61.25)	< 0.001

Notes: CI, confidence interval; HCV, hepatitis C virus. [1]Tuberculosis or a fungal, bacterial, viral, or parasitic infection meeting WHO clinical stage 3/4 criteria. [2]Hypertension, type 2 diabetes, coronary artery disease or stroke, chronic kidney disease, or other organ-system disease. Risk ratios were not estimable where an outcome was absent in one group (chronic kidney disease). p-values from chi-square test (Fisher's exact where expected cell counts were below 5).

Mortality

Nine of 103 (8.7%) discordant patients died during the study period, compared with 3 of 579 (0.5%) non-discordant patients (RR 16.9, 95% CI 4.6–61.3, p < 0.001) (Table 3, Fig. 3). Cause of death was not classified by AIDS versus non-AIDS aetiology in the source records.

Predictors of discordance

In multivariable logistic regression, older age (aOR 1.07 per year, 95% CI 1.05–1.10, p < 0.001), lower baseline CD4 count (aOR 0.99 per cell/mm3, 95% CI 0.99-1.00, p < 0.001), and tuberculosis (aOR 2.56, 95% CI 1.44–4.54, p = 0.001) were independently associated with discordance. Sex, income, BMI, haemoglobin, baseline viral load, and the remaining comorbidities did not reach independent significance; estimates for bacterial infection (aOR 6.42, 95% CI 0.69–59.7) and coronary artery disease (aOR 5.52, 95% CI 0.75–40.9) had wide confidence intervals consistent with small numbers of affected patients rather than a precisely estimated effect (Table 4, Fig. 4).

Table 4
Multivariable logistic regression for predictors of immuno-virological discordance.

Predictor	aOR	95% CI	p-value
Age (per year)	1.07	1.05–1.10	< 0.001
Female sex	0.74	0.39–1.43	0.374
Monthly income (per INR)	1	1.00–1.00	0.580
BMI (per kg per m2)	0.98	0.92–1.05	0.586
Baseline hemoglobin (per g/dL)	0.97	0.85–1.11	0.692
Baseline CD4 count (per cell/mm3)	0.99	0.99–1.00	< 0.001
Baseline viral load (per copy/mL)	1	1.00–1.00	0.105
Tuberculosis	2.56	1.44–4.54	0.001
Fungal infection	0.91	0.39–2.12	0.824
Bacterial infection	6.42	0.69–59.73	0.102
Syphilis	2.64	0.66–10.49	0.169
HCV co-infection	3.44	0.94–12.57	0.062
Type 2 diabetes	0.43	0.16–1.16	0.095
Hypertension	0.76	0.33–1.78	0.526
Coronary artery disease	5.52	0.75–40.92	0.094

Notes: aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; HCV, hepatitis C virus. Model included 15 predictors against 103 discordant outcomes (approximately 6.9 events per variable); estimates for bacterial infection and coronary artery disease, each affecting fewer than 3% of the cohort, have wide confidence intervals and should be interpreted with caution (see Discussion, Strengths and limitations).

Discussion

In this North Indian tertiary-centre cohort, immuno-virological discordance affected 15.1% of PLHIV who had achieved virological suppression, and it was associated with a markedly higher burden of AIDS-defining events, non-AIDS comorbidity, and all-cause mortality. These associations were independent of the specific opportunistic infection or comorbidity examined, and the pattern was consistent across every clinical domain we assessed.

Our prevalence estimate sits above several Indian reports and within the range described internationally. A Mysuru cohort reported 5.6% discordance using a stricter 12-month CD4 increment definition [2], while a Western Indian cohort reported 9.7% [4] and a Bengaluru referral series reported 13.6% among patients specifically investigated for poor immune recovery [3]. In Tigray, Ethiopia, prevalence was 11.5% in a comparably sized cohort [5]. Large hospital-based cohorts in China (8637 patients) and Indonesia have reported broadly similar rates using varying definitions [6, 7], and a systematic review of 20 studies found prevalence ranging from 8% to 45%, reflecting differences in the CD4 threshold and follow-up duration used to define discordance [10]. Our threshold (CD4 < 250 cells/mm3 despite suppression) is less stringent than some 12-month-increment definitions, which plausibly explains part of the difference from the lowest Indian estimates.

Age and baseline CD4 count were the two most consistent predictors of discordance in our analysis, a finding that mirrors the international literature closely. In the EuroSIDA cohort, incomplete CD4 recovery clustered in older patients and those starting ART at lower CD4 counts [11]; the same two predictors emerged as the strongest determinants of immunological non-response in the large Chinese and Indonesian cohorts noted above [6, 7], and in our data discordant patients started ART with a median CD4 count roughly a third that of non-discordant patients. This consistency across very different settings supports baseline CD4 count as a structural determinant of long-term immune recovery, most likely reflecting thymic and lymphoid tissue damage that occurs before treatment begins and that ART cannot fully reverse [14]. A complementary mechanistic explanation for the age association comes from work

linking pre-treatment immune senescence, rather than chronological age alone, to a reduced capacity for CD4 reconstitution after ART initiation [20].

Tuberculosis was the strongest infection-related predictor of discordance in our cohort (adjusted OR 2.56) and the largest contributor to the AIDS-defining event composite. This is consistent with tuberculosis's recognised role in sustaining immune activation and impairing CD4 recovery even once viral replication is controlled, and with its prominence in other Indian and Ethiopian discordance cohorts [2, 3, 5, 21]. A Bihar ART-centre cohort similarly found advanced WHO clinical stage and low CD4 count as the strongest correlates of HIV-tuberculosis co-infection [22], and a paediatric cohort study reported that baseline CD4 count, more than tuberculosis co-infection itself, determined the trajectory of immune recovery [23], consistent with our finding that baseline immune status and tuberculosis acted as independent rather than fully overlapping predictors. Syphilis and hepatitis C co-infection showed a similarly strong association; for hepatitis C in particular, cohort data indicate that co-infection itself impairs CD4 recovery [24], while successful direct-acting antiviral treatment of hepatitis C has been shown to partially restore CD4 recovery even among prior immunological non-responders [25], together suggesting that hepatitis C contributes mechanistically to discordance rather than merely marking a higher-risk population. Men were over-represented among discordant patients in our cohort, in keeping with a multicentre European analysis that found women achieved better immunological recovery than men on comparable regimens despite similar baseline severity [26].

The higher burden of non-AIDS events, particularly hypertension, in our discordant group adds to a small but growing literature linking incomplete immune recovery to cardiometabolic and renal risk. In the SMART trial cohort, poor early CD4 recovery was associated with a higher combined rate of non-AIDS events and death, including cardiovascular disease [14], and an Italian multicentre cohort reported a directly comparable 1.65-fold higher hazard of severe non-AIDS events (malignancy, infection, renal failure, cardiovascular events, and liver decompensation combined) among patients unable to raise their CD4 count above 200 cells/mm3 despite effective ART [12]. This aligns with recent meta-analytic evidence that low CD4 count independently predicts cardiovascular events in PLHIV alongside conventional risk factors [15], that ART-treated PLHIV carry a higher burden of metabolic syndrome than ART-naive peers [16], that hypertension alone affects roughly one in five PLHIV in comparable African cohorts [17], and that chronic kidney disease remains an under-recognised but clinically important comorbidity in this population [27]. Undernutrition, reflected in our cohort by the lower weight and BMI of discordant patients, has also been linked to poorer CD4 recovery and higher morbidity in PLHIV, particularly in resource-limited settings [28]. Our cross-sectional comparison of comorbidity prevalence cannot establish a causal ordering between discordance and non-AIDS disease. It remains plausible that the relationship runs in both directions, with chronic inflammation from non-AIDS disease itself contributing to poor CD4 recovery.

The mortality difference we observed (8.7% versus 0.5%, RR 16.9) is larger than that reported in most published discordance cohorts, though our confidence interval is wide given the small number of deaths. International cohorts have generally reported a two- to four-fold excess mortality risk in discordant responders [8, 9, 13], and multicountry Asian ART cohort data, which include Indian sites, similarly identify low CD4 count, older age, and comorbidity as the dominant predictors of mortality after long-term ART [29] and of virological failure where routine viral load monitoring is unavailable [30]. A single-centre cohort from New Delhi receiving third-line ART reported a comparable mortality rate of 8.7% among patients with advanced treatment failure [31], suggesting that the excess mortality we observed in discordant patients approaches that seen in a substantially more treatment-experienced Indian population. The wider gap in our data relative to most international cohorts most likely reflects the additional burden of tuberculosis and other opportunistic infections layered onto pre-existing immune failure in a high-burden, resource-constrained setting, rather than a uniquely severe biological effect of discordance itself. Because cause of death was not classified in the source records, we cannot determine what proportion of these deaths were directly attributable to AIDS-defining illness as opposed to non-AIDS or unrelated causes.

Strengths and limitations

This is, to our knowledge, one of few Indian cohorts to report all-cause mortality alongside AIDS-defining and non-AIDS clinical outcomes in the same group of patients classified by immuno-virological discordance, rather than discordance prevalence alone. The sample size (682, including 103 discordant patients) is comparable to or larger than most published Indian series on this topic.

Several limitations should be considered. First, this was a single-centre study at a tertiary government referral hospital; findings may not generalise to patients managed in private-sector or community-level ART programmes, or in other regions of India with different tuberculosis and nutritional profiles. Second, the ambispective design means the retrospective component relied on existing clinical records, which may under-ascertain milder opportunistic infections or comorbidities that were not formally documented. Third, we used a single cross-sectional CD4 count and viral load to classify patients rather than serial measurements, so we cannot describe the

trajectory of immune recovery over time, and some misclassification between transient and persistent discordance is possible. Fourth, cause of death was not classified by aetiology, which limits our ability to attribute excess mortality specifically to AIDS-defining versus non-AIDS causes. Fifth, non-AIDS malignancies were not systematically captured, likely leading to an underestimate of the total non-AIDS disease burden; longer follow-up would be needed to capture conditions with a longer latency. Sixth, the multivariable logistic regression model carried approximately 6.9 events per variable, below conventional guidance of at least 10; estimates for infrequent predictors (bacterial infection, coronary artery disease) should be treated as imprecise rather than as evidence of no association. Finally, as with any observational comparison, residual confounding cannot be excluded, and associations between discordance and downstream events should be interpreted as associational rather than causal given the study design.

Conclusions

In this North Indian tertiary-centre cohort, immuno-virological discordance affected around one in seven PLHIV who had achieved virological suppression on ART, and was associated with a substantially higher burden of AIDS-defining events, non-AIDS comorbidity, and all-cause mortality. Older age, low baseline CD4 count, and tuberculosis co-infection identified patients at highest risk of discordance. These patients may benefit from closer clinical monitoring, targeted screening for tuberculosis and non-AIDS comorbidity, and earlier ART initiation where feasible, to reduce the window of low CD4 count during which much of this excess risk appears to accrue.

Abbreviations

AIDS
acquired immunodeficiency syndrome
aOR
adjusted odds ratio
ART
antiretroviral therapy
BMI
body mass index
CD4
cluster of differentiation 4
CI
confidence interval
HAART
highly active antiretroviral therapy
HCV
hepatitis C virus
HIV
human immunodeficiency virus
IPT
isoniazid preventive therapy
NCD
non-communicable disease
PLHIV
people living with HIV
RR
risk ratio
SD
standard deviation
WHO
World Health Organization.

Declarations

Ethics approval and consent to participate

This study involved the analysis of data collected under the oversight of the Institutional Ethics Committee of AIIMS New Delhi (Reference No. AIIMSA01022/21.02.2024). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants for the prospective component of data collection.

Consent for publication

Not applicable. This manuscript does not contain any individual person's identifiable data, images, or case details.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Karthik K M: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing - original draft. **Suresh Bangla**: Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Project administration. **Naveet Wig**: Conceptualization, Methodology, Supervision, Writing - review & editing. **Neeraj Nischal**: Conceptualization, Methodology, Clinical expertise, Supervision, Writing - review & editing. **Arvind Kumar**: Methodology, Clinical expertise, Supervision, Writing - review & editing. **Ranveer Singh Jadon**: Methodology, Investigation, Clinical expertise, Writing - review & editing. **Upendra Baitha**: Methodology, Clinical expertise, Supervision, Writing - review & editing. **M A Khan**: Methodology, Formal analysis, Statistical analysis, Validation, Writing - review & editing. **Satnam Singh**: Methodology, Investigation, Data curation, Validation, Writing - review & editing.

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Availability of data and materials

The de-identified dataset supporting the conclusions of this article, and the analysis code used to generate all results, tables, and figures, are available from the corresponding author on reasonable request. Individual participant names have been removed from the dataset and replaced with sequential study identifiers to protect confidentiality.

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Figures

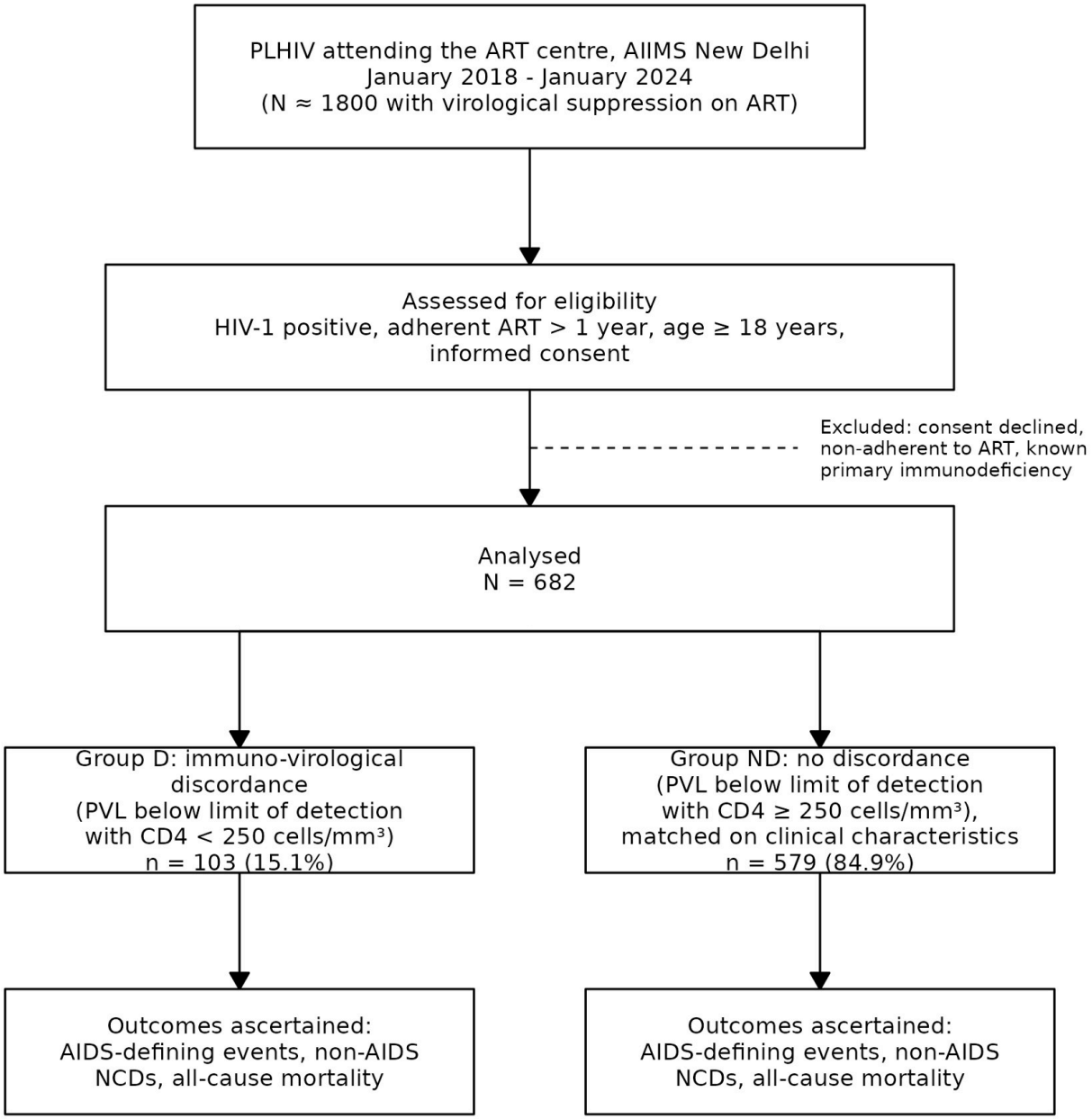


Figure 1

Study flow diagram. PLHIV, people living with HIV; ART, antiretroviral therapy; PVL, plasma viral load.

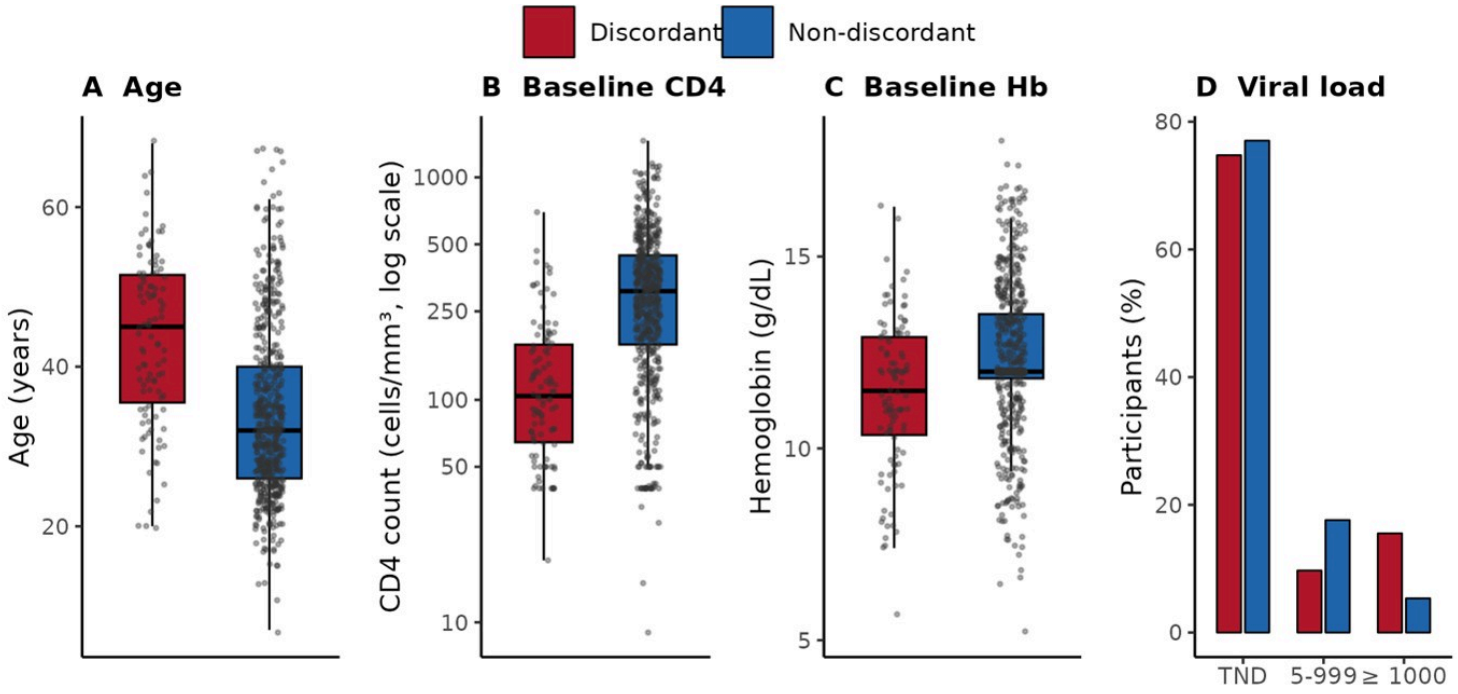


Figure 2

Baseline clinical and immunological profile by discordance status. (A) Age. (B) Baseline CD4 count (log scale). (C) Baseline haemoglobin. (D) Baseline viral load category. Boxes show median and interquartile range; points show individual participants. Red = discordant (Group D); blue = non-discordant (Group ND). TND, target not detected.

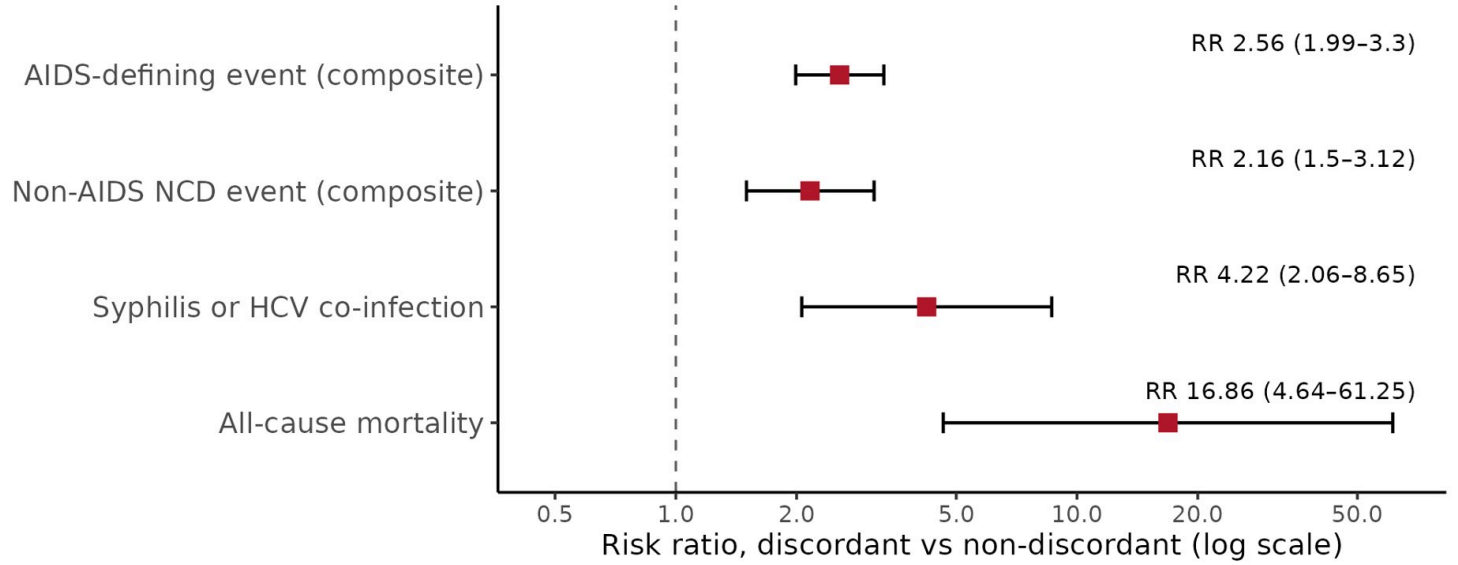


Figure 3

Risk ratios for AIDS-defining events, non-AIDS events, co-infection, and all-cause mortality, discordant versus non-discordant patients. Squares show the point estimate; horizontal lines show the 95% confidence interval. Dashed vertical line indicates a risk ratio of 1 (no difference).

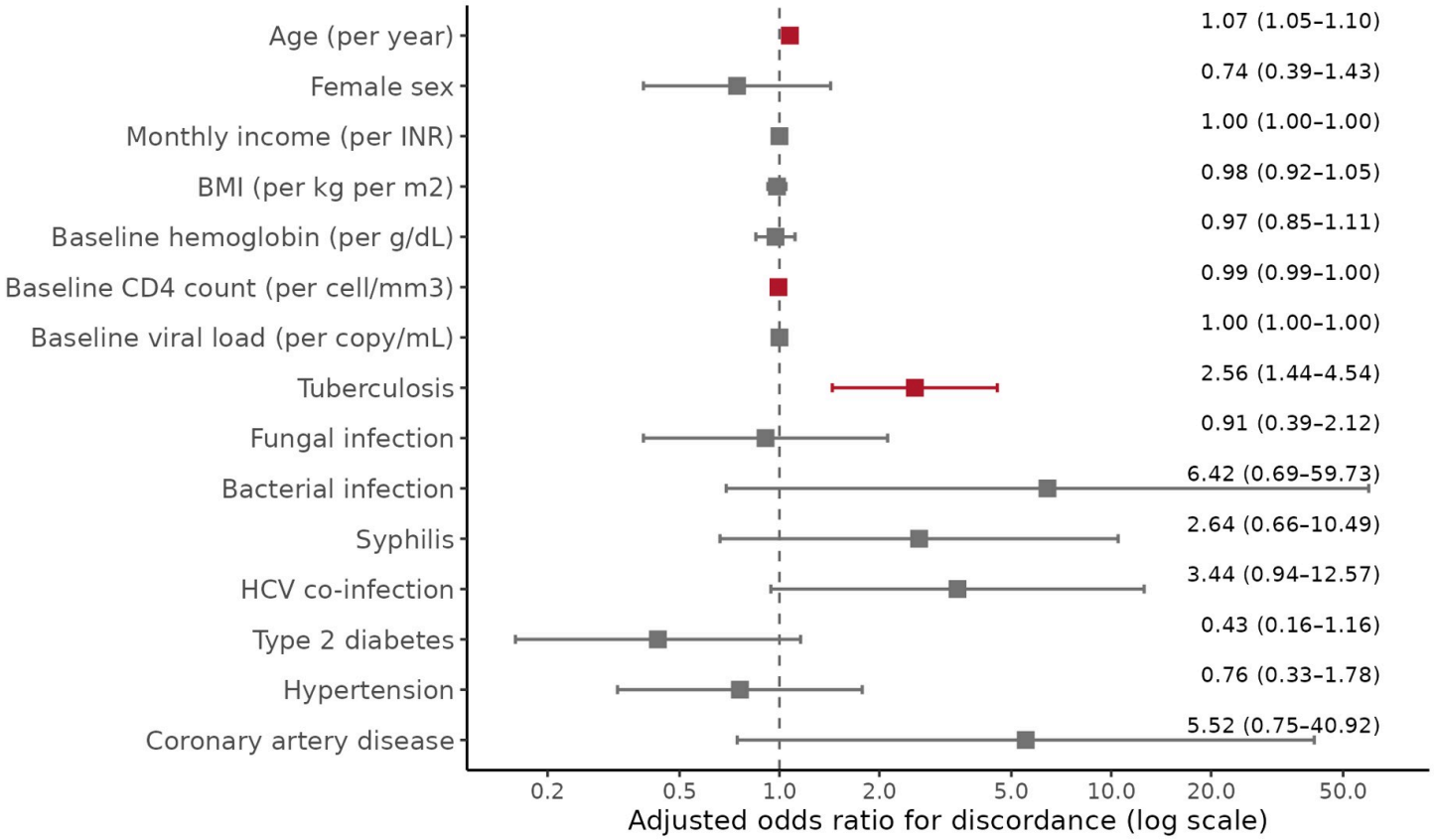


Figure 4

Forest plot of the multivariable logistic regression for predictors of immuno-virological discordance. Squares show the adjusted odds ratio; horizontal lines show the 95% confidence interval. Red indicates $p < 0.05$; grey indicates a non-significant association. Dashed vertical line indicates an odds ratio of 1.