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Original Research Article

HIGH VIROLOGICAL SUPPRESSION BUT PERSISTENT DISCORDANT IMMUNE RESPONSE IN THE DOLUTEGRAVIR ERA: A RETROSPECTIVE COHORT STUDY OF FIRST-LINE ART OUTCOMES IN SOUTH INDIA (2021–2024)

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ABSTRACT

Background: The global transition to Integrase Strand Transfer Inhibitor (INSTI)-based Antiretroviral Therapy (ART) has revolutionised HIV management. Aligning with UNAIDS targets, India's National AIDS Control Organisation (NACO) designated the fixed-dose combination of Tenofovir, Lamivudine, and Dolutegravir (TLD) as the preferred first-line regimen in 2020. TLD rapidly suppresses viral replication and possesses a high genetic barrier to resistance. However, achieving virological suppression does not guarantee full clinical recovery. Clinicians increasingly recognise "Discordant Immune Response" (DIR)—when patients suppress HIV-1 RNA but fail to achieve meaningful CD4+ T-cell reconstitution—as a critical bottleneck. Driven by prolonged untreated viremia and immunosenescence, DIR leaves patients at elevated risk for opportunistic infections, emerging non-communicable diseases, and early mortality. In resource-limited settings, many people living with HIV (PLHIV) still present with Advanced HIV Disease (AHD; CD4 < 200 cells/mm³). As India advances toward the NACP-Phase VI "Surakshit Plus" targets, granular programmatic data is urgently required to evaluate paired virological and immunological trajectories in the modern TLD era. **Materials and Methods:** We conducted a retrospective, longitudinal cohort study using programmatic data from our Antiretroviral Therapy (ART) centre in Chennai, Tamil Nadu, India. The cohort comprised all adult PLHIV (≥18 years) newly initiated on first-line ART between January 1, 2021, and December 31, 2024. We extracted anonymised data from electronic medical records, including demographics, baseline/latest CD4 counts, baseline/latest viral loads, and ART regimens. Virological Suppression was defined as a follow-up viral load < 1,000 copies/mL. Anchored to NACO's Cotrimoxazole cessation guidelines, we strictly defined DIR as the persistent failure to achieve an absolute CD4+ count ≥ 350 cells/mm³ despite a minimum of 12 months of virologically suppressive ART. We utilised IBM SPSS Statistics for data curation, Wilcoxon signed-rank tests for paired immunological data, and a multivariate binary logistic regression model to identify independent predictors of DIR. **Result:** We newly initiated 1,151 patients on ART (median age: 46.0 years; 57.9% male). Our centre achieved exceptional programmatic retention, restricting pure attrition to a mere 5.4%. Baseline immunosuppression remained severe. A staggering 45.1% of the cohort presented with AHD. We tracked subsequent virological outcomes. Contemporary Dolutegravir-based regimens demonstrated extraordinary efficacy, successfully suppressing circulating viral burdens in 90.7% of tested patients. We executed paired nonparametric evaluations on 835 individuals possessing strict baseline and follow-up data. The pharmacological intervention

definitively reconstructed cellular immunity, driving median CD4+ counts from 233 to 425 cells/mm³ ($p < 0.001$). Massive cohort-level success masked a critical, localized failure. Within the strictly virologically suppressed cohort (n=669), 26.8% entirely failed to cross the safe 350 cells/mm³ threshold. Our multivariate regression model definitively isolated baseline AHD as the primary biological culprit for this Discordant Immune Response. Late presenters faced a catastrophic 4.76-fold increased risk of immunological paralysis (aOR: 4.76, 95% CI: 3.21–7.05, $p < 0.001$). Advancing age independently compounded this risk. Female sex acted as a profound biological shield, cutting failure risk in half (aOR: 0.49). Finally, patients requiring Protease Inhibitors as 2nd-line or 3rd-line or Salvage regimens exhibited massively elevated DIR probabilities (aOR: 2.58). This stark metric mathematically captures the irreversible immunological scarring sustained while actively failing initial Dolutegravir-based therapies prior to escalation. **Conclusion:** Transitioning to Dolutegravir-based ART successfully optimised virological suppression and minimised programmatic attrition in South India. However, high pharmacological efficacy cannot reverse the permanent biological penalty of late HIV presentation. Patients initiating therapy with AHD frequently develop DIR, remaining immunologically vulnerable despite total viral clearance. Public health strategies need to evolve to address this challenge. We suggest expanding community-level index testing, utilising upfront CBNAAT/Truenat alongside the revised NACO 10-Symptom screening tool, and establishing targeted clinical pathways for DIR patients, including intensified NCD screening and prolonged prophylaxis.

INTRODUCTION

We revolutionised the global management of Human Immunodeficiency Virus (HIV) by widely adopting Integrase Strand Transfer Inhibitor (INSTI)-based Antiretroviral Therapy (ART). Seeking to secure the UNAIDS epidemic control targets, India's National AIDS Control Organisation (NACO) transitioned its programmatic guidelines in 2020–2021. NACO designated the fixed-dose combination of Tenofovir, Lamivudine, and Dolutegravir (TLD) as the definitive preferred first-line regimen.[1] Clinical trial researchers and public health evaluators consistently demonstrate TLD's extraordinary capabilities. The regimen exhibits superior tolerability. It provides a high genetic barrier to resistance. It rapidly suppresses viral replication.[2]

Achieving virological suppression does not secure complete functional clinical success. Clinicians increasingly recognise "Discordant Immune Response" (DIR), also termed Immunological Non-Response (INR), as a severe biological hurdle in the modern ART era. DIR strikes when patients successfully suppress plasma HIV-1 RNA replication but completely fail to achieve meaningful CD4+ T-cell reconstitution.[3] International researchers rigorously define DIR as the absolute failure to restore CD4+ counts above the safe clinical threshold of 350 cells/mm³ despite years of suppressive ART. This immunological paralysis traps patients in a prolonged state of biological vulnerability.[4] Pathologists attribute this blunting to extensive immunosenescence, persistent immune activation, and the irreversible exhaustion of CD4+ T-cells. Prolonged untreated viremia before ART initiation drives this catastrophic systemic damage.[5]

Resource-limited settings across Asia routinely see a massive proportion of people living with HIV (PLHIV) presenting to care with Advanced HIV Disease (AHD). We define AHD strictly as a baseline CD4 count below 200 cells/mm³.[6] Dolutegravir potently inhibits the integration of viral DNA with the host DNA, halting the subsequent transcription and further steps of viral replication. It cannot immediately reverse the architectural lymphoid damage established in these late-presenting patients. Consequently, patients exhibiting DIR face a significantly elevated risk for opportunistic infections, non-AIDS-related morbidities, and early mortality despite their strict adherence to modern ART.[7]

India currently drives toward the ambitious NACP-Phase VI "Surakshit Plus" targets. We require granular programmatic data to evaluate the paired virological and immunological trajectories of patients consuming modern regimens. We therefore evaluated a contemporary cohort of PLHIV. We initiated these patients on first-line ART between January 2021 and December 2024 at the ART centre, linked to the HIV Centre-of-Excellence, Government Hospital of Thoracic Medicine, Government Stanley Medical College, Chennai, Tamil Nadu. We quantified the absolute rate of virological suppression in the INSTI era. We subsequently identified the baseline clinical predictors of Discordant Immune Response.

MATERIALS AND METHODS

Study Design and Setting: We conducted a retrospective, longitudinal cohort study. We utilised programmatic data from our Antiretroviral Therapy (ART) centre, linked to the HIV Centre-of-Excellence, Government Hospital of Thoracic Medicine, Government Stanley Medical College, Chennai, Tamil Nadu, India. Our facility operates

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strictly under NACO guidelines. We provide comprehensive HIV care. We mandate routine virological and immunological monitoring for all registered patients.

Study Population: We assembled a study cohort comprising all adult PLHIV (≥18 years), newly registered at our facility, and initiated on first-line ART from January 1, 2021, to December 31, 2024. We selected this precise timeline to isolate clinical outcomes exclusively within the mature TLD implementation era. We ensured every included patient possessed a minimum of 12 months of longitudinal follow-up before data extraction in early 2026. We enforced strict exclusion criteria. We excluded patients who were initiated on ART before 2021. We excluded individuals transferred into our facility already consuming second-line therapies or failing legacy regimens.

Data Collection and Operational Definitions: We extracted anonymised programmatic data from the centre's electronic medical records. We operationally defined all clinical outcomes utilising WHO and NACO standardised clinical thresholds [1, 8]:

- Virological Suppression: We defined suppression as a follow-up plasma HIV-1 RNA viral load dropping below 1,000 copies/mL.
- Advanced HIV Disease (AHD): We defined AHD as a baseline CD4+ count falling below 200 cells/mm³ precisely at the time of ART initiation.
- Discordant Immune Response (DIR): We anchored our definition to current NACO guidelines. NACO dictates clinicians can only discontinue Cotrimoxazole Preventive Therapy (CPT) when a patient's CD4 exceeds 350 cells/mm³. We strictly defined DIR as the persistent failure to achieve an absolute CD4+ count of ≥ 350 cells/mm³ despite a minimum of 12 months of virologically suppressive ART. This absolute threshold ensures we do not erroneously classify patients who remain at clinical risk for opportunistic infections as immunological responders based solely on arbitrary delta CD4 increases.

Statistical Analysis: We performed all data curation and statistical analyses utilising IBM SPSS Statistics. We assessed continuous variables for normality using the Shapiro-Wilk test. We summarised non-parametric continuous data (CD4 counts and viral loads) using medians and Interquartile Ranges (IQR). We analysed paired immunological data (baseline versus latest CD4 counts) utilising the Wilcoxon signed-rank test to determine the absolute statistical significance of immune reconstitution.

We constructed a multivariate binary logistic regression model to identify independent predictors of Discordant Immune Response. We entered variables exhibiting a p-value < 0.20 in preliminary univariate analyses into the final multivariate model. We calculated Adjusted Odds Ratios (aOR) with 95% Confidence Intervals (CI). We considered a two-tailed p-value of < 0.05 statistically significant.

RESULTS

Baseline Characteristics and Programmatic Retention (2021–2024): We had newly initiated 1,151 patients on ART from January 1, 2021, to December 31, 2024. The cohort demonstrated a median age of 46.0 years (IQR: 36.5–54.0). Males predominated the population (57.9%, n=666). Females followed closely (41.4%, n=476). Transgender individuals constituted a small minority (0.8%, n=9). The cohort exhibited severe immunosuppression at baseline. We recorded a median baseline CD4+ count of 233 cells/mm³ (IQR: 88–456). Advanced HIV Disease afflicted a staggering 45.1% (n=519) of the cohort at baseline.

We maintained the vast majority of our active cohort (74.8%) on standard first-line Dolutegravir-based regimens (TLD). We utilised alternative first-line regimens (e.g., Abacavir-based) for 4.0%. We escalated 21.0% to Protease Inhibitor-based regimens. [Table 1].

Table 1: Baseline Characteristics and Core Clinical Outcomes (N = 1,151)

Clinical Characteristic		Value (n, %, or Median)
Demography	Total Cohort (2021-2024)	N = 1,151
	Age, Median (IQR)	46.0 (36.5 - 54.0)
	Male Sex	666 (57.9%)
	Female Sex	476 (41.4%)
	Transgender	9 (0.8%)
Baseline Immune Status	Baseline CD4 < 200 (Advanced HIV Disease)	519 (45.1%)
	Median Baseline CD4 (IQR)	233 (88 - 456)
ART regimen details	Maintained on Standard TLD Regimen	861 (74.8%)
	Switched to Alternative 1st-Line Regimen	46 (4.0%)
	Escalated to Protease Inhibitor-based Regimens	242 (21.0%)
Treatment status at data collection	Alive and continuing ART at our centre	571 (49.6%)
	Transferred Out to peripheral centres	369 (32.1%)
	Programmatic Attrition (LFU/MIS/Opt Out)	62 (5.4%)
	Died	149 (12.9%)
Virological and Immunological outcomes	Virological Suppression (<1000 copies)	737 / 813 (90.7%)
	Discordant Immune Response (CD4 < 350)	179 / 669 (26.8%)

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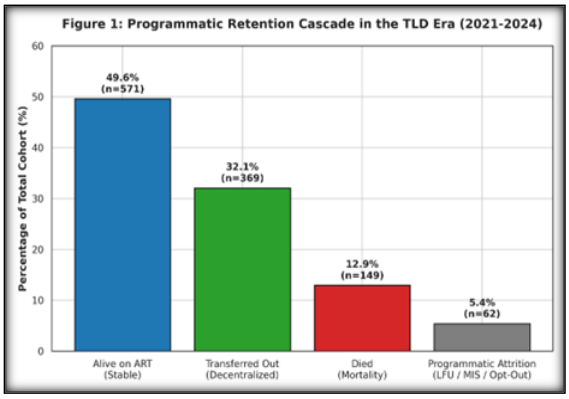
We evaluated the clinical care cascade. Our centre demonstrated exceptional programmatic retention. We restricted pure programmatic attrition, which we strictly defined as patients lost to Follow-Up (LFU), missing in the system (MIS), or Opted Out, to merely 5.4% (n=62) of the total cohort. We successfully stabilized 32.1% (n=369) of the cohort. We formally transferred these patients out to decentralised peripheral networks. Mortality claimed 12.9% (n=149) of the cohort. The active living cohort exhibited retention rates that perfectly align with the ambitious NACO Phase VI targets [Figure 1].



Virological Suppression and Overall Immune Reconstitution: We aggressively tracked virological outcomes following the initial Anti-Retroviral Therapy. Current Dolutegravir-based Antiretroviral Therapy (ART) demonstrated extraordinarily high efficacy. Among the 813 patients supplying valid follow-up plasma data after six months of continuous therapy, exactly 737 individuals successfully suppressed their circulating viral burden below 1,000 copies/mL. This secures a definitive 90.7% virological suppression rate [Figure 2].

We subsequently executed paired nonparametric evaluations utilising the Wilcoxon signed-rank test on 835 patients who possessed both baseline and follow-up CD4+ data to definitively quantify absolute immune reconstitution. This statistical analysis captured a profound longitudinal recovery architecture. The cohort generated 631 positive recovery ranks against a mere 201 negative ranks, forcing a definitive Z-score of -15.953 ($p < 0.001$). In a clinical context, this overwhelming asymmetry of positive ranks proves that the vast majority of patients experienced continuous, measurable biological healing rather than stagnation or decline. This statistical momentum manifested clinically as a robust leap in median CD4+ reserves. Absolute cellular counts jumped from a severely depleted baseline of 233 cells/mm³ to a latest follow-up of 425 cells/mm³, delivering a median functional increase of +156 cells/mm³. Consequently, the data confirms that this modern pharmacological intervention definitively reconstructs cellular immunity.

Discordant Immune Response (DIR) and Clinical Predictors: Massive cohort-level success masked a critical, localised failure. A distinct subset of patients developed a Discordant Immune Response. We isolated 669 individuals who successfully achieved virological suppression and possessed paired immunological data. Within this strictly suppressed group, an alarming 26.8% (n=179) entirely failed to drive absolute CD4+ counts above the safe clinical threshold of 350 cells/mm³ [Figure 2]. We deployed a multivariate binary logistic regression model to unearth the independent clinical predictors driving this immunological paralysis [Table 2].

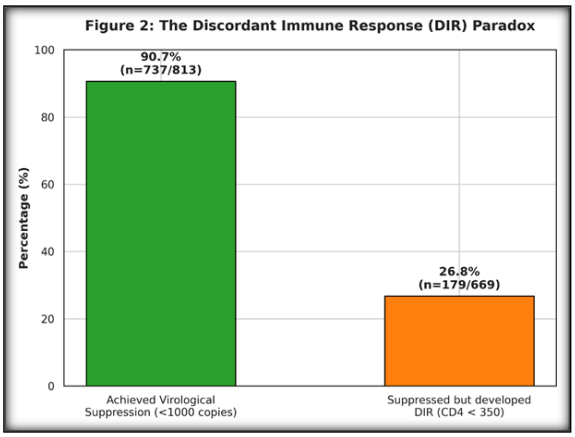


Table 2: Multivariate Binary Logistic Regression Identifying Independent Predictors of Discordant Immune Response

Predictor Variable	Adjusted Odds Ratio (aOR)	95% Confidence Interval (CI)	p-value
Advanced HIV Disease (Baseline CD4 < 200)	4.76	3.22 – 7.05	< 0.001
Older Age (per 1-year increase)	1.04	1.02 – 1.06	< 0.001
Female Sex (vs. Male)	0.49	0.33 – 0.73	< 0.001
Protease Inhibitor-based Regimens (vs. TLD)	2.58	1.66 – 4.01	< 0.001

(Note: The multivariate model tightly controlled for baseline confounding. Statistical significance established at $p < 0.05$. Reference categories: CD4 ≥ 200, Male Sex, Standard TLD Regimen).

The model definitively isolated baseline Advanced HIV Disease (AHD) as the primary biological culprit. Initial immune depletion inflicts permanent structural damage. Patients presenting to care with AHD carry a catastrophic 4.76-fold increased risk of subsequent immunological failure (aOR: 4.76, 95% CI: 3.22 – 7.05, $p < 0.001$).

Advancing age independently compounds this risk. Each chronological year accelerates the probability of DIR (aOR: 1.04, 95% CI: 1.02 – 1.06, $p < 0.001$), empirically validating the severe clinical impact of thymic immunosenescence. Conversely, female sex acts as a profound biological shield. It literally cuts the risk of immunological failure in half (aOR: 0.49, 95% CI: 0.33 – 0.73, $p < 0.001$). Finally, treatment

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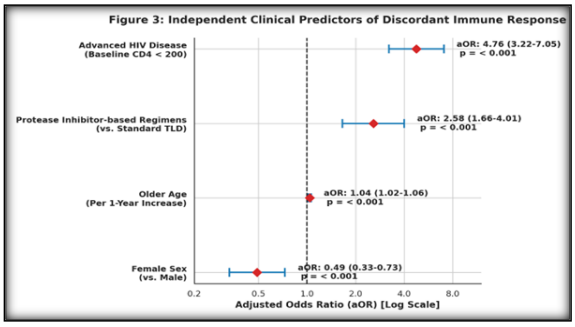
history dictates recovery ceilings. Patients requiring Protease Inhibitor-based regimens exhibited massively elevated DIR probabilities (aOR: 2.58, 95% CI: 1.66 – 4.01, p < 0.001). This stark metric mathematically captures the cumulative, irreversible immunological scarring these patients sustained while actively failing their initial Dolutegravir-based therapies before escalation with Protease Inhibitor-based regimens [Figure 3].



DISCUSSION

We provide a highly rigorous evaluation of first-line ART outcomes during the mature Dolutegravir era (2021–2024) in a South Indian cohort. Our primary findings isolate a critical duality in modern HIV management. INSTI-based regimens achieve exceptional rates of virological suppression. Delayed diagnosis permanently blunts functional immunological recovery.

Our centre's programmatic success strongly validates the feasibility of India's NACP-Phase VI "Surakshit Plus" targets. Our centre restricted pure programmatic attrition to approximately 5% over a longitudinal cohort. We also effectively maximised the proportion of living patients maintained on uninterrupted ART. The 90.7% virological suppression rate observed in our cohort perfectly aligns with recent programmatic evaluations from Western India. Our analysis definitively proves TLD halts viral replication highly effectively.[2]

The phenomenon of Discordant Immune Response remains a persistent biological bottleneck. We utilised the stringent clinical threshold of < 350 cells/mm³. We observed a substantial subset of virologically suppressed patients failing to achieve adequate immune reconstitution. Our empirical data robustly support recent international immunological analyses. Profound initial immune depletion causes irreversible thymic exhaustion.[4,5] HIV destroys the lymphoid architecture during untreated viremia. Merely suppressing the virus with TLD fails to regenerate naïve CD4+ T-cells. Consequently, these immunological non-responders remain deeply vulnerable.

CONCLUSION

We successfully optimised virological suppression and minimised programmatic attrition in our ART centre by transitioning to NACO guidelines implemented Dolutegravir-based first-line ART. High pharmacological efficacy cannot reverse the permanent biological penalty of late presentation. Patients initiating therapy with Advanced HIV Disease frequently develop Discordant Immune Responses. They remain immunologically vulnerable despite achieving total viral clearance.

Public health strategists must urgently evolve national protocols to bridge the gap between virological suppression and true clinical recovery. We suggest the following feasible interventions:

1. **Aggressive Upstream Screening:** Healthcare networks must vastly expand community-level index testing. We must identify and initiate PLHIV well before CD4 counts catastrophically decline below 200 cells/mm³.
2. **Modernised Co-Infection Diagnostics:** Clinicians managing late presenters must drastically expand the utilisation of upfront Nucleic Acid Amplification Testing (CBNAAT/Truenat) for Tuberculosis. We must rigidly apply the revised NACO 10-Symptom (10S) screening tool. Healthcare networks must integrate the novel Cy-TB skin test to optimise Latent TB Infection (LTBI) screening. This will perfectly target the rollout of TB Preventive Treatment (TPT).
3. **Advanced Care for DIR Patients:** NACO guidelines currently mandate continued CD4 monitoring until the 350 cells/mm³ threshold is crossed. The national program shall introduce targeted clinical pathways for patients who permanently stall. Clinicians shall subject identified DIR patients to intensified screening for emerging non-communicable diseases (NCDs) and malignancies. We may permanently prolong CPT prophylaxis for this demographic. We should clinically acknowledge their persistent biological vulnerability despite programmatic viral suppression.

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