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Immunological Trajectory of HIV Patients on 4-Year Antiretroviral Therapy: A 13-Year Observational Study from Khorramabad

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Abstract
Introduction: The gradual decline in CD4+ T-cell counts following HIV infection leads to impaired immune function and serves as a primary determinant of the clinical course in HIV-infected patients. Antiretroviral therapy increases $CD4^+$ lymphocyte counts, thereby enhancing immunity and reducing opportunistic infections and mortality. This study aimed to investigate the effect of three-drug antiretroviral regimens on $CD4^+$ cell counts in HIV-infected patients in Khorramabad. In this observational cohort study, data from 242 HIV-infected patients receiving either NNRTI-based (n=181) or INSTI-based (n=61) regimens were analyzed. $CD4^+$ T-cell counts were measured at baseline and at 6 months, 1, 2, 3, and 4 years post-treatment initiation. Generalized Estimating Equations (GEE) models were used to evaluate longitudinal changes in absolute $CD4^+$ T-cell counts, and an independent t-test was performed to compare the mean change from baseline between groups. The INSTI-based group had a significantly lower baseline $CD4^+$ T-cell count compared to the NNRTI-based group (331 vs. 452 cells/µL). The mean increase in $CD4^+$ T-cell count from baseline was significantly greater in the INSTI-based group (406 cells/µL) compared to the NNRTI-based group (299 cells/µL) (P=0.002). However, GEE analysis demonstrated that patients on the NNRTI-based regimen maintained significantly higher absolute $CD4^+$ T-cell counts throughout follow-up compared to those on the INSTI-based regimen (P<0.001), which likely reflects their higher baseline values. Both regimens were associated with improvements in $CD4^+$ T-cell counts. The INSTI-based regimen showed a greater mean increase from baseline, while the NNRTI-based regimen maintained higher absolute $CD4^+$ T-cell counts over time. Due to the observational design, substantial baseline imbalances between groups, and the small sample size in the INSTI group during long-term follow-up, no causal claims of superiority can be made for either regimen. These hypothesis-generating findings require confirmation through randomized controlled trials with balanced baseline characteristics.

Keywords: HIV, Antiretroviral therapy, $CD4^+$ lymphocyte count, Longitudinal studies.

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Introduction

HIV is responsible for the most severe form of pathogen-induced immune system destruction in humans, leading to the progressive loss of $CD4^+$ T helper cells. The decline in the T helper cell population progressively weakens the immune system. As the infection progresses to acquired immunodeficiency syndrome (AIDS), the immune system loses its capacity to prevent infections by other pathogens, ultimately leading to death from opportunistic infections (1). Additionally, HIV infects other cell types, such as macrophages, dendritic cells, and resting T-cell subsets. These host cells also play a critical role in both innate and adaptive immunity. All three types of cells frequently act as viral reservoirs, containing transcriptionally inactive proviruses (2). This feature allows HIV to establish a persistent infection that evades detection and eradication by immune cells and therapeutic interventions (3). Although the natural history of HIV infection without antiretroviral therapy may vary among patients, a typical pattern is generally observed in these individuals. Primary infection with HIV leads to the development of both cellular and humoral immune responses to the virus, which is accompanied by a long incubation period (averaging 10 years), during which the patient is usually asymptomatic. Despite the absence of specific clinical symptoms during this period, the immune system progressively deteriorates and ultimately leads to a decline in $CD4^+$ T-cell count (4).

The progressive destruction of the immune system that occurs in most patients who do not receive antiretroviral therapy eventually leads to overt clinical disease and, in advanced stages, progresses to AIDS, characterized by persistent and severe underlying signs and symptoms, opportunistic infections, or malignancies (4). Currently, antiretroviral therapy constitutes a lifelong treatment that reduces mortality and disability in HIV-infected patients at various clinical stages and greatly diminishes the transmission rate of the virus; however, it does not have the capability to entirely eradicate the virus or completely restore the infected individual's immune system. To date, approximately 25 ART drugs have received approval for treating HIV, encompassing the drug classes NRTI, NNRTI, PI, and INSTI. Zidovudine (AZT) was the first drug evaluated in humans in 1985 and became widely available in 1987. Subsequently, in the early 1990s, NRTI drugs received FDA approval and became available on the market. Further research facilitated the use of combination therapy, commonly referred to as HAART, which is often administered as a triple-drug regimen. This approach has demonstrated the capability to reduce mortality and hospitalization rates associated with HIV-related diseases by 60 to 80%. Nevertheless, it should also be noted that the disadvantages of combination therapy include side effects and the development of drug resistance, which deprives many patients of the long-term benefits of drug therapy (5). Currently, there are 18 antiretroviral drugs available in Iran. The initial ART regimen can be categorized into a preferred regimen and an alternative one.

According to recent studies, the prevalence of primary drug resistance to NNRTIs (efavirenz/nevirapine) exceeds 10%. In these circumstances, if drug resistance testing is unavailable to evaluate drug susceptibility, it is not recommended to use an NNRTI-based regimen; instead, a combination therapy with the highest probability of effectiveness and drug susceptibility should be employed. Consequently, the INSTI-based regimen has been chosen as the preferred option in Iran. Therefore, initiating treatment with alternative regimens requires a convincing reason; otherwise, the superior regimen should be utilized. Currently, the majority of patients are receiving a three-drug regimen, with most drug combinations selected from the following options, based on the patient's condition and drug availability: NRTI + INSTI-based regimen (preferred regimen), NRTI + PI-based regimen (alternative regimen), and 2NRTI + NNRTI-based regimen (alternative regimen) (6). Similar to other medical decisions, initiation of treatment depends on the risk-benefit ratio of the treatment. Historically, the indication for initiating ART was a $CD4^+$ cell count of less than 200 cells/μL (while for adults, this threshold ranged from 200 to 350 cells/μL). However, according to new guidelines, antiretroviral therapy should now be

commenced as soon as possible in all individuals living with HIV, regardless of the clinical stage of disease or $CD4^+$ T-cell count (7). According to the DHHS panel, viral load, $CD4^+$ cell count, and drug resistance should be determined prior to initiation of therapy. Furthermore, the panel outlines the timing for viral load assessment, $CD4^+$ T-cell count, and drug resistance testing as follows (8). The $CD4^+$ T-cell count is the most important clinical indicator for evaluating immune function in HIV-infected patients. It also plays a major role in determining the necessity for commencing prophylactic therapy against opportunistic infections (9). Typically, a virologic response is observed six months after the initiation of treatment. However, in cases where the initial viral load is very high, the suppression of viral load may occur gradually. Generally, a reduction of at least one logarithm is expected within four weeks. The overall goal of ART is to suppress viral load to a level that prevents the development of drug resistance (9). Currently, HIV viral load is recognized as the most important indicator for evaluating the clinical status of infected patients, monitoring disease progression, understanding the natural course, and investigating the pathogenesis of HIV infection. It also serves as an indicator for assessing the efficacy and sufficiency of ART drugs, as well as evaluating the effectiveness of vaccines and estimating the patient's survival time (10).

The clinical course of HIV infection is largely determined by the depletion of $CD4^+$ T-lymphocytes, which leads to progressive immunosuppression. Antiretroviral therapy (ART) aims to counteract this decline by increasing $CD4^+$ T-cell count, an effect associated with enhanced immune competence and a consequent reduction in opportunistic infections and mortality. Based on this pathophysiology, the present observational study was designed to evaluate the effect of a three-drug ART regimen on $CD4^+$ T-cell count levels in a cohort of HIV-infected individuals in Khorramabad, Iran. The findings of this study offer an overall understanding of the treatment impact on these patients, facilitating improved and more effective management and decision-making regarding this significant disease in Khorramabad.

Materials and Methods

Study Design and Population

This investigation was designed as a retrospective longitudinal observational study following a defined cohort of HIV-positive patients in Khorramabad. The study population comprised all individuals who initiated a triple antiretroviral therapy (ART) regimen between 2001 and 2013, and for whom complete medical records were available at local behavioral disease counseling centers. The various ART regimens were categorized based on their mechanisms of action, including nucleoside Reverse Transcriptase Inhibitor (NRTI)-based regimens, non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, integrase strand transfer inhibitor (INSTI)-based regimens, and protease inhibitor (PI)-based regimens.

Ethical Approval and Administrative Permissions

Prior to the initiation of any data collection, all necessary administrative permissions were secured. Formal approval was granted by the Ministry of Health, the Deputy for Research and Technology, and the Center for Infectious Diseases of the Deputy for Health at Lorestan University of Medical Sciences (LUMS) to conduct this study. Subsequently, the study protocol received formal approval and obtained the ethical approval code IR.LUMS.REC.1402.385 from the University Ethics Board. This process ensured that the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Data Collection and Variables

Following ethical and administrative approval, researchers accessed the patient records at the counseling centers. A pre-designed, structured checklist was utilized to systematically extract the required data points in a standardized manner, thereby ensuring consistency and minimizing extraction errors. All data were handled with strict confidentiality; patient identifiers were removed, and each record was assigned a unique study code to anonymize the information prior to analysis.

The specific information extracted encompassed key demographic variables—namely age, gender, and level of education—to characterize the cohort. The primary clinical outcome of interest was the $CD4^+$ T-cell count. This immunologic marker was recorded at baseline (pre-treatment initiation) and subsequently through serial measurements at six months, one year, and then annually for four years post-treatment initiation, allowing for the analysis of immunological recovery trends over the medium term.

Inclusion and Exclusion Criteria

To ensure a homogeneous and evaluable study population, the following criteria were applied:

Inclusion criteria: All patients aged ≥18 years who were diagnosed with HIV infection and initiated either an NNRTI-based or INSTI-based antiretroviral regimen during the study period. Patients were required to have at least one $CD4^+$ T-cell count measurement at baseline and at least one follow-up measurement after six months of treatment initiation to be eligible for the longitudinal analysis.

Exclusion criteria: Patients were excluded from the study if they met any of the following conditions: 1. incomplete baseline or follow-up data; 2. co-infection with other viral diseases such as hepatitis C (HCV) or human papillomavirus (HPV), which could independently affect immune status; 3. documented treatment discontinuation or switching to a different regimen before completing six months of therapy; 4. death during the follow-up period; 5: emigration or transfer to another healthcare facility, resulting in loss to follow-up; and 6: pregnancy or any other condition that could confound $CD4^+$ T-cell count interpretation.

Handling of Missing Data and Attrition

Given the observational and retrospective nature of this study, complete follow-up data were not available for all patients. Patients who discontinued treatment, switched regimens, died, or were lost to follow-up due to emigration were excluded from subsequent time points. No imputation methods were applied for missing $CD4^+$ T-cell count measurements**;** instead, only available data at each time point were analyzed, allowing for the inclusion of participants with incomplete follow-up data. To assess the potential impact of attrition on our findings, we conducted sensitivity analyses comparing baseline characteristics of patients who completed the full follow-up period with those who were lost to follow-up or excluded. These analyses are presented in the supplementary materials.

Statistical Analysis

Following data collection, all extracted information was entered into SPSS 23. Descriptive statistics, including frequencies, proportions, means, standard deviations, and medians with interquartile ranges, were calculated to summarize the baseline demographic and clinical characteristics of the study population.

To evaluate the longitudinal changes in $CD4^+$ T-cell counts over the four-year follow-up period, the Generalized Estimating Equations (GEE) model was employed. This approach was selected because it accounts for within-subject correlations across repeated measurements, handles unbalanced data (i.e., varying numbers of observations per patient), and provides robust standard error estimates even in the presence of missing data. Two GEE models were constructed: Model I examined the effect of the treatment regimen on mean absolute CD4+ T-cell counts over time without adjustment, while Model II adjusted for potential confounding variables, including age and gender. The NNRTI-based regimen was set as the reference category in both models.

Additionally, to compare the magnitude of immune recovery between the two treatment groups, an independent samples t-test was performed to evaluate the mean change in $CD4^+$ T-cell count from baseline to the end of the follow-up period.

All statistical tests were two-sided, and a P-value of less than 0.05 was considered to indicate statistical significance. Results are reported as beta coefficients (B) with 95%

confidence intervals (CIs) for the GEE models, and as mean differences with standard deviations for the t-test analyses.

Results

The progressive reduction in sample size over the four-year follow-up period is a common challenge in observational cohort studies of HIV-infected populations. A total of 10,385 patients diagnosed with HIV in Lorestan Province are registered at the Communicable Diseases Center of the Vice-Chancellery for Health, Lorestan University of Medical Sciences. From this provincial registry, 242 patients residing in Khorramabad were identified and included in the present study. The reduction from 242 patients at baseline to 137 patients at the end of the four-year follow-up was primarily attributed to treatment discontinuation, death, emigration, and loss to follow-up. Notably, our sensitivity analyses revealed no significant differences in baseline characteristics between patients who completed the study and those who were lost to follow-up, suggesting that the observed attrition did not introduce substantial bias into our primary effect estimates.

Description of the patients studied in terms of demographic and contextual variables

This study found that 116 (47.9%) of the participants were female and 126 (52.1%) were male. The mean age of the patients was 43.69 ± 8.48 years, as shown in Table 1. Among the participants, 9 (3.6%) were illiterate, 50 (20.7%) had a middle school education, 79 (32.6%) had a high school education, 87 (36%) had a diploma, and 17 (7%) had a university education.

Table 1. Frequency Distribution of Demographic and Background Variables in the Studied Patients

Variable	Category	Frequency	Percentage
Gender	Female	116	47.9
	Male	126	52.1
Educational Level	Illiterate	9	3.6
	Middle School	50	20.7
	High School	79	32.6
	Diploma	87	36.0
	University	17	7.0
Duration of ART (Antiretroviral Therapy)	At least 6 months	222	90.0
	At least 1 year	208	85.9
	At least 2 years	183	75.6
	At least 3 years	155	64.0
	At least 4 years	137	56.6
Age (Mean ± SD)	43.69 ± 8.48	—	—

Description of the patients studied in terms of medications used

Analysis of antiretroviral regimens among HIV patients revealed distinct patterns of drug utilization. The most frequently prescribed drugs were emtricitabine (FTC) and tenofovir (TDF), forming the framework of treatment for 72.3% (n=175) and 73.5% (n=178) of patients, respectively. Efavirenz (EFV) was also a common component, observed in 71.9% (n=174) of regimens. Lamivudine (3TC) and zidovudine (AZT) were each used in 27.6% and 25.2% of cases (n=66 and n=61, respectively), while dolutegravir (DTG) was part of the regimen for 25.2% (n=61) of patients. The protease inhibitor lopinavir/ritonavir (LPV/r) and nevirapine (NVP) were employed infrequently, appearing in only 2.4% (n=6) and 0.4% (n=1) of treatment plans, respectively.

Regarding the classification of regimens, 165 patients (68.1%) received an NNRTI-based regimen (NNRTI + 2 NRTI), 61 patients (25.2%) received an INSTI-based regimen (INSTI + 2 NRTI), and 16 patients (6.7%) received a PI-based regimen (PI + 2 NRTI). It should be noted that patients whose PI-based regimen was subsequently changed to an INSTI-based regimen were excluded from the study, as PI-based regimens were removed from the national AIDS treatment protocol in Iran due to medication shortages and their associated high complication rates.

Average CD4+ T-cell count of the patients at various time intervals according to drug regimen

As mentioned before, a total of 242 patients (22.3%) satisfied the predefined inclusion criteria and were subsequently enrolled. During follow-up, the number of active participants dropped to 222 at 6 months, 208 at 1 year, 183 at 2 years, and 137 at 3 years. The primary reason for this attrition was premature treatment discontinuation prior to the 4-year follow-up mark. During the study period, the number of patients maintaining each regimen over time was evaluated. Among those receiving an NNRTI-based regimen (NNRTI + 2 NRTI), 181 patients were initially on this regimen at baseline. Of these, 179 patients continued the regimen for at least 6 months, 170 for at least 1 year, 154 for at least 2 years, 136 for at least 3 years, and 136 for at least 4 years. The mean CD4+ cell count in this group was 452 cells/μL at baseline, which increased to 560 cells/μL after at least 6 months, 609 cells/μL after 1 year, 673 cells/μL after 2 years, 728 cells/μL after 3 years, and 751 cells/μL after 4 years of treatment.

Among patients receiving an INSTI-based regimen (INSTI + 2 NRTI), 61 individuals were initially on this regimen at baseline. Of these, 41 individuals continued for at least 6 months, 29 for at least 1 year, 13 for at least 2 years, 1 individual for at least 3 years, and 1 individual for at least 4 years. The mean CD4+ T-cell count in this group was 331 cells/μL at baseline, which increased to 514 cells/μL after at least 6 months, 471 cells/μL after at least 1 year, 535 cells/μL after at least 2 years, 648 cells/μL after at least 3 years, and 737 cells/μL after at least 4 years of treatment (Table 2).

Table 2: Mean CD4+ cell Counts of the Studied Patients Across Different Time Intervals by Drug Regimen

Drug Regimen	Measure	Baseline	≥ 6 months	≥ 1 year	≥ 2 years	≥ 3 years	≥ 4 years
NNRTI + 2 NRTIs	N	181	181	179	170	154	136
	Mean	452.44	560.50	609.69	673.61	728.24	751.50
	SD	326.11	791.29	369.06	388.07	372.66	370.46
	Median	370	442	528	579	714	701
INSTI + 2 NRTIs	N	61	41	29	13	1	1
	Mean	331.00	514.00	471.00	535.00	648.00	737.00
	SD	305.66	407.17	347.98	406.96	—	—
	Median	261	432	400	437	648	737
Total	N	242	222	208	183	155	137
	Mean	421.00	552.00	590.00	663.00	727.00	751.00
	SD	324.76	735.05	368.52	389.91	371.51	369.10
	Median	360	439	525	576	712	703

Comparison of CD4+ T-cell counts of patients at different time intervals based on drug regimen

The results of the GEE model (Model I) indicated a statistically significant difference in the mean absolute CD4+ T-cell count over the follow-up period between the two treatment groups. Specifically, patients receiving the NNRTI-based regimen (NNRTI + 2 NRTI) demonstrated a higher mean absolute CD4+ cell count over time compared to those on the INSTI-based regimen (INSTI + 2 NRTI), with an average difference of approximately 42 units (202 vs. 160 cells/μL, respectively; P<0.001). This pattern remained consistent after adjusting for gender and age in Model II, where the NNRTI-based regimen was associated with a mean absolute CD4+ count that was 182.17 units greater than the INSTI-based regimen (P<0.001) (Table 3).

It is important to emphasize that these findings reflect comparisons of absolute CD4+ T-cell counts measured during the follow-up period, rather than the magnitude of change (i.e., increase) from baseline. The observed higher absolute counts in the NNRTI group must be interpreted with considerable caution, as baseline CD4+ T-cell counts were substantially imbalanced between the groups (452 cells/μL for the NNRTI group vs. 331 cells/μL for the INSTI group). Consequently, the higher absolute counts in the NNRTI group over time may largely be attributed to their higher starting point rather than a superior treatment effect. Therefore, while the GEE models demonstrate a statistical association between regimen type

and absolute CD4$^+$ T-cell counts, these results should not be interpreted as evidence that the NNRTI-based regimen produces a greater immunologic recovery or is clinically superior to the INSTI-based regimen. A more appropriate analysis for comparing treatment efficacy would involve evaluating the change in CD4$^+$ count from baseline or employing a model that adjusts for baseline CD4$^+$ T-cell counts, which is a key limitation of the current analysis.

Table 3. Modeling the Effect of Two Antiretroviral Regimens on the Mean CD4 Count at Different Time Points in the Studied Patients Using the GEE Model

Model	Regimen	B Coefficient	95% CI (Lower)	95% CI (Upper)	P-Value
Model I*	NNRTI + 2 NRTIs	202.42	102.357	302.496	< 0.001
	INSTI + 2 NRTIs	Reference	—	—	—
Model II**	NNRTI + 2 NRTIs	182.17	83.943	280.404	< 0.001
	INSTI + 2 NRTIs	Reference	—	—	—

*: Modeling the effect of drug regimen type on average CD4$^+$ cell count
**: Modeling the effect of drug regimen type on average CD4$^+$ cell count by adjusting for the effect of age and gender variables

To further elucidate the immune recovery dynamics, we also compared the mean change in CD4$^+$ T-cell count from baseline to the end of the follow-up period between the two groups. The results of an independent t-test demonstrated that patients receiving the INSTI-based regimen experienced a significantly greater mean increase in CD4$^+$ T-cell (406 cells/µL) compared to those on the NNRTI-based regimen (299 cells/µL) ($P<0.05$).

At first glance, this finding appears to contrast with the GEE model results, which showed higher absolute CD4$^+$ T-cell counts in the NNRTI group over time. However, this apparent contradiction is readily explained by the substantial baseline imbalance between the groups: the NNRTI group started with a considerably higher baseline CD4$^+$ T-cell count (452 vs. 331 cells/µL). While the NNRTI group maintained a higher absolute count throughout the follow-up period—likely due to its higher starting point—the INSTI group demonstrated a more pronounced gain from its lower baseline, reflecting a potentially greater immunologic recovery rate.

Taken together, these complementary analyses suggest that while absolute CD4$^+$ T-cell counts remained higher in the NNRTI group over time, the INSTI-based regimen was associated with a more substantial increase in CD4$^+$ T-cell counts from baseline. This underscores the importance of distinguishing between absolute values and changes over time measures when evaluating treatment efficacy, and highlights the need for further studies with balanced baseline characteristics or adjusted analyses to determine the true comparative effectiveness of these regimens.

Discussion

The findings of this study indicated that the utilization of both NNRTI-based and INSTI-based regimens enhances CD4$^+$ T-cell count over time; however, the implementation of INSTI-based regimens appeared to lead to a greater increase in CD4$^+$ T-cell count compared to NNRTI-based regimens. Although CD4$^+$ T-cell count is gradually being phased out as a biomarker for HIV infection status (11) and is being replaced by the CD4$^+$/CD8$^+$ ratio, as the CD4$^+$/CD8$^+$ ratio has been shown to predict an increased risk of mortality and serious non-AIDS events even among ART-treated individuals achieving CD4$^+$ cell count >500 cells/µL (12), CD4$^+$ cell count remains an important factor for clinicians when evaluating ideal regimens. According to Helberg et al., a declining CD4$^+$ T-cell count, even in patients with improved viral load, can elevate the risk of cardiovascular disease, cancer, and mortality (13). The relevance of CD4$^+$ T-cell count persists for the longevity of HIV-infected individuals, and its increase may help in reducing the likelihood of comorbidities and opportunistic infections (11).

Similar studies have focused on the effect of INSTI-based regimens on treatment-experienced HIV-infected individuals. Sun et al. switched 53 HIV-infected patients who were on NNRTI-based or PI-based therapy and had

achieved a stable viral load to an INSTI-based regimen. The linear mixed-effects model showed a statistically significant increase in $CD4^+$ cell count over time after switching to an INSTI-based regimen (P = 0.015). Higher baseline $CD4^+$ cell count was associated with higher $CD4^+$ T-cell count after transitioning to an INSTI-based regimen (P = 0.001). They concluded that switching to an INSTI-based regimen was associated with increased $CD4^+$ cell count in ART-experienced individuals living with HIV (11). The results of that study were consistent with the present study.

A multicenter study by Castagna et al. evaluated the efficacy of an INSTI-based regimen (dolutegravir) in a treatment-experienced population with integrase inhibitor-resistant virus. The investigators concluded that dolutegravir had a positive effect on the immune response, leading to an increase in $CD4^+$ T-cell count (64+ cells/µL from baseline after 24 weeks) even in a treatment-experienced population with INSTI-resistant virus (14).

Another study by Pozniak et al. evaluated the safety and efficacy of switching from an NNRTI-based to an INSTI-based regimen. Participants were treatment-experienced individuals on NNRTI-based regimens who were virologically stable and were randomly assigned to continue on an NNRTI-based regimen or switch to an INSTI-based regimen. The results showed that the INSTI-based regimen was equally effective but had significantly fewer side effects. The study found no difference in $CD4^+$ T-cell count gains between the NNRTI-based and INSTI-based groups (15). Due to the conflicting results of the current studies regarding the relationship between $CD4^+$ cell count and INSTI-based regimens, clinicians may face difficulties in discerning the benefits of switching therapies.

As previously mentioned, the $CD4^+/CD8^+$ ratio predicts an increased risk of mortality and serious non-AIDS events even among ART-treated individuals who achieve $CD4^+$ T-cell count >500 cells/µL. The $CD4^+/CD8^+$ ratio has been revealed to predict non-AIDS complications and mortality after adjustment for baseline $CD4^+$ T-cell count in two European studies (12). Therefore, the $CD4^+/CD8^+$ ratio appears to be of greater value than $CD4^+$ cell count alone. In a retrospective cohort study by Sabina Herrera, NNRTI-based regimens were demonstrated to be more effective in normalizing this ratio than other regimens (16). Additionally, in a comparative study, JL Adams et al. indicated the efficacy of various antiretroviral drug classes in treating HIV-infected patients with high viral loads. In this multicenter retrospective cohort study, patients with high viral loads initially receiving NNRTI-based regimens were more likely to achieve viral suppression by 6 months on ART compared with those receiving INSTI-based and PI-based regimens (17). Therefore, although different studies have shown conflicting results comparing the effects of antiretroviral drugs on elevating $CD4^+$ T-cell count, the results of other studies indicate that the use of INSTI-based regimens yields better outcomes than NNRTI-based regimens.

Conclusion

Although $CD4^+$ T-cell counts improved with both regimens, the INSTI-based group demonstrated a trend toward a more pronounced increase in our study population. Given the observational nature of the study, these results should be viewed as hypothesis-generating rather than confirmatory of superiority.

Both regimens were associated with improved $CD4^+$ T-cell counts. The INSTI-based regimen showed a greater increase from baseline, while the NNRTI-based regimen maintained higher absolute counts. However, the substantial baseline imbalance between the two groups (452 vs. 331 cells/µL) suggests that the higher absolute T-cell counts observed in the NNRTI group may largely reflect their higher starting point rather than a superior treatment effect.

Due to the observational design, baseline differences, and limited sample size in the INSTI group during long-term follow-up, no causal claims of superiority can be made for either regimen. These findings are hypothesis-generating and require confirmation in well-designed randomized controlled trials with balanced baseline characteristics and comprehensive adjustment for confounders.

Limitations

Several important limitations should be considered when interpreting our findings. First, our adjusted analysis only controlled for age and gender, as these were the only variables consistently recorded across all patient records. Other potentially important confounders—including baseline CD4 T-cell count, viral load, duration of infection, adherence to ART, opportunistic infections, coinfections (HBV/TB), and socioeconomic factors—were not included in the adjusted model due to incomplete or unavailable data. This may introduce residual confounding and bias our effect estimates.

Second, the absence of viral load data limits our ability to assess virological suppression. Third, the retrospective design inherently restricts our ability to control for unmeasured confounders.

Fourth, the small sample size in the INSTI-based regimen group during the later years of follow-up (years 3 and 4), reflecting the historical predominance of NNRTI-based regimens in our setting during the study period, limits the generalizability of our long-term comparative findings. Therefore, our primary conclusions are drawn from the 6-month, 1-year, and 2-year follow-up data, where sample sizes were adequate for meaningful statistical inference.

Future prospective studies with comprehensive data collection protocols and larger cohorts with longer follow-up, particularly as INSTI-based regimens become more widely adopted, are warranted to confirm these observations.

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