

The Predictive Value of Lactate Dehydrogenase for Viral Suppression in Newly Diagnosed People Living With HIV on Antiretroviral Therapy: A Retrospective Cohort Study

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Purpose: Rapid initiation of antiretroviral therapy (ART) in people living with HIV (PLWH) is crucial for achieving viral suppression and improving clinical outcomes. Serum lactate dehydrogenase (LDH) levels serve as a readily accessible and rapid clinical biomarker, has significant predictive potential in various viral diseases. This study aims to evaluate the predictive value of LDH levels for viral suppression in the context of rapid ART initiation.

Patients and Methods: LDH levels were measured in 393 newly diagnosed PLWH who received rapid initiation of ART and were subsequently followed up. The PLWH were stratified based on tertile LDH levels and study endpoints. Kaplan-Meier analysis was conducted to generate survival curves, and Cox regression analysis was utilized to confirm the independent prognostic factors for viral suppression.

Results: The overall viral suppression rate was 94.1%. Compared to the low LDH tertile, the middle and high LDH tertiles exhibited longer times to first viral suppression (38 vs 84 vs 88 days, respectively, $P < 0.001$). Kaplan-Meier analysis revealed that PLWH in high LDH tertile showed the worst prognosis for viral suppression (Log rank test, $P < 0.001$). Multivariate Cox regression analysis identified LDH tertile as a significant predictor of viral suppression (HR = 0.714, 95% CI = 0.553–0.922, $P = 0.010$ for middle vs low tertile; HR = 0.575, 95% CI = 0.443–0.747, $P < 0.001$ for high vs low tertile).

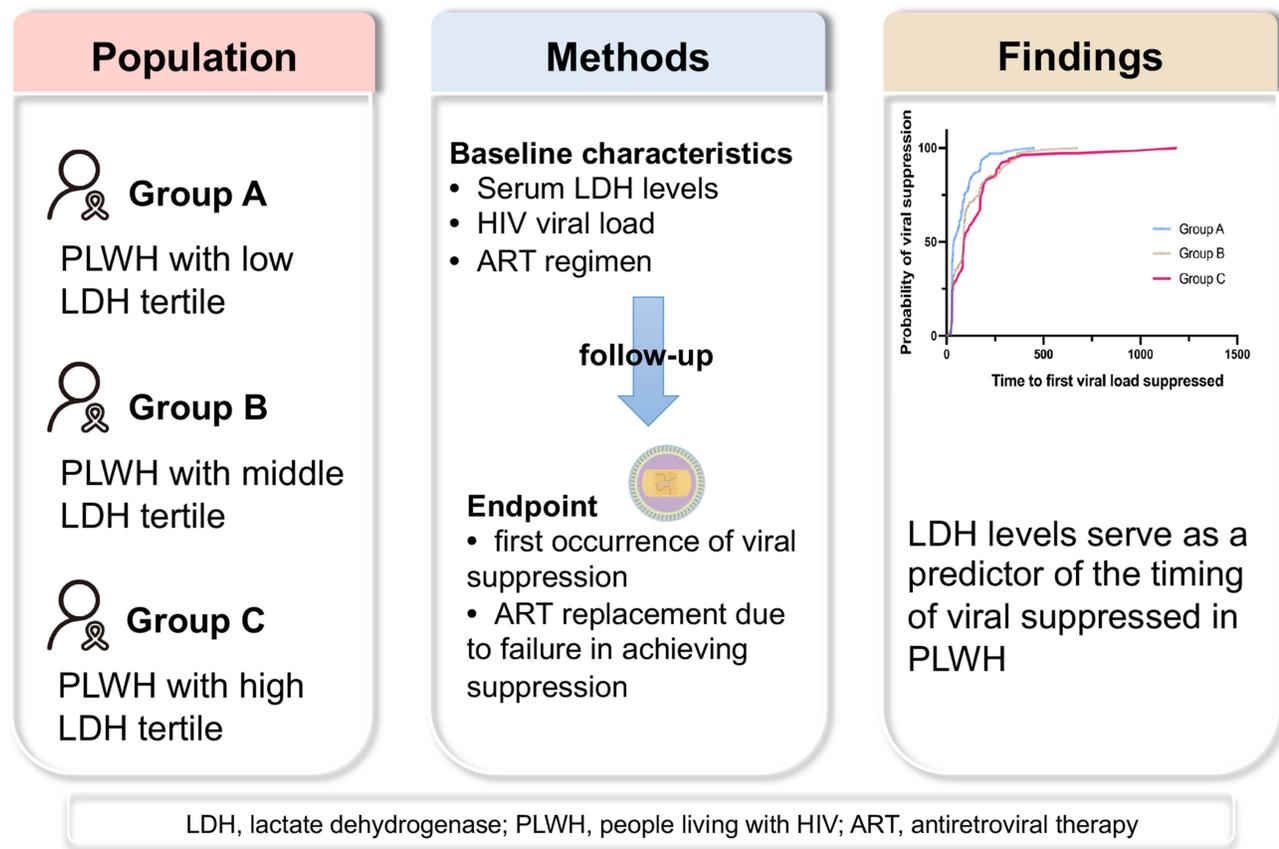
Conclusion: LDH levels function as a prognostic indicator for predicting the timing of viral suppression in PLWH on ART. A comprehensive evaluation of LDH levels is beneficial in establishing risk stratification in the context of rapid ART initiation.

Keywords: predictive value, lactate dehydrogenase, viral suppression, HIV

Introduction

The implementation of antiretroviral therapy (ART) has effectively reversed the previously increasing trends in Human Immunodeficiency Virus (HIV) related mortality, morbidity, and disease transmission. This success underscores the importance of achieving and maintaining viral suppression in healthcare management. Achieving and maintaining viral suppression stand as a paramount objective in managing individuals with HIV, with profound implications for disease progression, treatment effectiveness, and the emergence of HIV-1-related comorbidities.¹ Additionally, the benefits of viral suppression extend to both individual and public health.² Substantial evidence supports that people living with HIV (PLWH) cannot sexually transmit the virus if their viral load is maintained at or below 200 hIV RNA copies/mL.^{3–6} In the global HIV pandemic context, there is growing interest in viral suppression in clinical and epidemiological studies.

Graphical Abstract



The Rapid initiation of ART in PLWH is essential for improving clinical outcomes and controlling disease progression. Early initiation of ART significantly reduces viral load and prevents immune system deterioration, thereby decreasing morbidity and mortality from opportunistic infections and AIDS-defining illnesses.⁷ Additionally, prompt ART initiation improves time to viral suppression and retention in care, offering significant psychological benefits.⁸ Rapid ART aligns with the UNAIDS 95–95–95 targets by expediting viral suppression in a greater proportion of the HIV-positive population, contributing to epidemic control.⁹ However, not all antiretroviral drugs are appropriate for rapid ART initiation.¹⁰ The unequal distribution of medical resources and inconsistent economic conditions often delay access to optimal drugs recommended for rapid ART. Viral suppression is influenced by several factors, such as baseline viral load, adherence, ART regimens, treatment duration and the emergence of drug-resistant strains.¹¹ In this context, early identification of viral suppression in PLWH is critically important.

Lactate dehydrogenase (LDH) is an intracellular enzyme present in various organ systems, and deviations from normal values can result from multi-organ injuries, infections, and other conditions involving the upregulation of glycolytic processes.¹² Serum LDH levels serve as a readily accessible and rapid clinical biomarker, potentially benefiting viral suppression in the context of rapid ART initiation. Serum LDH levels are crucial for predicting the prognosis of various viral diseases. In chronic lymphocytic leukemia patients,¹³ a positive correlation existed between LDH levels and EBV-DNA copy numbers, which was linked to diminished survival time and accelerated disease progression. In pediatric *Mycoplasma pneumoniae* pneumonia patients,¹⁴ those with persistent *Mycoplasma* DNA positivity beyond 30 days from disease onset had significantly higher LDH levels than those with DNA negativity. This suggested a strong association between LDH levels and *Mycoplasma* DNA clearance. Nishijima et al¹⁵ compared

serum LDH levels in individuals with primary measles virus infection and reinfection, finding significantly higher LDH levels and viral loads in primary infections. The area under the curve for overall LDH levels was 0.87 (95% CI 0.74–1.00), indicating LDH as a valuable marker for differentiating between primary and reinfection. In COVID-19 patients,¹⁶ serum LDH levels were found to correlate with COVID-19 Ct values, demonstrating a positive association with higher viral loads.

Despite the considerable predictive potential of serum LDH levels in various diseases, limited data exist on its use as a biomarker for predicting viral suppression in PLWH. Predicting viral suppression in PLWH remains a clinical challenge. In resource-limited regions, cost-effective, compliant, and timely diagnostic indicators are imperative. LDH, as a routine clinical parameter, offers distinct advantages. Economically, incorporating LDH may provide a cost-efficient approach to diagnosis and monitoring, enhancing medical resource utilization. For patient compliance, LDH implementation can simplify treatment, improve adherence, and support long-term management. Timely LDH detection results facilitate swift disease status evaluation and treatment adjustments. Consequently, LDH as a comprehensive indicator promises economic benefits, improves compliance, and expedites diagnosis and monitoring, making it a practical choice for resource-limited settings. To address this, a retrospective cohort study was conducted to analyze the prognostic significance of serum LDH levels in achieving viral suppression among PLWH.

Materials and Methods

Data Source and Study Population

This retrospective cohort study was conducted between November 2018 and April 2024. Newly diagnosed PLWH who visited the outpatient department of Ningbo Yinzhou No.2 hospital were included. The inclusion criteria were as follows: (1) PLWH who were ART-naïve, meaning they had not previously received ART; (2) HIV viral load exceeding 200 copies/mL; (3) Age between 18–70 years. The exclusion criteria included overt infection, severe liver and kidney insufficiency, skeletal muscle injury, pulmonary embolism, myocardial infarction, a history of malignancy, prior use of ART or other antiviral drugs, and hospital admission for any reason within 30 days before cohort entry (including opportunistic infection or AIDS conditions). Ultimately, 393 participants met the inclusion and exclusion criteria (Figure 1).

Study Variables

Eligible patients underwent detailed medical history taking and laboratory examination at study entry. Demographic, clinical, and biochemical data, including age, gender, transmission category, ART regimen, CD4 and CD8 counts, HIV viral load, white blood cell (WBC) count, lymphocyte (LY) count, hemoglobin (HGB) concentration, platelet (PLT) count, and LDH levels, were obtained from medical records. Transmission categories were classified into three groups: men who have sex with men (MSM), heterosexuals, and “Unknown” for those unwilling to disclose their status. LDH levels were measured using an LDH assay kit (MedicalSystem Biotechnology, China), following the manufacturer’s instructions. The intra-assay coefficient of variation (CV) was 3.6%, and the inter-assay CV was 5.5%. Blood samples were collected in EDTA tubes and processed within two hours. Plasma LDH levels were measured spectrophotometrically by assessing the reduced forms of nicotinamide adenine dinucleotide at 340 nm. PLWH were divided into three groups based on tertile LDH levels: group A ($LDH \leq 178$ U/L), group B ($178 \text{ U/L} < LDH \leq 213$ U/L), and group C ($LDH > 213$ U/L).

Treatment

All subjects received a rapid initiation of ART containing two nucleoside reverse transcriptase inhibitors (NRTIs) with a third agent, which could be a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI). To streamline analyses, ART regimens were categorized into four types based on whether they were single-tablet regimens (STRs) or multi-tablet regimens (MTRs) and whether they included INSTIs. INSTI-based STR regimens included elvitegravir/cobicistat emtricitabine/tenofovir, alafenamide/emtricitabine/bictegravir, and lamivudine/dolutegravir. INSTI-based MTR regimens included tenofovir alafenamide fumarate + lamivudine + dolutegravir and tenofovir disoproxil fumarate + lamivudine + dolutegravir. Non-INSTI-based STR regimens included tenofovir disoproxil fumarate/lamivudine/abacavir. Non-INSTI-based MTR regimens included zidovudine + lamivudine + efavirenz, tenofovir alafenamide fumarate

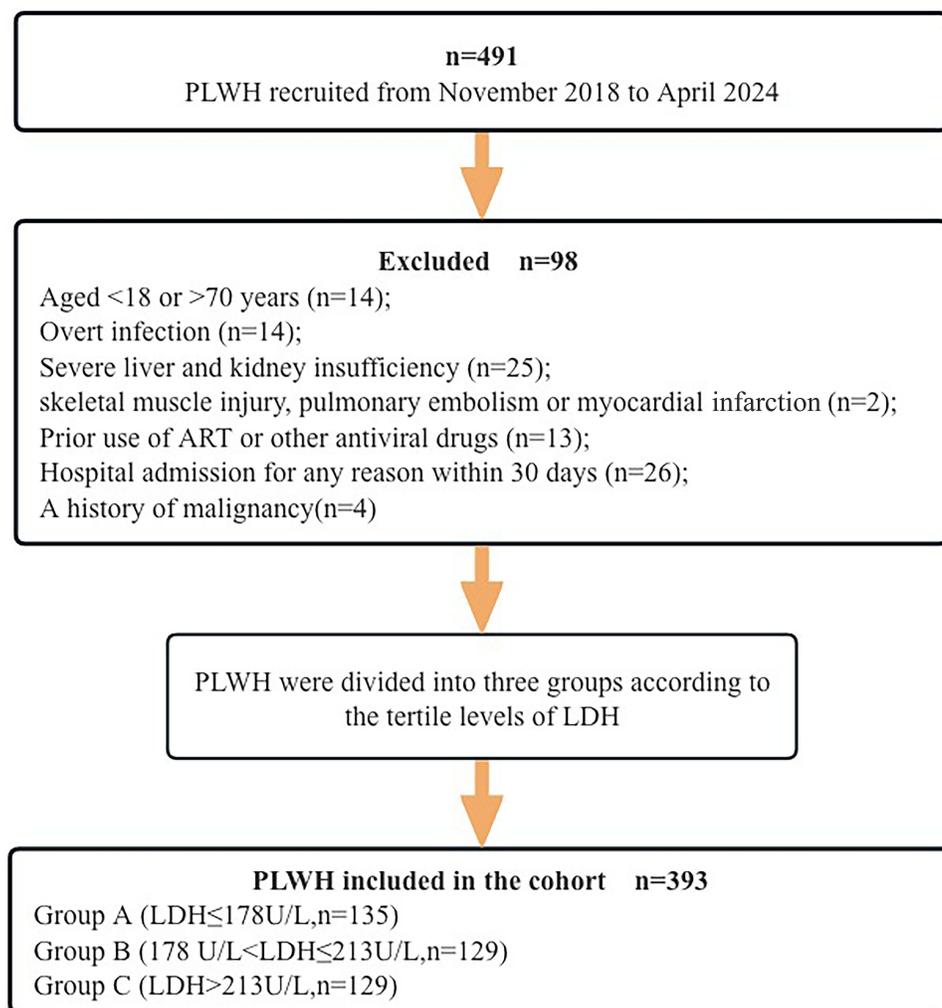


Figure 1 Flow chart of sample size.

+ lamivudine + efavirenz, tenofovir disoproxil fumarate + lamivudine + efavirenz, tenofovir disoproxil fumarate + lamivudine + abacavir, tenofovir disoproxil fumarate + lamivudine + nevirapine, zidovudine + lamivudine + lopinavir/ritonavir, tenofovir alafenamide fumarate + lamivudine + lopinavir/ritonavir, and tenofovir disoproxil fumarate + lamivudine + lopinavir/ritonavir.

Endpoint

The study endpoint was defined as successful viral suppression, with follow-up time measured from ART initiation to either the first occurrence of viral suppression or ART replacement due to failure in achieving suppression. HIV viral load was assessed at baseline, one month after treatment initiation, every three months thereafter, and during clinical disease progression. As the sole designated hospital for HIV in the region, our institution managed the diagnosis, treatment, and follow-up of all HIV patients in this area. Additionally, medical case managers were specifically responsible for follow-up activities. This management approach ensured the highest level of stability in follow-up care. Definitions of viral suppression varied globally, largely due to differences in healthcare infrastructure, resources, and ART availability. Based on our laboratory testing conditions, viral suppression was defined as HIV plasma RNA levels < 200 copies/mL throughout overall survival, indicating that PLWH cannot transmit HIV to their sexual partners.³ To obtain the required endpoints, we conducted a comprehensive review of the hospital database. PLWH were categorized into a successful viral suppression group or a failed viral suppression group based on the different endpoint events.

Ethics Approval and Consent to Participate

The Institutional Review Board of Ningbo Yinzhou No.2 hospital approved this study (2023–050), and written informed consent was obtained from all the participants. The preservation of data confidentiality was rigorously maintained through the complete exclusion of any personal identifiers. Furthermore, neither the raw data nor the derived data were disseminated to any third party. This study complied with the Declaration of Helsinki.

Statistical Analysis

IBM SPSS Statistics version 24.0 for Mac was used for statistical analysis. No formal sample size estimation was performed due to the lack of published data on similar research. All p-values were two-tailed, with significance set at $p < 0.05$. Categorical variables were described as numbers and frequencies (%), and continuous variables as medians (IQR). χ^2 -tests or Fisher's exact test were used to compare qualitative variables, and the Mann–Whitney *U*-test or Kruskal–Wallis *H*-test to was applied to compare continuous variables, as appropriate. Kaplan–Meier survival analysis was conducted to generate survival curves, with group comparisons performed using the Log rank test. HIV viral load was normalized by log₁₀ transformation. Univariable and multivariable Cox proportional hazards regression models were used to identify potential risk factors associated with the endpoints, with hazard ratios and 95% confidence intervals reported.

Results

Baseline Characteristics

In this study, we analyzed data from 393 eligible PLWH received ART, with a median age of 33 (25–49) years old, comprising 350 males and 43 females (Table 1). Of these, 180 (45.8%) PLWH were transmitted through MSM, 181 (46.1%) through heterosexual transmission, and 32 (8.1%) did not disclose their transmission category due to privacy protection. The most common ART regimen was non- INSTI-based MTRs (70.2%), followed by INSTI-based STRs (23.9%), INSTI-based MTRs (4.6%), and non- INSTI-based STRs (1.3%). As shown in Figure S1, no significant differences were observed in the number of censoring events across LDH tertiles (375 vs 397 vs 413, $P > 0.05$). Although repeated measurements of HIV viral load increased with LDH tertiles, the differences were not statistically significant (1.9 [2.98, 4.42] vs 2.08 [2.98, 4.61] vs 2.11 [2.94, 4.62], $P > 0.05$).

PLWH were categorized based on tertile LDH levels in different outcomes (Table 1). In the successful viral suppression group, statistical analysis showed that LDH levels were significantly associated with age, CD4 count, log HIV viral load, and time to first viral suppression ($P < 0.05$). However, no significant differences were found in gender, transmission category, ART regimen, CD8 count, WBC, LY, HGB, or PLT ($P > 0.05$). In the failed viral suppression group, no significant differences were observed in any variable, probably due to the small sample size. Additionally, apart from the transmission category ($P < 0.05$), no other variables showed statistical significance between the successful and failed viral suppression groups ($P > 0.05$).

Viral Suppression Rate

After a median time to first viral load suppressed of 84 (28–141.5) days, the overall viral suppression rate was 94.1%. Although viral suppression rates varied among the three groups, no statistically significant differences were observed due to the uniformly high suppression rates in PLWH (Figure 2A) (131/135 vs 120/129 vs 119/129, $P = 0.187$). However, the time to first viral load suppressed differed significantly among the three groups (Figure 2B). Compared to the low LDH tertile, the middle and high LDH tertiles exhibited longer times to first viral load suppressed (38 [28, 91] vs 84 [29, 154] vs 88 [30, 175] days, respectively, $P < 0.001$).

Kaplan-Meier Analysis

Kaplan-Meier survival analysis was performed to compare viral suppression across the three LDH tertiles and different ART regimens. As shown in Figure 3A, viral suppression was significantly lower in the middle and high LDH tertiles compared to the low LDH tertile (Log rank test, $P < 0.001$). As shown in Figure 3B, INSTI-based STRs demonstrated the

Table 1 Baseline Characteristics of PLWH According to LDH Tertiles in Different Outcomes

	Successful Viral Suppression Group				Failed Viral Suppression Group			
	Overall (n=370)	Group A (n=131)	Group B (n=120)	Group C (n=119)	Overall (n=23)	Group A (n=4)	Group B (n=9)	Group C (n=10)
Age (years, IQR)	33(26, 49)	30(25, 41) ^a	30(25, 46)	43(29, 53)	25(22, 52)	25(23, 45)	25(21, 38)	37(24, 60)
Gender (n, %)								
Male	329(88.9)	116(88.5)	107(89.2)	106(89.1)	21(91.3)	4(100.0)	8(88.9)	9(90.0)
Female	41(11.1)	15(11.5)	13(10.8)	13(10.9)	2(8.7)	0(0.0)	1(11.1)	1(10.0)
Transmission category (n, %)								
MSM	169(45.7) ^b	57(43.5)	60(50.0)	52(43.7)	11(47.8)	1(25.0)	5(55.6)	5(50.0)
Heterosexual	175(47.3)	63(48.1)	53(44.2)	59(49.6)	6(26.1)	1(25.0)	2(22.2)	3(30.0)
Unknown	26(7.0)	11(8.4)	7(5.8)	8(6.7)	6(26.1)	2(50.0)	2(22.2)	2(20.0)
ART regimen (n, %)								
Non-INSTI-based MTRs	256(69.2)	89(67.9)	89(74.2)	78(65.5)	20(87.0)	3(75.0)	8(88.9)	9(90.0)
Non-INSTI-based STRs	5(1.4)	1(0.8)	2(1.7)	2(1.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
INSTI-based MTRs	18(4.9)	3(2.3)	5(4.2)	10(8.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
INSTI-based STRs	91(24.6)	38(29.0)	24(20.0)	29(24.4)	3(13.0)	1(25.0)	1(11.1)	1(10.0)
CD4 count (cells/uL, IQR)	253.0(164.8, 348.3)	263.0(170.5, 365.0) ^a	258.0(195.8, 364.8)	231.0(121.0, 325.0)	217.0(165.0, 325.0)	252.0(151.8, 443.8)	219.0(168.5, 327.0)	207.0(146.8, 274.0)
CD8 count (cells/uL, IQR)	654.5(482.0, 931.3)	624.0(471.5, 869.5)	650.5(486.0, 935.8)	719.0(480.0, 1143.0)	794.0(551.0, 1235.0)	859.5(572.5, 1256.8)	792.0(568.5, 1245.5)	824.5(529.3, 1169.8)
HIV viral load (log copies/mL, IQR)	4.8(4.2, 5.4)	4.5(4.0, 5.1) ^a	4.9(4.4, 5.5)	4.9(4.4, 5.4)	5.1(4.7, 5.6)	5.1(3.7, 5.6)	5.1(4.6, 5.3)	5.4(4.6, 6.3)
WBC(10 ⁹ /L, IQR)	5.0(4.1, 6.2)	4.9(3.9, 6.0)	4.9(4.1, 5.9)	5.3(4.4, 6.4)	5.2(4.5, 9.0)	5.5(4.5, 5.7)	4.9(4.3, 6.3)	5.6(3.8, 6.3)
LY(10 ⁹ /L, IQR)	1.5(1.1, 1.9)	1.4(1.1, 1.8)	1.5(1.1, 1.9)	1.6(1.1, 2.1)	1.6(1.3, 2.1)	1.7(1.2, 2.1)	1.6(1.2, 2.1)	1.4(1.2, 1.9)
HGB(10 ⁹ /L, IQR)	148.0(138.3, 157.0)	148.0(139.0, 156.0)	149.0(141.0, 159.0)	145.5(131.0, 156.0)	147.5(134.8, 157.8)	158.5(154.8, 166.0)	148.0(139.0, 157.0)	135.0(123.5, 154.0)
PLT(10 ⁹ /L, IQR)	212.0(174.0, 248.0)	214.0(173.0, 243.8)	216.5(182.0, 256.8)	201.5(170.3, 240.8)	219.5(154.3, 245.3)	191.5(116.8, 275.3)	181.0(150.0, 227.5)	224.0(174.0, 283.5)
Time to first viral load suppressed (days, IQR)	81(28, 134)	38(28, 91) ^a	84(28, 142)	88(28, 175)	87(50, 178)	65(32, 232)	94(58, 175)	91(63, 202)

Notes: Group A (LDH≤178U/L); Group B (178 U/L < LDH≤213U/L); Group C (LDH>213U/L); ^aP < 0.05, Group A vs Group B vs Group C; ^bP < 0.05, successful viral suppression group vs failed viral suppression group. We used χ^2 -tests or Fischer's exact test to compare qualitative variables, and the Mann-Whitney U-test or Kruskal-Wallis H-test to compare continuous variables.

Abbreviations: LDH, lactate dehydrogenase; MSM, men who have sex with men; ART, antiretroviral therapy; INSTI, integrase strand inhibitor; MTRs, multiple-tablet regimens; STRs, single-tablet regimens; WBC, white blood cell; LY, lymphocyte; HGB, hemoglobin; PLT, platelet.

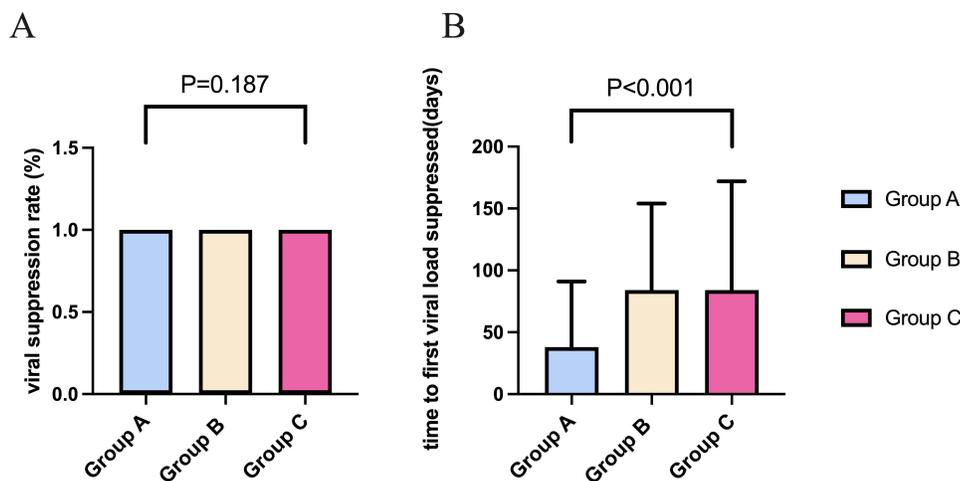


Figure 2 Viral suppression rate(A) and time to first viral load suppressed(B) in different LDH tertiles in PLWH. **Notes:** Group A (LDH≤178U/L); Group B (178 U/L < LDH≤213U/L); Group C (LDH>213U/L).

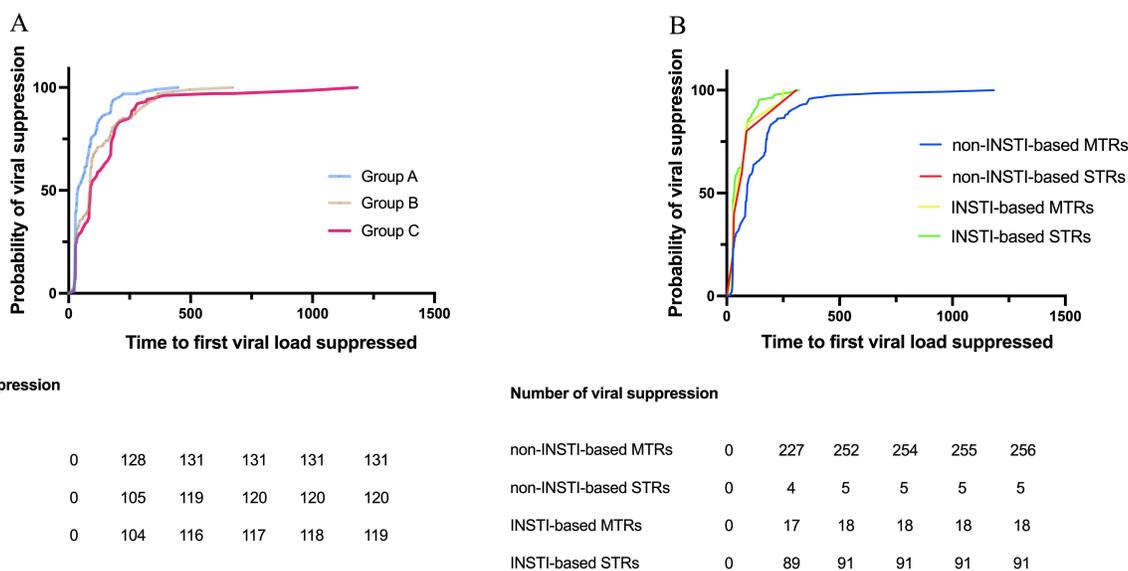


Figure 3 The cumulative rate of viral suppression in different LDH tertiles (A) and ART regimens (B) in PLWH. **Notes:** Group A (LDH≤178U/L); Group B (178 U/L<LDH≤213U/L); Group C (LDH>213U/L).

best prognosis for viral suppression compared to non-INSTI-based MTRs, followed by INSTI-based MTRs and non-INSTI-based STRs (Log rank test, $P < 0.001$).

Prognostic Analyses of Endpoint

Cox regression models were constructed to evaluate the endpoint of viral suppression after ART (Table 2). According to univariate regression analysis, the ART regimen, log HIV viral load, and LDH tertile were identified as significant predictors of viral suppression. Compared to the low LDH tertile, the middle (HR = 0.635, CI = 0.494–0.816, $P < 0.001$) and high LDH tertiles (HR = 0.555, CI = 0.431–0.716, $P < 0.001$) were significant predictors of viral suppression. Multivariate Cox regression analysis further confirmed that LDH tertile remained a significant predictor of viral suppression (HR = 0.714, 95% CI = 0.553–0.922, $P = 0.010$ for middle vs low tertile, and HR = 0.575, 95% CI = 0.443–0.747, $P < 0.001$ for high vs low tertile), along with the ART regimen and log HIV viral load.

Table 2 Cox Regression Analysis for Viral Suppression of PLWH on ART

Variables	Univariate Analysis	p value	Multivariate Analysis	p value
	HR (95% CI)		HR (95% CI)	
Age	0.998(0.991–1.005)	0.642		
Gender	1.285(0.928–1.780)	0.132		
Transmission category				
MSM	1.241(0.821–1.878)	0.306		
Heterosexual	1.367(0.905–2.065)	0.137		
Unknown	REF	–		–
ART regimen				
Non-INSTI-based MTRs	REF	–	REF	–
Non-INSTI-based STRs	1.281(0.527–3.110)	0.584	1.538(0.631–3.752)	0.344
INSTI-based MTRs	1.925(1.190–3.115)	0.008	2.481(1.516–4.059)	<0.001
INSTI-based STRs	2.128(1.658–2.730)	<0.001	2.022(1.574–2.597)	<0.001
CD4 count	1.001(1.000–1.001)	0.148		
CD8 count	1.000(1.000–1.000)	0.177		
Log HIV viral load	0.735(0.658–0.821)	<0.001	0.750(0.671–0.839)	<0.001
WBC	0.980(0.921–1.042)	0.520		
LY	0.960(0.821–1.121)	0.603		
HGB	1.000(0.993–1.007)	0.983		
PLT	1.000(0.998–1.002)	0.793		
LDH				
Low LDH tertile	REF	–	REF	–
Middle LDH tertile	0.635(0.494–0.816)	<0.001	0.714(0.553–0.922)	0.010
High LDH tertile	0.555(0.431–0.716)	<0.001	0.575(0.443–0.747)	<0.001

Abbreviations: MSM, men who have sex with men; ART, antiretroviral therapy; INSTI, integrase strand inhibitor; MTRs, multiple-tablet regimens; STRs, single-tablet regimens; WBC, white blood cell; LY, lymphocyte; HGB, hemoglobin; PLT, platelet; LDH, lactate dehydrogenase.

Discussion

According to the UNAIDS report, 71% (60–83%) of PLWH worldwide achieved viral suppression in 2022 (<https://www.unaids.org/en/resources/fact-sheet>). In our study, the viral suppression rate among PLWH was 94.1%. Our results exceeded the global average, while a gap remains in achieving the “95–95–95” target set by UNAIDS to combat the AIDS epidemic. Maintaining viral suppression remains a significant challenge in efforts to end the HIV epidemic. Variability in the duration of viral suppression is observed among individuals receiving the same treatment regimen. Therefore, identifying improved prognostic indicators is of great clinical significance in the current environment. In this study, we enrolled 393 ART-naïve patients in a retrospective cohort and investigated the association between LDH levels, time to viral suppressed and viral suppression outcomes using Cox regression analysis. Although no difference was observed in the viral suppression rate, LDH levels proved to be a reliable predictor of time to first viral load suppressed in PLWH, which was independent of ART regimen, baseline viral load, or other indicators.

In our study, INSTI-based STRs showed the highest efficacy in achieving viral suppression compared with other ART regimens. STRs, which combine several antiretroviral drugs into a single dose, offer a simplified dosing schedule. In contrast, MTRs often require a more complex treatment schedule but may offer greater flexibility in drug selection. Several studies have reported the association between STRs vs MTRs use and viral suppression, but the results are somewhat controversial. Five studies reported that the use of STRs positively affects viral suppression.^{17–21} Conversely, two studies found no significant relationship between STRs use and viral suppression.^{22,23} The positive effect of STRs may be attributed to improved adherence. A systematic review illustrated that PLWH show greater adherence to STRs than to MTRs.²⁴ The outcomes indicated that augmented adherence substantially heightens the probability of achieving viral suppression in observational contexts. INSTIs have been shown to achieve faster viral suppression compared to other antiretroviral drugs, such as PIs and NNRTIs.^{25,26} Studies have also highlighted that INSTI-based regimens are

highly effective across diverse populations, including pregnant individuals,²⁷ those with drug-resistant HIV strains and suboptimal adherence.²⁸ In our study, the use of STRs and INSTI can lead to faster viral suppression. When choosing between these regimens, factors such as patient preferences, potential drug interactions, and long-term treatment adherence should be considered, all of which contribute to the overall success of viral suppression in PLWH.

Elevated LDH levels were frequently observed in HIV-related complications, such as *Pneumocystis pneumonia* (PCP), lymphoma, and histoplasmosis, and are associated with poor prognosis. Among PLWH with non-Hodgkin lymphoma, elevated LDH levels strongly predicted an unfavorable prognosis following chemotherapy.²⁹ Wu et al developed a predictive model for assessing in-hospital mortality risk among PLWH with PCP in China. They identified LDH > 350 U/L as an integral component, indicating that elevated LDH levels correlate with poor prognosis in PLWH with PCP.³⁰ Additionally, LDH levels served as a predictor of mortality in PLWH with disseminated histoplasmosis.³¹ Similarly, case reports have shown that LDH levels are typically elevated during the acute phase of HIV infection, often accompanied by increased viral load.^{32–35} In our study, the differences in viral suppression rates across different LDH tertiles were statistically insignificant, indicating effective viral suppression in all PLWH. However, times to first viral load suppressed varied significantly, with lower LDH tertiles indicating faster viral suppression and better prognosis.

The elevation of serum LDH levels in PLWH occur through multiple mechanisms. In the context of opportunistic infections, the elevation of serum LDH levels are attributed to pathogen invasion, which causes direct tissue damage and releases LDH into the bloodstream.³⁶ Although our study excluded patients with opportunistic infections, elevated LDH levels were observed, likely through a mechanism distinct from that of opportunistic infections. This mechanism may be mediated by glycolysis. LDH functions as a key enzyme in the glycolytic pathway, responsible for converting pyruvate to lactate.³⁷ An enhanced glycolytic pathway can lead to elevated LDH levels. Since viruses lack their own metabolic pathways, they infect quiescent cells and induce metabolic activation to support genome replication and virion packaging. During infection, viral proteins interact with various cellular glycolytic enzymes, significantly increasing the glycolytic rate of the host cell.³⁸ HIV enhances host cell glycolysis, raising LDH levels. The mTOR pathway, a central regulator of cellular processes, plays a crucial role in HIV's regulation of glycolytic enzyme expression through its downstream effectors.³⁹ In summary, inhibiting the glycolytic pathway could be a therapeutic strategy against viral infections, with targeted LDH activity inhibition offering potential management for PLWH.

There were some limitations in this study. First, due to laboratory constraints, the minimum detectable HIV viral load in our study was 200 copies/mL, which was in line with WHO requirements to the best extent possible.⁴⁰ However, a more precise lower detection limit would improve the predictive accuracy for viral suppression in PLWH. Second, this cohort study was conducted on a Chinese population, so caution is necessary when extrapolating the findings to populations with diverse genetic backgrounds, considering potential variations and unique genetic factors. Additionally, this study did not explore other factors related to viral suppression, such as adherence and the emergence of drug resistance. Therefore, further prospective studies that incorporate treatment adherence and drug resistance are required to conclusively determine the predictive value of LDH in viral suppression.

Conclusion

Our study demonstrates that LDH levels serve as a predictor of the timing of viral suppression in PLWH. A comprehensive evaluation of LDH levels is beneficial in establishing risk stratification in the context of rapid ART initiation.

Data Sharing Statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Acknowledgments

We thank all of the participants of the study for their participation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by Medical Health Science and Technology Project of Zhejiang Province (Grant No. 2024KY1608).

Disclosure

The author(s) report no conflicts of interest in this work.

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