A Real-world Evidence-based Management of HIV by Differential Duration HAART Treatment and its Association with Incidence of Oral Lesions

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Abstract: Background: The efficacy of highly active antiretroviral therapy (HAART) can be estimated by the immunological response and the incidence of opportunistic infections.

Objective: This study aimed at evaluating the effectiveness of different durations of HAART in terms of immunological response markers (CD4 count and CD4/CD8 ratio) along with disease progression markers (incidence of oral lesions) in Chinese patients with HIV.

Methods: This single-center, retrospective, and real-world study included patients with HIV, grouped into a treatment group and treatment-naïve group, of which the former was further divided into 6, 12, and 18 months based on the treatment duration. The CD4 and CD8 cell counts were analyzed by the FACSCalibur flow cytometry. Kruskal-Wallis test was applied to determine the outcome of different duration of HAART. Oral examination was carried out according to the WHO type IV examination.

Results: In 246 patients with HIV, CD4 counts increased significantly post-HAART compared to pre-HAART in all three treatment groups (P<.001), while CD8 count decreased significantly (P<.05) in all three treated groups. A significant association of HAART with the CD4/CD8 ratio was observed (P<.001). A significant increase in CD4 count was observed between 12-months and 18-months treatment groups (P<.05). The occurrence of oral lesions reduced significantly in the treatment group.

Conclusion: We observed a better response to the HAART regimen with 18-months of duration than 12-months and 6-months therapies and reduction in oral lesions.

Keywords: Highly active antiretroviral therapy, duration of HAART therapy, HIV, real-world study, CD4 and CD8 count, immunological response.

1. INTRODUCTION

Human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS), which attacks the body's immune system [1-4]. According to the World Health Organization (WHO) 2018 report, around 37.9 million people were reported to live with HIV/AIDS worldwide [5]. In 2018, China reported a 14 % increase in HIV infections [6]. CD4+ T lymphocytes are the main targets of HIV, which leads to the development of opportunistic infections, such as oral lesions [7-12]. Likewise, CD8+ T cells also play a crucial role in controlling HIV replication during the early phase of infection [13-16].

Antiretroviral therapy (ART) helps in reducing morbidity and mortality associated with HIV [17-21]. However, ART only suppresses viral replication but does not eliminate the virus completely [22-25]. According to the 2016 WHO guidelines, regardless of CD4 count, treatment should be provided for all those living with HIV/AIDS [26]. Adhering to these guidelines, China committed to providing antiretroviral treatment for all people living with HIV, which increased coverage from 67 % in 2015 to 80 % in 2017 [27]. A study published in 2017 concluded that overall mortality was decreased by 63 % when ART was given immediately to HIV patients with low CD4 counts, highlighting the benefit of early treatment for improved health outcomes [19]. The Chinese government provided seven free antiretroviral drugs, among which the most effective drug combination was nevirapine (NVP)-containing regimens because of their convenience and tolerability [28]. Since lamivudine (3TC) + stavudine (d4T) + NVP and 3TC + zidovudine (AZT) + NVP...
showed similar virologic efficacy in Chinese patients compared to western countries [29], the use of 3TC + d4T and 3TC + AZT as the nucleoside analog combination in NVP-based antiretroviral therapy is considered as an effective regimen [28].

Studies have demonstrated that the prevalence of drug-resistant HIV variants in treatment-naïve individuals is around 7.1% on average [30]. Drug-resistant HIV-1 strains in treatment-naïve individuals have significant implications for the successful management of ART as it restricts therapy options and increases the risk of treatment failure; thus, the first-line therapy has to be adjusted accordingly [30, 31].

The efficacy of highly active antiretroviral therapy (HAART) is estimated by the immunological response and the incidence of opportunistic infections [32-35]. The resultant increase in absolute CD4+ T cells and a decrease in HIV viral load are biomarkers for immune suppression and response to treatment [36-39]. In addition, the overall immune dysfunction is more precisely described by the CD4/CD8 ratio [19, 40]. Studies have also reported that along with CD4+ cells, the CD4/CD8 ratio serves as a marker in the determination of the efficacy of HAART therapy [41-44]. HAART therapy has also been reported to be associated with a transient and temporal increase in CD-4 cell count for a differential duration based on predisposing genetic factors. In most of the patients, the improvement in CD-4 counts is observed for the first 3 to 6 months after initiation of HAART treatment [45]. Multiple studies have reported the short- and long-term association of HAART with immunological markers and specific opportunistic infections in a different patient population. However, oral lesions, a most common opportunistic infection, have seldom been reported in association with HAART therapy and the duration of HAART therapy [46-48]. The observance of oral lesions in multiple stages of HIV disease progression suggests that oral lesions could be used as the optimal indicator of opportunistic infections to assess the effectiveness of HAART [49, 50]. Besides their diagnostic potential, they can also serve as clinical correlates with CD4+ and CD8+ cell counts [7, 51-53]. This study aimed at evaluating the immunological effects of HAART after different durations of HAART therapy and their association with the incidence of oral lesions in Chinese HIV-positive patients.

2. METHODS

2.1. Study Design and Duration

This retrospective, cohort, and real-world study included the data of HIV-positive patients attending the Kunming Third People’s Hospital Infection Division and Kunming AIDS Clinical Diagnosis and Treatment Center from December 2017 to December 2019. Data were extracted from the respective medical records. The study protocol was approved by the Medical Ethics Committee of Kunming Third People’s Hospital (KG115-2003-45Z). All procedures followed ethical standards, and the study was conducted in accordance with the 1964 declaration of Helsinki and its amendments, good clinical practice guidelines, and applicable local laws and regulations. Since only anonymized patient data were used, the study was exempted from patient consent.

2.2. Inclusion Criteria

Adult patients diagnosed with HIV were included in the study. HIV was confirmed by laboratory examination as per the diagnostic criteria for HIV infection as laid out by Chinese standards (NCAIDS 2001) for all the individuals before inclusion into the study.

2.3. Study Outcomes

The primary objective of the study was to determine the effectiveness of different duration of HAART regimens by analyzing the temporal changes in CD4+ T-cell count and CD4/CD8 ratio. The secondary outcome was to assess the prevalence of oral lesions after the different duration of HAART regimens and compare the incidence of oral lesions in treatment-naïve HIV patients and patients undergoing HAART therapy as an indicator of opportunistic infections in both groups of patients.

2.4. T-cell Subset Count

T-cell subset count analysis was performed using the FACSCalibur flow cytometer [30] of Becton Dickinson (BD) Company with the reagent provided by BD Company via single-platform technology. During the study period, CD4 T lymphocyte counts were estimated at pretreatment and 6, 12, and 18 months of post-treatment. A total of 50 μl of whole blood was stained with 10 μl of Multitest reagent in Trucount tubes for 15 min (all from BD Biosciences). Once the red blood cells were lysed by fluorescence-activated cell sorting lysing solution (BD Biosciences), sample data were acquired using Cell Quest-Pro software (BD Biosciences).

2.5. Oral Health Assessment

Four senior dentists were trained to reduce the inter- and intra-examiner variability using the WHO standard criteria. A type IV oral examination was carried out with mouth mirrors, probes, and tongue depressors in natural illumination. All the suspected lesions were photographed, and the pathological diagnosis was made as far as possible.

The criteria used for the classification and diagnosis of oral manifestations of AIDS (EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus, 1993) [54], which divides oral manifestations into three categories: (1) oral manifestations closely related to AIDS infection; (2) oral manifestations related to AIDS infection; (3) oral lesions visible in AIDS infection that includes 32 representations, was used in this study for the oral lesion diagnosis. Furthermore, the diagnosis of oral damage is mainly based on clinical manifestations, and biopsy is performed only when necessary [54, 55].
Table 1. Patient epidemiology.

| Variable                        | Patients on HAART (n = 132) | Treatment-naive Patients (n = 114) |
|--------------------------------|-----------------------------|-----------------------------------|
| Age (years), mean (SD)         | -                           | 37.68 (14.28)                     | 39.82 (13.33)                     |
| Gender, n (%)                  | Male                        | 72 (54.5 %)                       | 78 (68.4 %)                       |
|                                | Female                      | 60 (45.5 %)                       | 36 (31.6 %)                       |
| Marital status, n (%)          | Unmarried                   | 39 (29.5 %)                       | 31 (27.2 %)                       |
|                                | Married                     | 78 (59.1 %)                       | 67 (58.8 %)                       |
|                                | Divorced                    | 12 (9.1 %)                        | 15 (13.2 %)                       |
|                                | Widowed                     | 3 (2.3 %)                         | 1 (0.8 %)                         |
| CD4 cell count (cells/mm³), mean (SD) | -                           | 278.87 (168.90)                  | 308.04 (218.74)                  |
| CD8 cell count (cells/mm³), mean (SD) | -                           | 1009.05 (609.07)                 | 977.42 (633.17)                  |
| Route of infection, n (%)      | Drug                        | 17 (12.9 %)                       | 5 (4.4 %)                         |
|                                | Sexual transmission         | 111 (84.1 %)                      | 100 (87.7 %)                      |
|                                | Unknown                     | 4 (3.0 %)                         | 9 (7.9 %)                         |

HAART: Highly active antiretroviral therapy; SD: Standard deviation; CD4: Cluster of differentiation 4; CD8: Cluster of differentiation 8.

2.6. HAART Usage Plan

All antiviral drugs were provided free of charge by the government, and the plan was based on the Guidelines for AIDS Diagnosis and Treatment from “AIDS Group of the Infectious Diseases Branch of the Chinese Medical Association” [56]. HAART was used for 6, 12, and 18 months, which was given in either of these two schemes:

[a] Scheme 1: One non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTIs): efavirenz (EFV) 600 mg, once a day or NVP 200 mg, twice a day + 3TC 300 mg, once a day + AZT 300 mg, twice a day or tenofovir (TDF) 300 mg once daily.

[b] Scheme 2: One protease inhibitor (PI) and two NRTIs: lopinavir/ritonavir (LPV/R) 400 mg/100 mg twice daily + 3TC 300 mg, once a day + AZT 300 mg, twice a day or TDF 300 mg once daily.

2.7. Statistical Analysis

Descriptive variables were expressed as the median and interquartile range (IQR). The effectiveness of different durations of HAART therapy was assessed by using the standard mean difference of the post- and pre-HAART CD4 and CD8 counts. CD4/CD8 ratio was used as a marker of immunological response. The difference of pre- and post-CD4 and CD8 was calculated, and the Kruskal-Wallis test was applied to assess the statistical significance of the observed treatment effect (standard mean difference). The incidence of oral lesions in treatment-naive and HAART-treated patients was compared by the Chi-square test. Univariate logistic regression analysis was used to determine the association between the presence or absence of oral condition and immunological response (CD4/CD8 ratio).

3. RESULTS

3.1. Demographic Characteristics

Overall, 246 HIV-positive patients were included in the study, of which 132 patients were on HAART therapy, and 114 were treatment-naive patients. The demographic characteristics of the included patients are given in Table 1. The mean age of patients in the HAART group was 37.68±14.28 years and treatment-naive patients was 39.82±13.33 years. The median age of males and females was 37 (IQR 30-45) and 39 (IQR 28-43) years, respectively, in the HAART group. The gender distribution of patients was almost equal in the HAART group, while the male-female ratio was 2:1 in treatment-naive patients. The treatment group was further divided into three groups based on HAART duration, i.e., 6, 12, and 18 months (n = 42, 45, and 45, respectively).

3.2. Effectiveness of Differential Duration of HAART on CD4 and CD8 Cell Count

The median pre-HAART CD4 count was 310.5 cells/mm³ (IQR, 174.75-453.75), 257 cells/mm³ (IQR, 134.5-371.5), and 275.5 cells/mm³ (IQR 81.45-346.75) in 6, 12, and 18 months HAART treatment groups, respectively. Similarly, the median pre-HAART CD8 count was 922 cells/mm³ (IQR, 641.5-1366.25), 988 cells/mm³ (IQR, 630-1224.25), and 843 cells/mm³ (IQR, 561-1117.25) cells/mm³ among 6, 12, and 18 months HAART treatment groups, respectively. The median post-HAART CD4 count was 448.5 cells/mm³ (IQR 310.85-535.7), 410 cells/mm³ (IQR 216-584.4), and 432 cells/mm³ (IQR 282-581) in 6, 12, and 18 months HAART treatment groups, respectively. The median post-HAART CD8 count in 6, 12, and 18 months HAART treatment groups was 728.5 cells/mm³ (IQR, 530.18-1194.13), 786.7 cells/mm³ (IQR 646.1-1108), and
647 cells/mm$^3$ (523-905), respectively (Table 2). CD4 count improved significantly post-HAART in all three groups ($P<.001$), while a significant reduction in CD8 cells was observed in all the three groups ($P<.05$). There was no significant difference in the CD-4 and CD-8 count change after HAART therapy among the groups.

The ratio of pre-HAART CD4/CD8 was 0.34, 0.31, and 0.34 and the post-HAART CD4/CD8 counts were 0.67, 0.62, and 0.78 among 6, 12-, and 18-months HAART therapy groups, respectively (Table 2). A significant improvement in the CD4/CD8 ratio was observed post-HAART therapy ($P<.001$).

Comparing the difference in CD4 and CD8 counts change after treatment between the three treatment groups, a significant increase in CD4 count was observed from 6-months to 18-months ($P=0.028$). Although there was a reduction in CD8 count from 6-months to 18-months, it was not statistically significant ($P=0.92$). Furthermore, pairwise Mann-Whitney U-tests revealed a significant difference in treatment effect between 12-months vs. 18-months ($P=0.04$).

3.3. Incidence of the oral lesion and its association with duration of HAART

The different types of oral lesions observed were periodontitis, gingivitis, oral candidiasis, aphthous ulcer, and hairy leukoplakia. Of all the lesions, periodontitis was found to have the highest incidence in both treatment groups (48.49 %) and treatment-naïve patients (44.7 %), followed by gingivitis in patients on HAART (37.1 %), whereas hairy leukoplakia in treatment-naïve patients was observed (15.8 %). The aphthous ulcer had the least incidence in both treatment (0.8 %) and treatment-naïve patients (0.9 %) (Table 3).

### Table 2. Descriptive statistics of the study population.

| Variable               | Median Pre-HAART CD4 (IQR) (cells/mm$^3$) | Median Pre-HAART CD8 (IQR) (cells/mm$^3$) | Mean Pre-HAART CD4/CD8 (SD) | Median Post-HAART CD4 (IQR) (cells/mm$^3$) | Median Post-HAART CD8 (IQR) (cells/mm$^3$) | Mean Post-HAART CD4/CD8 (SD) |
|------------------------|------------------------------------------|-------------------------------------------|-----------------------------|-------------------------------------------|-------------------------------------------|-----------------------------|
| Gender                 | Male                                     | 249.5 (114.5-366)                         | 811 (554-1335)              | 0.31 (0.36)                               | 427.85 (227.85-577.22)                   | 736.45 (542.25-1073.15)     |
|                        | Female                                   | 284 (191.75-414)                         | 944.5 (680.25-1143.75)      | 0.35 (0.22)                               | 454.2 (329.25-558.35)                 | 694.15 (533.65-1022.575)    |
| Marital status         | Single                                   | 325.5 (259.25-448.25)                    | 787 (573-1210)              | 0.45 (0.45)                               | 494.65 (365.82-611.57)                | 717.4 (573.4-957.8)         |
|                        | Married                                  | 222 (117.78-351)                         | 914 (566.5-1158)            | 0.27 (0.20)                               | 387.3 (229.35-534.5)                 | 713.7 (524.6-1085.95)       |
|                        | Widowed                                  | 331 (222.5-393)                          | 1103 (937.5-1687)           | 0.30 (0.21)                               | 385.6 (246.75-420.35)                | 678.9 (463.45-1313.25)      |
|                        | Separated/divorced                       | 346 (243.4-436.75)                       | 1168 (927.25-1790)          | 0.31 (0.14)                               | 587 (327.5-749)                     | 1055 (639.4-1227)           |
| Duration of HAART      | 6 months                                 | 310.5 (174.75-453.75)                    | 922 (641.5-1366.25)         | 0.34 (0.20)                               | 448.5 (310.85-535.7)                | 728.5 (530.18-1194.13)      |
|                        | 12 months                                | 257 (134.5-371.5)                        | 988 (630-1224.25)           | 0.31 (0.23)                               | 410 (216-584.4)                     | 786.7 (646.1-1108)          |
|                        | 18 months                                | 275.5 (81.45-346.75)                     | 843 (561-1117.25)           | 0.34 (0.42)                               | 432 (282-581)                      | 647 (523-905)              |

CD4: Cluster of differentiation 4; CD8: Cluster of differentiation 8; HAART: Highly active antiretroviral therapy; IQR: Interquartile range; SD: Standard deviation.

### Table 3. Incidence of oral lesions.

| Oral Manifestations  | Patients on HAART | Treatment-naive Patients (n = 114) |
|----------------------|-------------------|-----------------------------------|
|                      | 6 months (N = 42) | 12 months (N = 45) | 18 months (N = 45) | Overall (n = 132) | n (%) |
|                      |                   | n (%) | n (%) | n (%) | n (%) |
| Periodontitis        | 25 (59.52)        | 19 (42.22) | 21 (46.66) | 64 (48.5 %) | 51 (44.7 %) |
| Gingivitis           | 12 (28.57)        | 18 (40) | 19 (42.22) | 49 (37.1 %) | 14 (12.3 %) |
| Oral candidiasis     | 3 (7.14)          | 3 (6.66) | 3 (6.66) | 9 (6.8 %) | 5 (4.4 %) |
| Aphthous ulcer       | 1 (2.38)          | -     | -     | 1 (0.8 %) | 1 (0.9 %) |
| Hairy leukoplakia    | 2 (4.76)          | 3(6.66) | 2 (4.44) | 7 (5.3 %) | 18 (15.8 %) |

HAART: Highly active antiretroviral therapy.
Table 4. Association between oral lesions (disease progression biomarkers) and various clinical and demographic factors.

| Variable       | OR  | Lower Limit | Upper Limit | P-value |
|----------------|-----|-------------|-------------|---------|
| 6 months       | 1.00| -           | -           | -       |
| 12 months      | 0.779| 0.123       | 4.726       | 0.781   |
| 18 months      | 0.466| 0.077       | 2.411       | 0.372   |
| Pre-CD4        | 0.993| 0.985       | 1.00        | 0.081   |
| Pre-CD8        | 1.001| 1.00        | 1.004       | 0.046   |
| Post-CD4       | 1.005| 1.001       | 1.011       | 0.080   |
| Post-CD8       | 0.997| 0.994       | 0.999       | 0.008   |
| Age            | 1.020| 0.966       | 1.089       | 0.506   |
| Gender         | 1.306| 0.348       | 5.380       | 0.695   |
| Post CD4/CD8   | 0.197| 0.040       | 0.899       | 0.028   |

HAART: Highly active antiretroviral therapy; CD4: Cluster of differentiation 4; CD8: Cluster of differentiation 8; OR: Odds ratio.

Of 126 patients assessed for oral lesion, 88.1% of patients had an incidence of one or more oral lesions. Treatment with HAART significantly reduced ($P$<.001) the incidence of oral lesions compared to treatment-naïve patients. Univariate logistic regression analysis of the occurrence of an oral lesion with CD4 and CD8 counts showed no significant correlation in all treatment duration (6, 12, 18 months) groups, but a significant change was observed with post CD4/CD8 count ($P$=.029; Table 4). No association was observed with different regimens of HAART on oral lesions ($P$=.99).

4. DISCUSSION

HIV infection is characterized by a progressive decrease in the absolute number of circulating CD4 cells and the CD4/CD8 cell ratio [57, 58]. HAART is the main antiretroviral therapy used for treating HIV-infected patients [59]. It increases the number of CD4 cells, reduces the viral load of HIV, and restores the immune function at varying degrees, thus leading to improved quality of life and prolonged lifespan of HIV-infected patients, but does not completely eradicate the disease [57]. Thus, quantitation of CD4 cells is essential in the staging and monitoring of HIV-positive patients [53, 60]. During ART, an increase in CD4 cell counts should be accompanied by a decline in CD8 cell counts to maintain a normal CD4/CD8 cell ratio as an increase in CD8 count indicates treatment failure [61, 62]. In the present study, the efficacy of HAART for different durations was studied in terms of CD4 and CD8 counts, their ratio, and incidence of oral lesions. HIV depletes CD4 cells in peripheral blood and lymphoid tissue, leading to CD8 cell dysfunction. Results of the present study also indicated an increase in CD4 count and a decrease in CD8 count from pretreatment to post-treatment with HAART in all the three groups (6, 12, and 18 months) with a CD4/CD8 ratio below 1, which was in accordance with previous studies, thus validating our findings [61, 63, 64].

The clinical outcome of HIV-positive patients treated with HAART can be better explained by considering both CD4 count and CD4/CD8 ratio rather than CD4 alone as evidence suggested CD4/CD8 ratio as a biomarker and referred to as immunostimulatory marker for non-AIDS morbidity and chronic inflammation [41, 65-68]. In untreated HIV infection, CD8 cell counts increase as CD4+ cell counts decline [62]. In the context of our study, the same was observed in treatment-naïve patients. With the increase in the duration of treatment from 6 to 18 months, CD4 count also increased. This is in accordance with the study by Smith et al., in which an increase in CD4 count was observed from 6 to 24 months [64]. A study by Shyam et al. also reported an increase in CD4 cell count with an increase in the duration of HAART treatment from 3 to 9 months [42]. Also, in the present study, a significant improvement in CD4 cell count was observed in 12 versus 18 months; this may indicate the benefits of a long-term effect of HAART.

According to international research and clinical experience, in the first 1 to 4 years before the onset of AIDS, various oral lesions are manifested, which may be due to decreased CD4 count [69]. Moreover, several studies have reported an inverse correlation between the CD4 cell count and oral lesions prevalence in HIV-positive patients, where a higher incidence of oral lesions was observed with a lower CD4 count (<200/μl) [11]. In the current study, patients in the HAART group had a mean (SD) CD4 cell count (cells/mm$^3$) of 278.87 (168.90), which may be the reason for a higher incidence of oral lesions than in treatment-naïve. Furthermore, we noticed a significant difference in the incidence of oral lesions in patients with or without HAART, which is consistent with a study by Umadevi et al., in which a difference in the incidence of oral lesions was reported with HAART ($P$<.05) [22]. Another study on the analysis of long-term effects of HAART also demonstrated similar results [46]. A study by Rao et al. reported a high incidence of periodontal disease in the patients, followed by hyperpigmentation [70]. The present study also found a high incidence of periodontal disease compared to other lesions. The exception here is that a few studies showed a low CD4 cell count with the prevalence of oral lesions, whereas, in others, a higher CD4 count exacerbated clinical symptoms along with oral lesions [71]. This indicates that although CD4
count is more important in predicting disease progression, it is not consistent with the development or remission of oral lesions [71].

The strength of the present study is using CD4/CD8 ratio along with CD4 count as a marker for evaluating treatment efficacy of different durations of HAART therapy. The results obtained could aid the clinicians in making informed decisions in predicting the progression of HIV-induced opportunistic infections, such as oral lesions and AIDS. Since the current study was conducted in a real-world setting, the results were more varied, unlike the previous studies, which showed a consistent increase in the CD4 and CD8 counts after the HAART regimen [72].

The study's limitation is that it did not consider viral load as a disease progression biomarker, which could have been correlated with CD4 counts for better predictability. An adequate sample size with various drug combinations would have allowed us to better demonstrate the predictability of disease progression. Also, the consideration of pre-HAART duration would have explained the absolute effect of HAART duration and prognosis.

CONCLUSION

This study demonstrated that the HAART regimen with 18 months of duration showed higher efficacy in terms of CD4 count and CD4/CD8 ratio than 12 months and 6 months therapies. Furthermore, the incidence of oral lesions, which was a measure of opportunistic infections, differed significantly in their occurrence among the HAART-administered patients and treatment-naïve patients, proving the efficacy of HAART in improving quality of life and fewer occurrence of oral lesions in Chinese HIV-positive patients. Further studies can consolidate these findings and influence informed decision-making by the prescribers and regulatory bodies involved in the management of HIV.

LIST OF ABBREVIATIONS

| Acronym | Full Form |
|---------|-----------|
| HIV     | Human Immunodeficiency Virus |
| NVP     | Nevirapine |
| AZT     | Zidovudine |
| 3TC     | Lamivudine |
| d4T     | Stavudine |
| HAART   | Highly Active Antiretroviral Therapy |
| ART     | Antiretroviral Therapy |
| AIDS    | Acquired Immunodeficiency Syndrome |
| NNRTI   | Non-nucleoside Reverse Transcriptase Inhibitor |
| NRTI    | Nucleoside Reverse Transcriptase Inhibitor |
| PI      | Protease Inhibitor |
| SD      | Standard Deviation |
| TDF     | Tenofovir |
| EFV     | Efavirenz |

AUTHORS' CONTRIBUTIONS

All authors contributed to data analysis, drafting, and revising the article. They gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Medical Ethics Committee of Kunming Third People’s Hospital (KG115-2003-4SZ).

HUMAN AND ANIMAL RIGHTS

No animals were used in the studies that are the basis of this research. The study on humans was conducted in accordance with the 1964 declaration of Helsinki and its amendments.

CONSENT FOR PUBLICATION

All the participants provided written informed consent for the publication of this research.

STANDARDS OF REPORTING

This paper has been written using STROBE guidelines.

AVAILABILITY OF DATA AND MATERIALS

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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