



Comparison of Viral Loads Between Recent DTG-Based and Previous EFV-Based Regimens in HIV Treatment at the ART Center, Provincial Hospital, MIHS, Janakpur, Madhesh Province, Nepal.

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KEYWORDS

Viral Load, Antiretroviral Therapy, Time Series Forecasting, Regression Analysis, Viral Suppression.

ABSTRACT:

Introduction

Dolutegravir (DTG)-based triple therapy is emerging as the preferred approach for both initiating and maintaining HIV treatment over the Efavirenz (EFV)-based regimen in people living with HIV (PLHIV). Study is based on the viral load suppression during three years of treatment at the ART center.

Methods

This analysis is divided into two groups' namely DTG and EFV-based regimen. There are altogether 224 patients in each regimen before and after the use of Dolutegravir (DTG) regimen for three years from June 1st 2019 to May 30th 2023. Patients virologically assessed for at least 48 weeks in all 3 years (2019, 2020, and 2023). on standard ART. Out of 224 patients, 63 patients all those who had viral load more than 20 copies/ml in 2019 are selected for the analysis.

Results

A total of 63 patients were included in this analysis. Participants were on ART for 48 weeks on EFV-based regimen in 2019 before using DTG based regimen in 2020. In 2019, the mean VL was 11,784.6 copies/ml, and by 2020, the mean VL had decreased to 6,442.0 copies/ml. In 2023, the viral load decreased achieving 0 to 20 copies/ml, although a small subset continued to exhibit persistent viremia. Also, correlation between age and viral load showed a gradual increase in the negative correlation over time, suggesting that younger individuals may experience higher viral loads, mainly due to lower adherence to ART or differences in immune response.

Also, tests showed significant reductions in viral load from 2019 and 2023 with p value less than 0.01 and age groups in 2023 showed no significant impact on viral load. Regression analysis indicated that neither age nor sex significantly influenced viral load levels in 2023.

Conclusions

This study insights into the effectiveness of ART in controlling between 2019 and 2023. The negative correlation between age and viral load highlights the importance of targeted interventions for younger individuals to improve adherence and long-term outcomes. Test shows significant reductions in viral load across the years. However, persistent viremia in a subset of individuals indicates the need for continued monitoring and interventions to address treatment failure and resistance. Further research



should explore the factors contributing to persistent high viral loads, especially in younger populations.

Introduction

Viral load (VL) in HIV patient is a main marker for study the effectiveness of treatment. Antiretroviral therapy (ART) has been found to be significantly effective in viral load suppression. In spite of using the ART treatment, some of the patient still have detectable viral load indicating either failure of treatment or suboptimal adherence to therapy. This study focus on the effectiveness of ART treatment on viral load suppression in patient having viral load more than 20 copies per ml.

Since acquired immune deficiency syndrome (AIDS) was first recognized as a serious communicable disease in 1981, an estimated 35.3 million (32.2–38.8 million) people were living with HIV by 2012 [1]. According to UNAIDS and WHO estimates, this number increased to 38.4 million (33.9–43.8 million) in 2021. A key mechanism in HIV infection is the stable integration of the reverse-transcribed viral genome into the host chromatin. Integrase inhibitors (INIs) are a class of antiretroviral drugs that specifically target the strand transfer reaction during this integration process. They are effective against HIV-1 strains resistant to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors [2]. Unlike other viral enzymes that have human counterparts, integrase enzymes are absent in mammalian cells, making integrase inhibition highly virus-specific and associated with low toxicity [3].

Literatures show that the combination antiretroviral therapy (cART) made revolution in HIV treatment. Combination antiretroviral therapy significantly boosted patient outcomes and changing HIV into a improved chronic condition as well as better life expectancy with respect to that of the general population [4,5]. cART is known to achieve durable virologic suppression (VS), enhance CD4+ cell recovery, reduce morbidity and hospitalization rates, lower mortality, and prevent HIV transmission [4,6–8]. However, adverse effects remain a major concern with ART regimens, often leading to treatment switches, discontinuation, or non-adherence [9].

Research has demonstrated that ART is highly effective in reducing viral load in HIV-positive individuals, with most patients achieving undetectable levels after sustained adherence to treatment [12]. However, treatment failure and resistance remain significant challenges for a small group of individuals [14]. Previous studies have examined the demographic factors, such as age and sex, that influence viral load outcomes. For instance, younger individuals are often at higher risk for treatment failure due to lower adherence to ART [15]. Additionally, viral load monitoring and forecasting models such as ARIMA have been used to predict trends in viral load, enabling proactive treatment adjustments [16].

Dolutegravir (DTG, S/GSK1349572), a newer-generation integrase inhibitor, has gained attention for its superior efficacy and favorable safety profile. It effectively inhibits HIV integrase and viral replication at nanomolar concentrations in cell culture assays [11]. Pharmacokinetic studies have demonstrated that DTG has a long plasma half-life, eliminating the need for a booster. Furthermore, clinical trials have shown significant reductions in plasma HIV-1 viral load across all DTG-based regimens compared to placebo ($p < 0.001$), with a mean decrease of 1.51–2.46 log₁₀ copies/mL [13].

Methods

Whole blood samples collected from each participant were processed to obtain plasma, and HIV viral load was measured using real-time PCR. Viral suppression was defined as having a viral load of <50 copies/mL, in accordance with WHO guidelines. Here 0 is supposed for viral load less than 20. Descriptive statistics, paired t-tests, chi-square tests were used to check association between sex, age, and virological suppression. All statistical analyses were performed using R software [17].

Trend of viral load from 2019 to 2023

Study of the viral load is carried out for those patients whose viral load was more than 20 in 2019. Study shows



significant decline in viral load over time indicating the effectiveness of the treatment.

Table 1 contains viral load summary for three years.

Table1: Summary statistics of viral load

| Viral load | Minimum | 1st Q | Median | Mean | 3rd Qu | St. Dev. | Maximum |
|------------|---------|-------|--------|---------|--------|----------|-----------|
| 2019 | 21.00 | 40.50 | 105.50 | 11784.6 | 3610.0 | 31625.25 | 168249.00 |
| 2020 | 0.00 | 0.00 | 0.00 | 6442.0 | 77.50 | 19225.36 | 107880.00 |
| 2023 | 0.00 | 0.00 | 0.00 | 858.2 | 0.00 | 4962.65 | 35700.00 |

In 2019, the median VL was 105 copies/ml, with a high mean VL of 11,784.6 copies/ml, suggesting the presence of individuals with extremely high viral replication. During 2020, the median VL declined to 0, whereas more than 50% of patient had unnoticeable VLs, although some of patient had detectable viral load (max: 107,880 copies/ml). Furthermore, viral load suppression was sustained in the majority in 2023 in most individual indicating effectiveness of ART therapy. Decline in SD over the time indicates more individual achieved consistent viral suppression. Also, few people still exhibited high viral loads in 2023, indicating the need for targeted interventions for those experiencing treatment failure.

Study shows increasing negative correlation over time which indicates that younger persons may be experiencing elevated viral loads, especially due to lower treatment adherence, immune response difference, or social/behavioral factors. Older persons have better adherence to treatment protocols, leading to lower VLs. This indicates better target for younger people.

Welch Two Sample t-test

Welch Two Sample t value is 1.41 with p-value = 0.1658. There was no significant difference in viral load between males and females in 2019 (p = 0.1658). Although males had a higher mean viral load (16,227.17 vs. 6,082.50),

the wide confidence interval and high standard deviation suggest substantial variability in the data. We have also analyzed the impact of age on viral load for 2023 with resulting p value 0.60 for 4 degrees of freedom concluding that age does not have a significant impact on viral load of 2023.

Linear regression

It suggests that neither age nor sex have a statistically significant effect on the viral load in 2023. Also, R-squared value is low indicating that the predictors in the model do not explain much of the variation in viral load which suggest that other factors not included in the model may better explain the variation in viral load. Also, it is seen that Fisher's Exact Test yielded a p-value of 1 suggesting that there is no significant association between sex and viral load levels for 2023.

Table 2 represents the frequency of viral load (VL) measurements in three different years (2019, 2020, and 2023) across three viral load categories'

Table 2: Viral loads in different groups

| Viral load | Less than 50 | 50-1000 | ≥ 1000 |
|------------|--------------|---------|--------|
| 2019 | 18 | 25 | 20 |
| 2020 | 46 | 4 | 13 |
| 2023 | 55 | 6 | 2 |

Above data shows a notable decline in higher viral loads from 2019 to 2023. This trend may reflect improvements in treatment or management strategies for the population under study. The shift towards smaller viral loads indicates the effectiveness of ongoing interventions maintaining viral load threshold of 1000.

The Chi-squared test for viral load frequencies between 2020 and 2023 with Chi-squared statistic= 9.2686 and p-value = 0.0097 showed a significant result indicating that the distribution of viral load differs significantly between these two years. Furthermore, observed frequencies suggest that viral loads were more concentrated in the interval 0-50 in 2023 with respect to 2020. Also, The Chi-squared test for viral load frequencies between 2019 and 2023 with Chi-squared statistic = 57.247 and p-value = 3.706e-13 suggests an even stronger significant result.



This indicates a very significant change in the distribution of viral load categories between these two years. The data suggests that in 2023, there were far more individuals with lower viral loads (0-50), indicating better viral load control compared to 2019. Table 3 shows the viral load sex wise

Table 3: Viral load sex wise

| Viral Load | 2019 | | | 2020 | | | 2023 | | |
|------------|--------|------|-------|--------|------|-------|--------|------|-------|
| | Female | Male | Trans | Female | Male | Trans | Female | Male | Trans |
| 0-50 | 7 | 11 | 0 | 21 | 24 | 1 | 24 | 30 | 1 |
| 50-1000 | 11 | 13 | 1 | 0 | 4 | 0 | 1 | 5 | 0 |
| ≥ 1000 | 8 | 12 | 0 | 5 | 8 | 8 | 1 | 1 | 0 |

Paired t-test Results

The paired t-test between viral load in 2019 and 2020 showed a mean difference of 5342.54, with a p-value of 0.1247 indicating that there is no statistically significant difference in viral load between these two years. Similarly, paired t-test for viral load in 2020 and 2023 revealed a mean difference of 5583.87, with a p-value of 0.03123 indicating a statistically significant decrease in viral load from 2020 to 2023.

A significant difference was also found between viral load in 2019 and 2023. The mean difference is of 10,926.41 with a p-value of 0.009194 suggesting a significant reduction in viral load over this period. Also, 95% confidence interval for the mean difference is 2803.78 to 19,049.04 which supports this finding.

We have also performed Wilcoxon signed-rank test with p-values: 2019 against 2020 having p-value 0.0004165, 2020 vs. 2023 having p-value 0.02176 and 2019 against 2023 having p-value 0 indicating significant differences in viral load across the years. Specifically, viral load differs significantly between all pairs of years,

suggesting notable changes in viral load over this period. These findings suggest the need for further investigation into the factors contributing to these changes, especially given the statistical significance of the results.

The Kruskal-Wallis test also reveals a highly significant difference in viral load for 2019, 2020, and 2023. The p-value is nearly zero indicating that the viral loads differ significantly between the years, suggesting that there are significant temporal changes in viral load, ensuring further exploration of potential factors driving these changes.

The linear mixed model suggests a significant reduction in viral load from 2019 to 2023. The viral load in 2023 is clearly lower compared to 2019 while the change from 2019 to 2020 is not statistically significant indicating that viral load may have decreased significantly by 2023, may be due to improved treatment as well as disease management strategies. Variability between subjects is accounted for, showing that individual differences contribute to the overall variability in viral load.

The model also accounts for individual subject variability, with considerable differences observed between subjects. The residual variance indicates that there is still unexplained variability in viral load after accounting for the fixed effects of year.

Ethical

Approval

This study did not require ethical approval as it involved analysis of anonymized secondary data already collected as part of routine clinical care.

Results

The summary statistics for VL across 2019, 2020 and 2023 indicate significant changes in viral load levels. In 2019, the mean VL was 11,784.6 copies/ml, and by 2020, the mean VL had decreased to 6,442.0 copies/ml, with a higher proportion of individuals achieving undetectable viral loads. In 2023, the viral load had further decreased, with a majority of individuals achieving 0 to 20 copies/ml, although a small subset continued to exhibit persistent viremia. Also, correlation between age and viral load showed a gradual increase in the negative correlation over time, suggesting that younger individuals may experience higher viral loads, mainly due to lower adherence to ART or differences in immune response.



Also, the paired t-tests, Wilcoxon signed-rank tests, and Chi-squared tests showed significant reductions in viral load from 2019 and 2023 with p value less than 0.01. The ANOVA test for age groups in 2023 showed no significant impact on viral load. Furthermore, the regression analysis indicated that neither age nor sex significantly influenced viral load levels in 2023.

Discussion

Dolutegravir (DTG, S/GSK1349572) works primarily by inhibiting the enzymatic activity of HIV-1 integrase, which catalyzes the insertion of viral DNA into the chromosomes of infected CD4⁺ lymphocytes [20,21].

Later in 2020, Nepal adopted DTG containing regimen as a preferred first-line regimen for adults, adolescents, and pregnant or breastfeeding women. Dolutegravir (DTG, S/GSK1349572) works primarily by inhibiting the enzymatic activity of HIV-1 integrase, which catalyzes the insertion of viral DNA into the chromosomes of infected CD4⁺ lymphocytes [18,19]. Despite the potential variability of real-world data, the effectiveness and tolerability outcomes for DTG+3TC+TDF was generally consistent across studies included in this analysis. These results should provide reassurance to clinicians that treatment of HIV with DTG+3TC+TDF can be effective in diverse virologically suppressed, People living with HIV who have an undetectable viral load should be told that, along with achieving better health, there is zero risk of transmitting HIV through sex as long as they continue to take their antiretroviral therapy as prescribed. treatment-emergent integrase mutation induced by RAL.

Further, they should receive encouragement for reaching this threshold while addressing adherence and exploring other barriers that may exist to reaching an undetectable viral load. Therefore, DTG in combination with other antiretroviral drugs (ARTs) has a higher virological efficacy and a higher barrier to resistance compared with RAL-based therapy and EFV-based regimens. When selecting viral load testing technologies, HIV programs should consider all available options and sample types giving priority to widespread access. PCR is inherently variable, yet all WHO prequalified viral load technologies can identify people living with HIV as unsuppressed, suppressed and undetectable.

Conclusions

This study provides valuable insights into the effectiveness of ART in controlling viral load over time, with a significant reduction in viral load observed between 2019 and 2023. The findings underscore the role of ART and treatment adherence in achieving viral suppression. The negative correlation between age and viral load highlights the importance of targeted interventions for younger individuals to improve adherence and long-term outcomes. Statistical tests confirmed significant reductions in viral load across the years, supporting the effectiveness of ongoing treatment strategies. However, persistent viremia in a subset of individuals indicates the need for continued monitoring and interventions to address treatment failure and resistance. Further research should explore the factors contributing to persistent high viral loads, especially in younger populations.

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Consent to Participate

All participants involved in the study were fully informed about the nature, purpose, and potential implications of the study.

Consent to Publish

The authors confirm that all participants have provided their consent for the publication of data derived from the study. No identifying personal information has been disclosed, ensuring confidentiality and privacy.

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