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Research Article

A Comparative Analysis of Viral Load Suppression in between Dolutegravir- and Efavirenz-based Regimens in People Living with HIV/AIDS at Provincial Hospital, Madhesh Institute of Health Science (MIHS), Janakpur, Madhesh Province, Nepal

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Abstract

Background: Dolutegravir (DTG)-based triple therapy is becoming a new paradigm for both the initiation and maintenance of HIV treatment over the Efavirenz (EFV)-based regimen for people living with HIV/AIDS. We sought to determine the changes in viral load suppression among patients treated for 3 yrs at ART Center, Provincial Hospital, Janakpur, MIHS, Nepal.

Objective: Our study aimed to evaluate and compare the virological suppression in DTG versus EFV-based regimen for human immunodeficiency virus (HIV) treatment in Provincial Hospital, Janakpur.

Methods: This is a retrospective cohort study including people living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) who were transitioned to Tenofovir/Lamivudine/Dolutegravir, previously on Tenofovir/Lamivudine/Efavirenz regimen for at least 12 months and who had their viral load test done before transition. This analysis is divided into two groups' namely Dolutegravir (DTG) and Efavirenz (EFV)-based regimen. There are altogether 224 patients in each regimen before and after the use of DTG-based regimen for three years from June 1st 2019 to May 30th 2023. Out of 224 Patients, no of Males, Females, and Trans-genders(TG) are 101, 117, and 6 respectively. Among them, 45.02% are males, 52.23% female and 2.67% TG. The medical records of patients were reviewed from records available at the antiretroviral therapy (ART) center of Janakpur Provincial Hospital. Patients were virologically assessed for 48 weeks in each of 3 years.

Results: Two hundred twenty four people living with HIV/AIDS who transitioned to a DTG-based regimen previously on EFV-based regimen for at least 12 months were included in this study. The majority of the patients (81.70%)%) had suppressed viral load of fewer than 50 copies/mL before the switch. Following the transition, 91.52% of the patients had suppressed viral load of fewer than 50 copies/mL.

Conclusion: Dolutegravir-based antiretroviral regimen led to low or undetectable viral load following a switch from Efavirenz-based regimen.

Keywords: Antiretroviral Therapy; HIV; Viral Load; Dolutegravir; Efavirenz

Introduction

Since acquired immune deficiency syndrome (AIDS) was first identified as a serious communicable disease in 1981, an estimated 35.3 (32.2-38.8) million people were living with HIV in 2012 [1]. According to UNAIDS and WHO estimates, this data increased to 38.4 (33.9-43.8) million in 2021. Stable integration of the reverse-transcribed viral genome into host chromatin forms a significant mechanism during HIV infection. Integrase inhibitors (INIs) are a class of antiretroviral drugs targeting the strand transfer reaction during the integration process. It is active against HIV-1 strains that are resistant to nucleoside or nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors [2]. Unlike other enzymes that exist in viruses and humans, integrase enzymes are absent in mammalian cells. Therefore, blockade of integrase is highly specific to viruses and is associated with low toxicity [3].

A fast-track strategy to end the HIV epidemic calls for low and middle-income countries to adopt the Joint United Nations Agency on HIV/AIDS (UNAIDS) 95-95-95 global target; 95% of people living with HIV (PLHIV) should know their status, 95% of those who know their status should receive antiretroviral treatment (ART) and 95% of those in care should have a suppressed viral load by 2030. The World Health Organization (WHO) recommends viral load assessment for all PLHIV as a key intervention for treatment monitoring in PLHIV and achieving the third 95 [2]. However, the WHO-defined viral suppression threshold of < 1,000 RNA copies/mL underestimates adverse outcomes such as subsequent virologic failure and resistance mutations in patients with low-level viremia of 50-1000 copies/mL [16,17].

The emergence of combination antiretroviral therapy (cART) dramatically improved outcomes for patients with human immunodeficiency virus (HIV) infection, transforming it into a manageable chronic condition with a life expectancy similar to that in the general population [4,5]. Generally, cART results in durable virologic suppression (VS) and CD4+ cell repletion, with reduced morbidity, decreased hospitalization rates, and reduced mortality, in addition to preventing HIV transmission [4,6-8]. However, all ARTs are associated with adverse effects, which are the most common reasons for switching or discontinuing therapy and for treatment non-adherence [9].

Dolutegravir (DTG, S/GSK1349572), a new INI drug without such shortcomings, is under spotlight. It is an effective inhibitor of HIV integrase and HIV replication in cell culture assays even at low concentrations of nanomolar level [11]. Pharmacokinetic studies in people have also shown DTG has a long plasma half-life without the need for a booster [15].

Methods and findings

A whole blood sample from each participant was processed into plasma and HIV viral load was estimated using real-time PCR. HIV viral suppression was defined at a cut-off of <50 copies/mL as recommended by WHO. Analyses were conducted using descriptive statistics to establish the regional representative prevalence of viral suppression; Chi-square tests for associations between categorical variables (sex, age, virological suppression) are used. All the statistical calculations are performed using software R Core Team, 2022 [20].

Summary statistics of the viral load shows that for all three years, the viral load distribution is heavily skewed towards low or undetectable viral loads, as indicated by the 1st Quartile, Median, and Min values being below 50 copies/ml. Viral load tends to be

higher in 2019 compared to 2020 and 2023, where the mean is significantly lower, suggesting a possible overall decrease in viral load from 2019 to 2023.

Using a threshold of HIV RNA <1000 copies/ml, 220(98.22%) patients on ART in 2023 for 48 weeks were virally suppressed, as shown in Table 1. Viral suppression rates were higher with DTG- (220, 98.22%) than EFV-based (206, 91.96%) regimen. A threshold HIV RNA <50 copies/ml, among patients with DTG- (205, 91.52%) in 2023 and EFV-based (183, 81.70%) in 2019, the maximum viral load values show a significant reduction from 2019 (183, 81.70%) to 2023 (205, 91.52%), which may indicate viral load suppression and improvements in treatment over the years.

Year	Viral Load Suppression		
	0 - 50	0 – 1000	>1000
2019 (EFV)	183(81.70%)	206 (91.96%)	20(8.93%)
2020 (DTG)	197(87.50%)	207(92.41%)	17(7.59%)
2023 (DTG)	205(91.52%)	220(98.22%)	04 (1.78%)

Table 1: Number of people having viral load suppression (Values in parenthesis indicate the percentage of people).

Pie chart for number of patients in all three groups are plotted for three years and are displayed in figure 1.

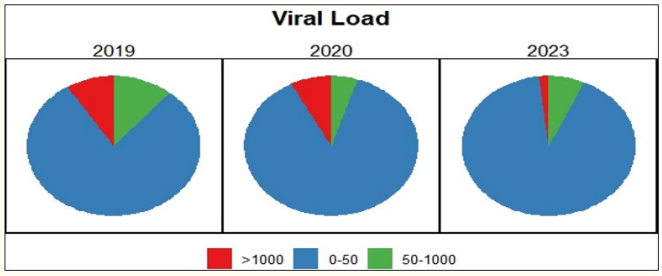

Figure 1: Pie charts by viral load for three years.

Viral load suppression is displayed using Cumulative frequency curve and shown in figure 2.

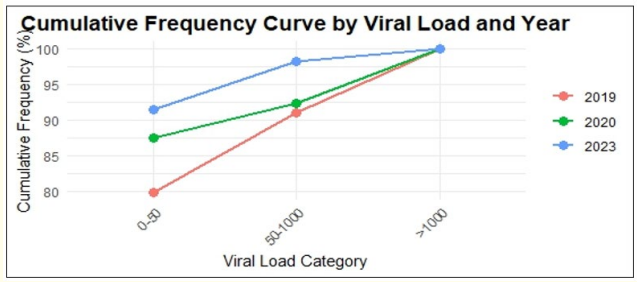

Figure 2: Cumulative frequency curve by viral load.

Paired t-test is used to test whether there is significant difference in viral load due to DTG-based regimen. Test reveals that t = 1.9269, df = 223, p-value = 0.05527, which indicates that there is strong evidence to suggest that the distribution of viral load categories is significantly different between 2019 (with EFV-based regimen) and 2023 (with DTG-based regimen). Based on this result, there is statistically strong significant evidence that DTG-based regimen is more effective than EFV-based in suppressing viral load, assuming a 10% significance threshold.

Pearson's Chi-squared test to compare effectiveness of DTG-based compared to EFV-based regimen and the chi square statistics is shown in Table 2.

Pearson Chi-Square	Value	df	Stastical Sig. (2-sided)
A. 2020/2019	6.4584	2	0.03959
B. 2023/2019	14.927	2	0.0005736
C. 2023/2020	8.865	2	0.01188

Table 2: Chi square statistics.

A. Pearson's Chi-squared test to compare effectiveness of DTG-based regimen in 2020 compared to EFV-based regimen in 2019.

Chi-square = 6.4584, df = 2, p-value = 0.03959. Since the p-value is less than the conventional significance level of 0.05, we reject the null hypothesis. This means there is strong evidence to suggest that the distribution of viral load categories is significantly different between 2019 (with Drug A EFV-based regimen) and 2020 (with Drug B DTG-based regimen). Based on this result, there strong statistically significant evidence that DTG-based regimen is more effective than EFV-based regimen in suppressing viral load, assuming a 5% significance threshold.

B. Pearson's Chi-squared test to compare effectiveness of DTG-based regimen in 2023 compared to 2019.

Chi-square = 14.927, df = 2, p-value = 0.0005736. Since the p-value is less than the conventional significance level of 0.05, we reject the null hypothesis. This means there is strong evidence to suggest that the distribution of viral load categories is significantly different between 2019 (with EFV-based regimen) and 2023 (with DTG-based regimen). Based on this result, there is statistically strong significant evidence that DTG-based regimen is more effective than EFV in suppressing viral load, assuming a 5% significance threshold.

C. Pearson's Chi-squared test to compare effectiveness of DTG-based regimen in 2023 compared to 2020.

Chi-square = 8.865, df = 2, p-value = 0.01188. Since the p-value is less than the conventional significance level of 0.05, we reject the null hypothesis. This means there is evidence to suggest that the distribution of viral load categories is significantly different between 2020 and 2023 (both with DTG-based regimen). Based on this result, there is statistically significant evidence that DTG-based regimen is more effective following 2 years treatment in suppressing viral load, assuming a 5% significance threshold.

Figure 3 shows the bar chart for different viral load group by years.

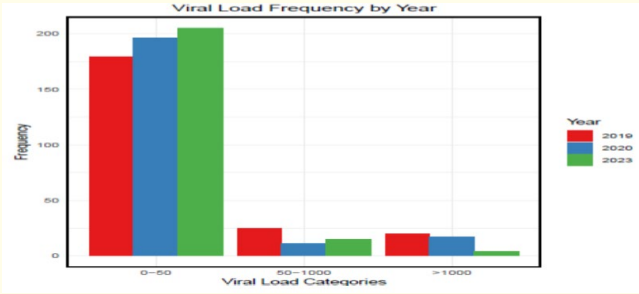

Figure 3: Bar chart for Viral load suppression by year.

Crosstab of viral load versus different gender Male, Female and Trans-gender are mentioned in table 3.

Viral Load	2019			2020			2023		
	Male	Female	TG	Male	Female	TG	Male	Female	TG
0-50	82	92	5	93	97	6	93	106	6
50-1000	11	13	1	2	9	0	6	9	0
>1000	8	12	0	6	11	0	2	2	0

Table 3: Viral load suppression by gender.

Bar diagram of viral load versus different genders Male, Female and Trans- gender are displayed in figure 4.

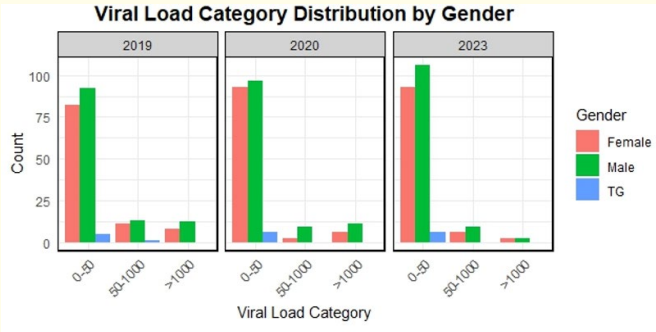

Figure 4: Viral load by gender.

Out of 224 Patients enrolled for study, no of Males, Females, and Trans-genders (TG) are 101, 117, and 6 respectively. Among them, 45% are Males, and 52.23% Female and 2.67% TG. A threshold HIV RNA <50, 50-1000, and >1000 copies/ml, viral loads suppression are predominant in male population, followed by females and TG in all 3 years. It may be beneficial for future research to explore other demographic factors, or larger sample sizes, to further confirm these findings and ensure that treatment effects are consistently observed across diverse populations.

Discussion

National HIV and testing guidelines in 2017 recommended the initiation of ART in all adults and adolescent HIV-infected patients

irrespective of CD4 count or clinical stage, as soon as found positive. DTG-based regimen is the preferred first-line regimen, and EFV-based is considered alternative first-line regimens. Later in 2020, Nepal adopted DTG containing regimen as a preferred first-line regimen for adults, adolescents, and pregnant or breastfeeding women and has also considered transitioning to DTG based regimen for adults and children who were on Efavirenz (EFV) and Nevirapine (NVP)- based regimens. It can be considered from these results that ART centers are strictly following the National guidelines for managing HIV patients in Nepal. In this study, the majority of the patients had viral suppression of 91.52%, using a threshold HIV RNA <50 copies/ml and 98.33% in a threshold HIV RNA <1000 copies/ml, with higher rate of suppression in dolutegravir than efavirenz-based therapy. Common factors associated with virological suppression were age and gender, emphasizing the need for innovative differentiated ART service delivery models to optimize viral suppression and achieve the national target of 95%.

Dolutegravir (DTG, S/GSK1349572) works primarily by inhibiting the enzymatic activity of HIV-1 integrase, which catalyses 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.

Previous reports have noted that no treatment-emergent integrase mutations were detected in the DTG group. But 19 cases with integrase inhibitor-associated resistance and 4 cases with NRTI mutations were detected [21-23]. Furthermore, significant reductions in plasma HIV-1 viral load from baseline were observed for all DTG regimen groups compared with placebo ($p < 0.001$, with a mean decrease of 1.51-2.46 log10 copies/ML [14]. However, there were no studies regarding viral load suppression following the switch to the TLD regimen in Nepal. In the TANGO study, DTG/Lamivudine (3TC) fixed-dose combination was non-inferior to remaining on a Tenofovir-based regimen through week 48 in virologically suppressed adults with no prior history of virologic failure or known major resistance mutations to NRTIs or integrase inhibitors. The findings of that study support the use of DTG/3TC as a switch option for HIV-infected patients with viral suppression on a 3 or 4 drug regimen. [24].

A retrospective study which was done in Sweden in HIV-1-infected ART naïve adults who were commenced on suppressive ART for at least 6 months showed that 10.3% of 736 patients had viral blips with viral load ranging from 56-138 copies/mL. In that study, they also found a higher baseline viral load in subjects with a viral blip and there was a subsequent risk of virological failure with viral blips [25].

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 programmes 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. Dried blood spots, in particular, will support national programmes to ensure access to viral load for all people living with HIV, complementing plasma sampling. Future research with larger sample sizes and additional variables could provide deeper insights into the factors affecting viral loads quality of life in this population.

Future Directions

This study suggests further research to explore the long-term effects of DTG on viral suppression across diverse populations. Furthermore, we recommend studies that include qualitative assessments for deeper insights into patient experiences with treatment.

Conclusion

In conclusion, switching from Efavirenz- to Dolutegravir-based regimen led to very low or untransmittable viral load in the studied population. Dolutegravir-based regimen can be considered virologically safe for transition in HIV/AIDS patients who are on Efavirenz-based regimens.

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