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Effectiveness and common side effects of Dolutegravir compared to Efavirenz-based regimens of combined antiretroviral therapy

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Abstract

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Background:
In 2016WHO recommended Dolutegravir, an integrase strand transfer inhibitor, as an alternative first-line treatment regimen to Efavirenz, a non-nucleoside reverse transcriptase inhibitor. In 2018, Zambia treatment guidelines recommended DTG based-regimens as first-line combinational antiretroviral therapy, and those on Efavirenz based-regimens had to be switched to Dolutegravir based regimens. The study aimed to determine whether there was a difference in time taken for patients to achieve viral suppression between those switched to Dolutegravir versus those initiated on Efavirenz based regimens.

Methods and Materials:
In this Ambispective cohort study, data were collected using the file records of clients from January 2018 to January 2020 and then clinical follow ups and results following up to January 2021. A total of 201 clients were included in this study whose files were resident at the Kitwe Teaching Hospital antiretroviral therapy clinic. Clients included in this study were those who had been initiated on either an EFV-based regimen or a Dolutegravir based regimen. To evaluate the amount of time it takes naïve clients to attain viral suppression (<1000 copies/mL), viral load was analyzed at 24, 48, and 96 weeks.

Results:
At 96 weeks, 92.2% naïve clients on Efavirenz regimen and 100% naïve client on Dolutegravir regimen had a viral load of <1000 copies/mL showing a significant difference in the viral load suppression between the Efavirenz based regimen (M=1.3) and Dolutegravir (M=0.4); t (1) =2.9, p = 0.004. At week 48 of being switched to DTG-regimen, 72.5% of clients had attained undetectable levels and Post hoc tests showed that CD4 counts after 48 weeks (mean rank = 2.42) were higher than those before the switch (mean rank = 1.60) and at 24 weeks (mean rank = 1.98) of treatment. It was observed that naïve clients experienced more side effects on the Efavirenz based regimen than on Dolutegravir regimen (p<0.001) and that clients experienced more side effects while they were on the Efavirenz based regimen than when they were switched to Dolutegravir regimen (p=0.0004).

Conclusion: There is better effectiveness of Dolutegravir based regimen as there are fewer side effects experienced and better viral suppression attainment than on an Efavirenz based regimen. Therefore, Dolutegravir based regimens should be considered as actual first line treatment regimen.

Keywords: *Dolutegravir, Efavirenz, Effectiveness, Side effects, time to viral suppression*

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INTRODUCTION

In 2019, about 690,000 people died of HIV/AIDS related causes, and 1.7 million people were newly infected with HIV globally [1]. To date, there is no cure for HIV; therefore, the treatment requires lifelong therapy. The use of Combinational Antiretroviral therapy (ART) has changed the outlook of living with the Human Immunodeficiency Virus (HIV) from certain fatal illnesses to an infection that can be managed chronically [2]. In 2014 the joint United Nations Programme on HIV and AIDS with its partners put in place the 95-95-95 targets, which stipulate that: 95% of the world's HIV positive population should be diagnosed, 95% of those diagnosed with HIV should be provided with and treated with antiretroviral therapy, and 95% of those on treatment with antiretroviral therapy should achieve viral suppression by 2030 to ensure the end of the AIDS epidemic as a public health threat by the year 2030 [3]. Having 95% of clients on antiretroviral therapy achieving viral suppression is being tackled by introducing antiretroviral drugs that can reduce viral load faster, have minimal and tolerable side effects, thus increased adherence and higher barrier to resistance.

A combination of three drugs is the current standard for chronic HIV therapy, and these are usually seen in a single tablet [3]. International HIV treatment guidelines recommend first-line use of two Nucleoside Reverse Transcriptase Inhibitors with a Non-Nucleoside Reverse Transcriptase Inhibitor, a boosted Protease Inhibitor, or an Integrase Strand Transfer Inhibitor to achieve sufficient HIV Ribonucleic acid (RNA) suppression [4]. The goal of combining antiretroviral therapy for treatment in clients with HIV infection include: reducing morbidity and mortality of AIDS and non-AIDS-associated causes, improvement of quality of life, reduction of plasma viral RNA load, prevention of transmission of HIV through sexual partners, needle-sharing partners, mother to infant, among others, prevention of drug resistance, improvement of immune function [5]. To ensure HIV treatment efficacy, safety, effectiveness, and tolerability are to be considered top of the list when prescribing therapy.

World Health Organisation Human Immunodeficiency Virus treatment guidelines [6] recommended Dolutegravir (DTG) as an alternative first-line treatment and for salvage regimens. Treatment guidelines for HIV [7] recommended Tenofovir Disoproxil Fumarate + Lamivudine/Emtricitabine + Efavirenz (TDF/XTC/EFV) for adults, pregnant and breastfeeding women and children above five years of age weighing 35 kilograms (Kg) or more as first-line combination antiretroviral therapy. Dolutegravir is expected to become the preferred first-line treatment pending critical data from additional clinical trials and real-life use [4]. In addition to DTG's excellent clinical profile, it has also been shown to be an economically attractive strategy in both treatment naïve and treatment-experienced patients compared to EFV-based regimens [8]. Efavirenz-based regimen treated patients have been seen to experience neurological and neuropsychiatric reactions which manifest mildly as nightmares, dizziness, insomnia, nervousness, and lack of concentration and more severely as depression, suicidal ideation, or even psychosis [9]. Studies have shown that the median time to viral suppression was 28 days among participants receiving Dolutegravir based regimens, as compared with 84 days among those receiving efavirenz-based regimens [10]. Therefore, this study aimed to determine whether there was a difference in time taken for patients to achieve viral suppression between those switched to DTG versus those initiated on EFV-based regimens. The common side effects were assessed and compared among participants on ENF- versus DTG-based regimens.

METHODS AND MATERIALS

Study design and setting

Between January 2018 and January 2021, an observational ambispective study was carried out at the Kitwe Teaching Hospital ART center, data were collected using the file records of clients from January 2018 to January 2020 and then clinical follow ups and results following up to January 2021. A total of 201 clients with HIV-1+, on first-line treatment and not on tuberculosis (TB) treatment, were recruited in this study. The clients included men, women, and children weighing above 30Kgs. Seventy-seven (77) clients were initiated on Efavirenz, sixty-two (62) clients were initiated on Dolutegravir, and sixty-two (62) experienced clients were switched from Efavirenz regimen to Dolutegravir regimen. Most paediatric clients were initiated on NVP-r due to weight restrictions and recommended protocol; therefore, there was a low number of paediatric clients in all targets.

Study approach

To evaluate the amount of time it takes naïve clients to attain viral suppression, analysis

of Viral Load was measured at 24 weeks after initiation and then at week 48, and then at week 96. To Asses, if patients with viral suppression who were switched to Dolutegravir based regimen remained virologically suppressed, Viral Load and CD4+ were analyzed at 24 weeks and 48 weeks to see if suppression was maintained and if undetectable levels had been achieved. Viral load was detected using Cobas Ampliprep/Cobas Taqman 96 that quantifies HIV RNA in Human plasma. Total CD4+ count was detected using BD FACSCount, which enumerates absolute lymphocyte counts of various lymphocyte subsets, including CD4+.

Study approach

Recruitment of clients was done via the ART centers SMARTCARE Database. Selected clients' physical files were accessed to confirm the initial regimen and eligibility to switch to DTG based regimens. SMARTCARE Database was then accessed to check on clinical follow-up appointments, pending laboratory tests, and results collection. Any missing results were followed up at the laboratory, and any pending VL or CD4+ samples were run.

Data analysis

An unpaired t-test was performed to compare viral load suppression and CD4 count between clients on EFV based regimen and DTG based regimen at 24 weeks, 48 weeks and 96 weeks. This test was also performed when comparing viral load and CD4 count of clients switched from EFV based regimen to DTG based regimen. In addition, to compare viral and CD4 count within treatment groups on the two regimens at different periods, the Friedman's test was used; followed by a Pairwise comparison using the Dunn Post Hoc Test with the Bonferroni correction. To assess if clients with viral suppression remain virally suppressed after switching from EFV-based regimens to DTG based regimens VL and CD4+ were analyzed 24 weeks after the switch to DTG based regimens and then at 48 weeks. Records of clients' results before the switch to DTG based regimens were compared to records after switching to DTG based regimens and reported as percentages and proportions. To assess adherence and compliance to treatment, dates of the review were noted. Common side effects of naïve clients on both regimens' data were collected from records of clients on both regimens and were described in proportions and assessed with the chi-square test; Side effects of experienced clients before and after the switch to DTG-based regimens, data was described using proportions and assessed with the chi-square test.

Data were analyzed using Microsoft Excel spreadsheets and Graph Pad Prism 7 statistical package. For statistical significance, a p-value less than 0.05 was significant

This data set can be found on figshare repository [11].

RESULTS

Baseline characteristics

A total of 139 naïve clients were recruited for this study, 75% of whom were adults. Of the 201 clients who participated in this study, 95 (47.3%) were female. Figure 1 shows below shows the distribution of naïve clients in each regimen.

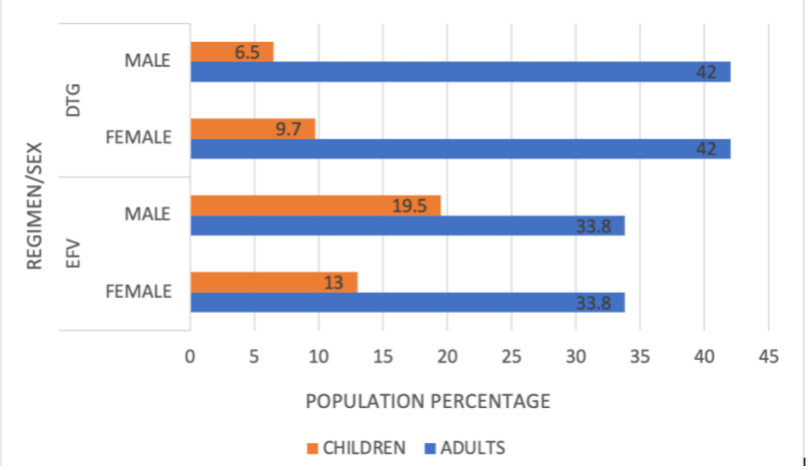

Figure 1. Naïve client's population distribution.

At week 24, 68 of 77 (88.3%) clients in the efavirenz-based regimen group and 52 of 62 (83.8%) clients in the Dolutegravir based regimen group had a viral load of fewer than 1000 copies per millilitre. In addition, there was no statistically significant difference in viral load suppression between the two treatment groups t = -0.76, p = 0.4504. The distribution of viral load results at week 24 for EFV and DTG based regimens is shown in Figure 2.

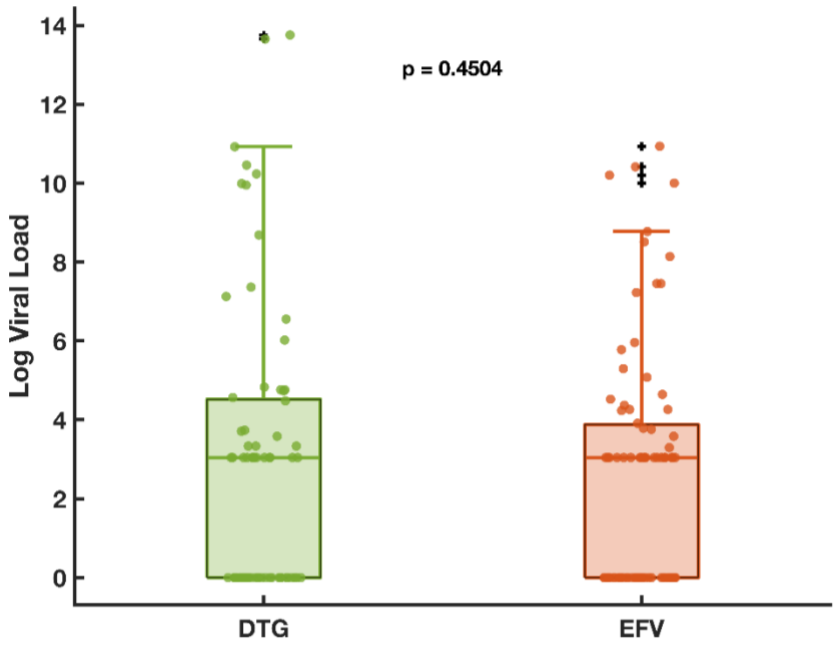

Figure 2. Naïve Clients' Viral Load results 24 weeks after treatment.

At week 48, 70 of 77 (90.9%) clients in the efavirenz-based regimen group and 61 0f 62 (98.3%) clients in the Dolutegravir based regimen group had a viral load of fewer than 1000 copies per milliliter; 27.2% and 16.1% of which were children in respective regimen groups. There was no statistically significant difference in viral load between the two treatment groups at week 48 t = 0.155, p = 0.123. The distribution of viral load results at week 48 for EFV and DTG based regimens is shown in Figure 3.

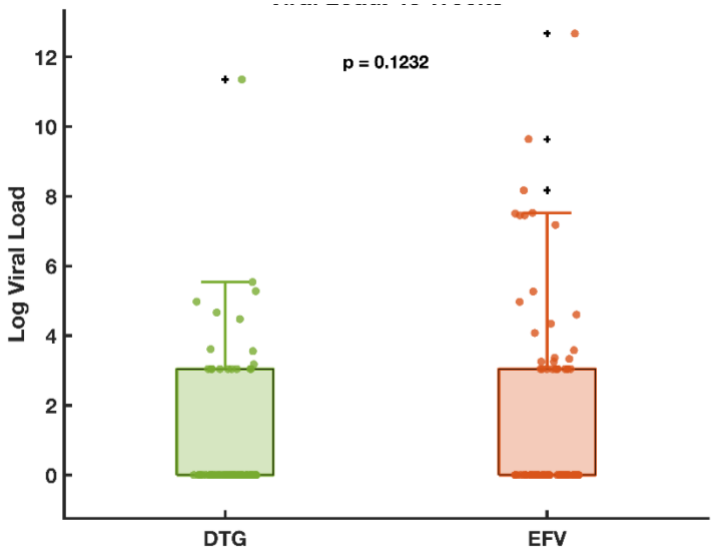

Figure 3. Naïve Clients' Viral Load results 48 weeks after treatment.

At week 96, 71 of 77 (92.2%) clients in the efavirenz-based regimen group and 62 of 62 (100%) clients in the Dolutegravir based regimen group had a viral load of less than 1000 copies per milliliter 28.5% and 16.1% of which were children in the respective regimen groups. In addition, there was a significant difference in the viral load suppression between the efavirenz-based regimen (M=1.3) and Dolutegravir (M=0.4); t (1) =2.9, p = 0.004. These results suggest that Dolutegravir based regimen is better than the efavirenz-based regimen at viral suppression after 96 weeks of treatment. The distribution of viral load results at week 96 is shown in Figure 4.

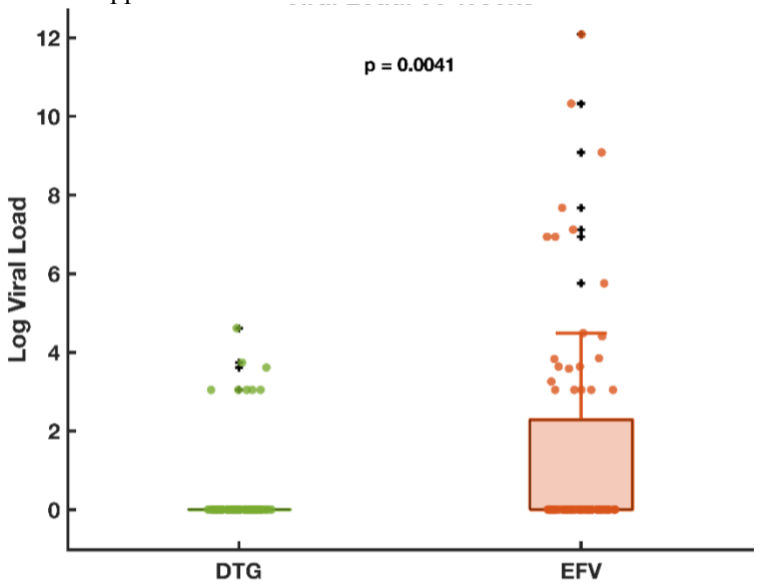

Figure 4. Naïve Clients' Viral Load results 96 weeks after treatment.

Of the 88.3% of clients in the efavirenz-based regimen group who attained viral suppression after 24 weeks, 5.8% of them reverted to a viral load of more than 1000 copies per milliliter at week 48, whereas no similar cases observed in the Dolutegravir based regimen group. Of the 92% of clients on the efavirenz-based regimen that attained viral suppression, 1.5% of them were no longer virologically suppressed by week 96. The following data is displayed in figure 5.

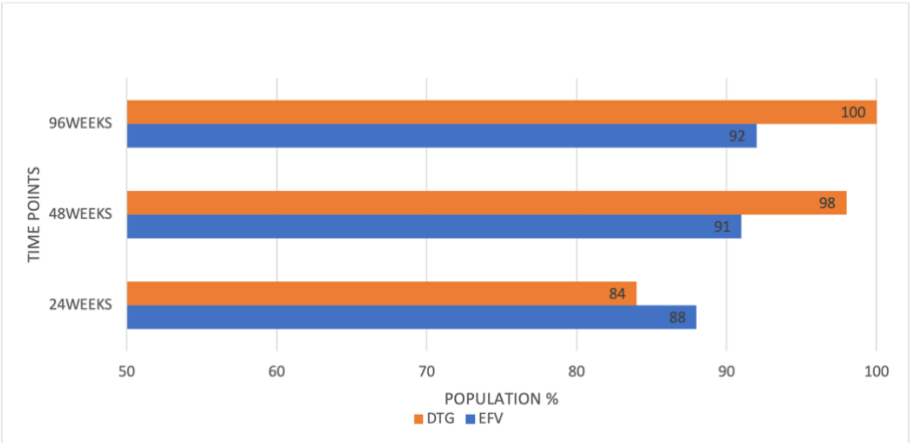

Figure 5: Naïve clients' attainment of viral suppression

Friedman's test was also carried out to assess the changes in CD4+ count and Viral load in participants on EFV-based treatment for 96 weeks.

For CD4 count, the test showed a significant difference, X^2_F (2) = 7.00 p = 0.030. Post hoc tests showed that CD 4 count after 96 weeks (mean rank = 2.42) was higher than for those at 24 weeks (mean rank = 1.67) of treatment. This improvement was statistically significant T = -0.75, z = -2.598, p = < 0.028. However, there was no significant difference between the other groups, 24 (mean rank = 1.67) to 48 (mean rank = 1.92) weeks, and 48 (mean rank = 1.92) to 96 (mean rank = 2.42) weeks, T = -0.25, z = -0.866, p = 1.0 and T = -0.500, z = -1.732, p = 0.25 respectively.

The Friedman's test also showed a significant difference in viral load X^2_F (2) = 18.753, p < 0.0001. The Post hoc test showed a similar distribution with that of CD 4 revealing a statistically significant improvement between 24 (mean rank = 2.28) and 96 (mean rank = 1.79) weeks of treatment T = -0.494, z = 3.062, p = 0.007. There was no significant difference between the other groups 24 (mean rank = 2.28) to 48 (mean rank = 1.94) weeks, and 48 (mean rank = 1.94) to 96 (mean rank = 1.79) weeks, T = -0.149, z = -0.927, p = 1.0 and T = 0.344, z = 2.135, p = 0.098 respectively.

A total of 62 clients switched from efavirenz-based regimen to dolutegravir based regimen were recruited for this study; 43.5% were female participants.

Whilst on efavirenz-based regimen 59 of 62 (95.2%) clients had a viral load of fewer than 1000 copies per milliliter; 55.9% of which had attained undetectable levels, after 24 weeks of being on dolutegravir-based regimen 43 0f 62 (69.3%) clients had attained undetectable levels 30.2% of which were children. All the clients that were not suppressed at the time of switching from the efavirenz-based regimen had achieved viral suppression after 24 weeks of being on the dolutegravir-based regimen, and 66.7% of the population had achieved undetectable levels by then. There was no evidence of clients reverting to the viral load of more than 1000 copies per milliliter. After 48 weeks of being on dolutegravir-based regimens, 45 of 62 (72.5%) clients had attained undetectable levels, 26.6% of whom were children. Two clients had reverted to a viral load of more than 1000 copies per milliliter by week 48. The following can be seen illustrated in Figure 6. A Friedman's test showed that there was no significant difference in viral load measured before switching to DTG, after 24 weeks on DTG and after 48 weeks on DTG, X^2_F (2) = 5.883 p = 0.053

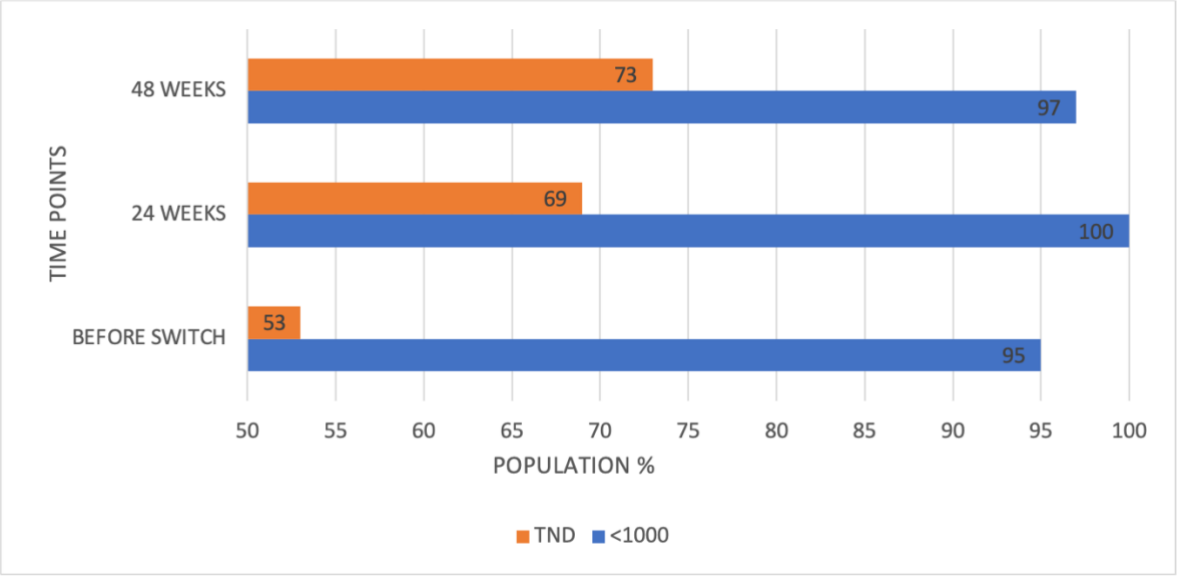

Figure 6. Experienced client's attainment of undetectable levels

Before switching to dolutegravir regimens, the mean CD4+ T-cell count was 487 per cubic millimeter, at 24 weeks after the switch, the mean CD4+ T-cell count was 545 per cubic millimeter showing a 10.6% increase, and the mean CD4+ T-cell count at 48 weeks was 619 per cubic millimeter, showing a 21.3% increase from the mean CD4+ T-cell count before the switch. A

Friedman's test showed a significant difference in CD4 count in participants on DTG treatment regimen, X^2_F (2) = 20.686 p < 0.0001. Post hoc tests showed that CD4 counts after 48 weeks (mean rank = 2.42) were higher than those before the switch (mean rank = 1.60) and at 24 weeks (mean rank = 1.98) of treatment. This improvement was statistically significant T = -0.820, z = -4.5, p = < 0.0001 and T = -0.34, z = -2.4, p = 0.049 respectively. However, Cd 4 counts before switch and at 24 weeks on DTG were not significantly different T = -0.39, z = -2.1, p = 0.1. see Figure 7.

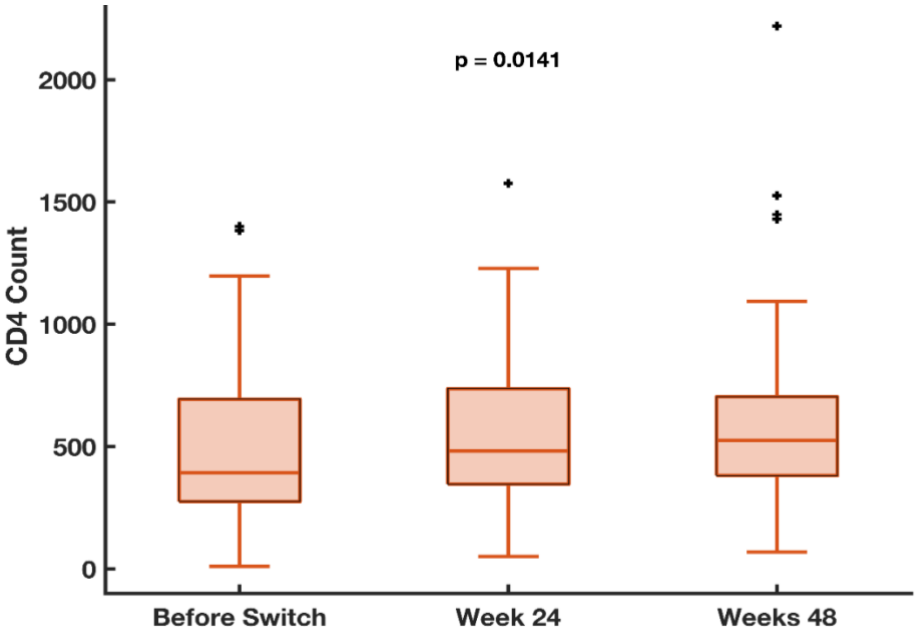

Figure 7. CD4+ total count results distribution

Side effects

For clients initiated on the efavirenz-based regimen, 54 of 77 (70.1%) clients did not complain of any side effects, 23.4% of which are children, while 42 of 62 (67.7%) clients initiated on dolutegravir based regimen, 19.0% of which were children, did not complain of any side effects. This is illustrated in figure 8

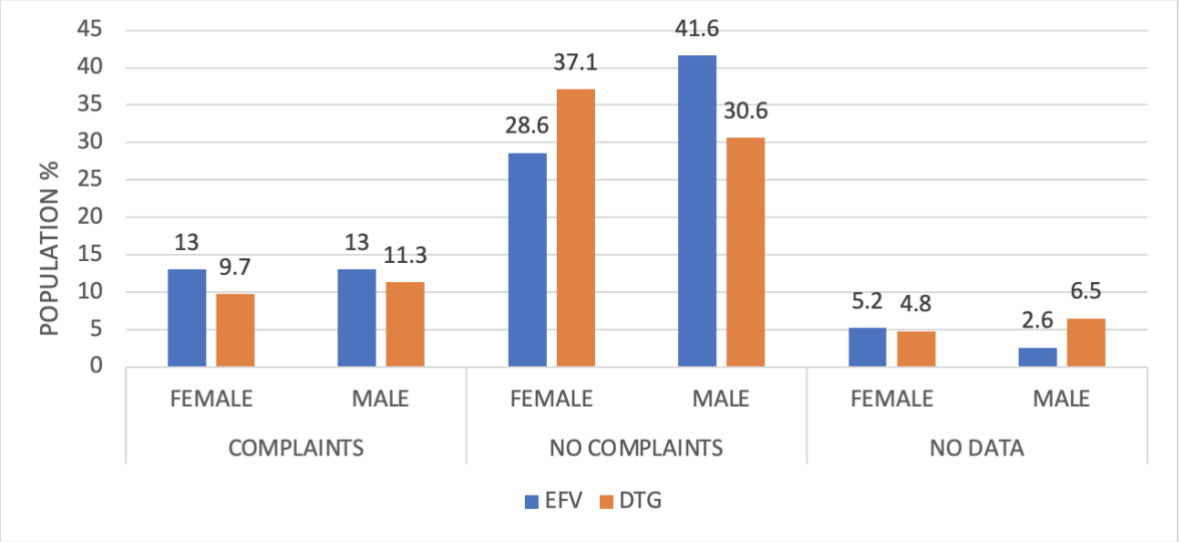

Figure 8: Naïve clients' response regimens

Appetite loss and fatigue were the most experienced side effects observed on naïve clients on efavirenz-based regimens, both seen at 39%. For naïve clients on DTG based regimens, the most common side effect experienced by the population was abdominal pain at 30.8%. The side

effect common to the majority of both populations was seen to be Fatigue. Statistics are shown in Table 1.

Table 1: Side effects experienced by Naïve clients

SIDE EFFECTS EXPERIENCED AND REPORTED	FREQUENCY n	
	EFV	DTG
Abdominal Pain	1	4
Appetite Loss	7	2
Dizziness	3	1
Fatigue	7	2
Headache	2	1
Nausea	1	1
Rash	5	2
Musculoskeletal	1	0
Weakness	1	0
Lymphadenopathy	1	0
Diarrhea	3	0
Weight Loss	2	0
Fever	0	2
Dry Cough	0	2
Fainting/Blackout	0	1
Neuropathology	0	2
No Data	5	7

For clients who switched from Efavirenz based regimens to Dolutegravir based regimens, 53 of 62 (85.5%) of the total population did not complain of any side effects. In comparison, on the Efavirenz regimen and 56 of 62 (90.3%) of the same clients did not complain of any side effects after being switched to Dolutegravir based regimen. The most common side effect experienced by the clients while on Efavirenz based regimen was dizziness at 33.3%, followed by appetite loss and fatigue, both seen at 22.2%. The most common side effect observed on the same clients after they had been switched to a dolutegravir based regimen was rash at 33.3%. Some of the information is shown in Figure 9.

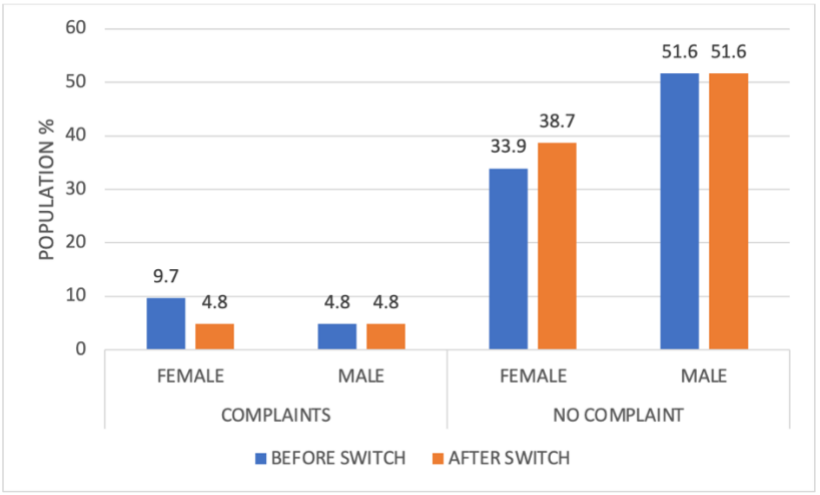

Figure 9. experienced client's response to regimen

DISCUSSION

In this study, we compared the effectiveness of Efavirenz-based regimens to Dolutegravir based regimens for the treatment of HIV-1 infection in clients at Kitwe Teaching Hospital ART center who were initiated on the said regimens between January 2018 and January 2021 by accessing their data through the SMART CARE Database. The results of this study showed that there was no notable difference in clients attaining viral suppression at 24 and 48 weeks on both regimens. However, at 96 weeks, the

population initiated on Dolutegravir regimen showed significance in attaining viral suppression compared to the Efavirenz initiated population. This shows that the Dolutegravir regimen is better at viral suppression than Efavirenz regimen after 96 weeks of treatment. This result can also be seen in a study conducted by [12] which showed the non-inferiority of Dolutegravir based regimen by week 144 with a subsequent superiority testing outcome which favored Dolutegravir based regimen due to fewer discontinuations resulting from less adverse events as compared to Efavirenz based regimens. It was also noted that there was no increase or decrease in the number of women attaining viral suppression throughout the study in the EFV-based regimen group, as one client did not achieve viral suppression throughout the study despite attending scheduled reviews and collection of medication. There were no pregnant women at the beginning of the study, and none of them reported being pregnant during the study, so there is no data to attribute to efavirenz-based regimen nor dolutegravir based regimens effectiveness during pregnancy. The median age of women was 34 and 39 for efavirenz-based regimens and dolutegravir based regimens, respectively showing that the population was within childbearing age. A follow-up on these women should be done if and when they do conceive to evaluate any neural tube defects (NTD) that may be expressed as a result of using the said regimens.

Clients who were virologically suppressed and switched from EFV-based regimen to DTG based regimen maintained viral suppression and steadily achieved undetectable levels by week 24. In contrast, those who were switched despite their viral load achieved viral suppression and undetectable levels by that time. At week 48, only 2 clients that had achieved viral suppression showed a viral load of more than 1000 copies/mL, after which further investigations showed that one client, an adolescent, had been inconsistent with taking their therapy and the other, an adult, had a virological failure. There was a steady increase in the mean total CD4 count throughout the study for those switched from EFV-based regimen to DTG based regimen. The study showed a significant increase in the mean CD4 count at 48 weeks after the switch showing a positive response to the new regimen. Despite some clients having viral loads of more than 1000 copies per milliliter, the highest being seen as 56130 copies at 24 weeks, 317813 copies at 48 weeks, and 176,899 copies at 96 weeks, this was observed on some clients initiated on efavirenz-based regimens. None of them was reported to be above WHO clinical stage 1. For clients initiated on dolutegravir based regimens, the highest number of copies observed was 939,871 copies at 24 weeks and 84,986 at 48 weeks; there was no observation of viral load above 1000 copies at 96 weeks. None of the clients with a viral load above 1000 copies at any of these time points were above WHO clinical stage 1.

Clients initiated on EFV-based regimens experienced more side effects than those initiated on DTG based regimens, the most common side effects being appetite loss and fatigue. EFV regimen is known for its neuropsychiatric effects, mainly abnormal dreams, sleep disturbances, nervousness, anxiety, depression, and dizziness [13]. Our study did not receive any report of neuropsychiatric effects apart from headaches and dizziness. Zambia Treatment guidelines [14] recommended using EFV 400mg to EFV 600mg as it had shown lesser toxicity, pill size, and discontinuation due to adverse events. There are fewer reports of neuropsychiatric effects, especially abnormal dreams, because of the reduced dose EFV regimen. This is attributed to numerous studies that report an association between Higher EFV plasma concentrations and CNS side effects [13]. This is a potential study for the future as there is little known about it. According to [15] drowsiness, malaise, fatigue, nausea, and dizziness are the most reported side effects for clients initiated on DTG regimen accounting for 33.4% collectively, and gastrointestinal effects took up only 13.3%.

On the contrary, the most common side effect experienced by naïve DTG based regimen clients observed in our study was abdominal pain, followed by appetite loss, fatigue, and rash, each seen at 15%. The most common side effect observed on the population of experienced clients on DTG based regimen was rash at 3.2%. Bonfati et al., [16] showed similar findings to our results as the side effects observed on 5.4% of their population included skin rash and abdominal pain. There was no significant evidence to show CNS effects of DTG regimen on the population, contrary to many studies, requiring a more extended observation period.

The population showed good adherence as there was no evidence of missed clinical review appointments or medication refill. There was only one report of non-adherence. Although patient self-report is the most frequently used means of assessing adherence, it overestimates adherence [17]. SMARTCARE Database does not show missed or late appointment dates once the appointed task has been indicated as done;

therefore, late medication pickups or postponed appointments could not be noted. Current adherence monitoring tools used are patient self-reporting and pharmacy adherence measures [18]. The optimal way to assess adherence is not known [19,20].

LIMITATIONS

The generalizability of the results is limited by the smaller population of pediatric clients, which was due to guidelines of weight-based dosing. Observation of CD4 for naïve clients initiated on Dolutegravir was not possible due to absent/missing records for about 90% of the clients. Due to a lack of data on CNS effects of EFV 400mg, the results cannot confirm the absence of abnormal dreams experienced by observed clients on EFV-based regimens in this study. The methodological choices were constrained by the lack of other adherence assessment methods.

CONCLUSION

There is a significant difference in the viral suppression attained by clients initiated on DTG regimen by 96 weeks of being on treatment. There are more side effects experienced on EFV based regimens compared to DTG based regimens. Clients show good adherence to both regimens. This shows that there is better effectiveness of DTG based regimen as there are fewer side effects experienced and better viral suppression attainment than on an EFV-based regimen. Therefore, Dolutegravir based regimens should be considered as actual first line treatment regimen.

DECLARATION

Competing interests There were no competing interests from all authors in this study.

Author contributions All co-authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of this work are appropriately investigated and resolved. TNP and SM conceptualized this study. TNP drafted the first draft which was shared with all co-authors. CC, MS1, KM, LH, RC, ON, SM and MS3 contributed to the data acquisition, analysis and interpretation. All co-authors reviewed the draft and gave their critical input leading to a revised final draft that was approved by all.

Ethics approval and consent to participate the study was approved by the University of Zambia Health Sciences Research Committee review board (protocol ID # 20203101007). Privacy and confidentiality were maintained through the use of unique identifiers for participants following informed consent.

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