ISSN 2795-1952 eISSN 2976-1107
DOI: https://doi.org/10.3126/mjmms.v4i8.77283

CCREACH
MedSpirit Alliance

ORIGINAL RESEARCH Open Access

Safety, Efficacy and Quality of Life Analysis of Dolutegravir versus Efavirenz Antiretroviral Therapy in HIV Patients at the ART Centre, Madhesh Institute of Health Sciences, Janakpur, Madhesh Province, Nepal

Rameshwar Mahaseth[1*] | Binod Kumar Yadav[2] | Lal Babu Sah Telee[3]| Ramdev Chaudhary[1]| Vijay Kumar Sah[4]

1. Department of Internal Medicine, Provincial Hospital, MIHS, Janakpur, Nepal.
2. Madhesh Institute of Health Science (MIHS), Janakpur, Nepal.
3. Department of Statistics, Tribhuvan University, Kathmandu, Nepal
4. Department of Internal Medicine, Janaki Medical College, Kshireswornathh -1, Nepal

Received: 19 June 2024
Revised: 18 September 2024
Accepted: 9 August 2024

***Correspondence**:
ramdsh@gmail.com(RM)

Funding details: Self

Citation:
Mahaseth R, Yadav BK, Telee LBS, Chaudhary R, Sah VK. Safety, Efficacy and Quality of Life Analysis of Dolutegravir versus Efavirenz Antiretroviral Therapy in HIV Patients at the ART Center, Madhesh Institute of Health Sciences, Janakpur, Madhesh Province, Nepal. *MedS. J.Med. Sci.* 2024;4(8):13-18.

Abstract:

Introduction: In several countries, the Dolutegravir (DTG)-based regimen is generally preferred as first-line antiretroviral therapy (ART) over the Efavirenz (EFV)-based regimen for people living with HIV (PLHIV). This study aimed to evaluate the safety and tolerance of DTG- versus EFV-based regimen for human immunodeficiency virus (HIV) treatment in ART Center, Provincial hospital, Janakpur, Nepal. We sought to determine Efficacy, the rate of adverse events (AEs) and quality of life (QOL) among patients treated at Provincial Hospital, but the evidence in developing countries is limited.

Materials and methods: This analysis is divided into two groups' namely DTG and EFV-based regimen_groups. There are altogether 40 patients in each regimen before and after the use of Dolutegravir (DTG) regimen for one year in ART Center, MIHS, Janakpur. Blood routine checkup were done for anemic, renal function, liver functions, and QOL assessments in each regimen groups.

Results: The median age was 31 years, 58% were male. Participants were on ART for 48 weeks on EFV- before using DTG based- regimen. The results revealed that 87.28% of total age groups in DTG based regimen had good quality of life (QOL) in 2021 than that of 65.46% in EFV based regimen in 2020. Almost 90.9 % of Migrants among high-risk groups in DTG-based regimen had good quality of life (QOL) in 2021 than that of 50% of EFV - based regimen in 2020.

Conclusions: DTG-based regimen was effective, well tolerated with improved quality of life (QOL) and less adverse effects (AEs).

Keywords: Anemia, Dolutegravir, Efavirenz, HIV, Quality of life.

INTRODUCTION

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]. 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]. 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 virological 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), 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]. 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]. Current guidelines from the World Health Organization (WHO), the US Department of Health and Human Services (DHHS), and the European AIDS Clinical Society (EACS) recommend first-line cART comprising a core agent (integrase strand inhibitor [INSTI], boosted protease inhibitor [PI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]) in combination with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) for treatment-naïve patients with HIV-1 [10,12,13,16]. Recommended or commonly used core agents include the INSTIs bictegravir (BIC), dolutegravir (DTG), cobicistatboosted elvitegravir (EVG/c), and raltegravir (RAL); the ritonavir-boosted PIs atazanavir (ATV/r), darunavir (DRV/r), and lopinavir (LPV/r); the NNRTIs efavirenz (EFV) and rilpivirine (RPV) and NRTIs lamivudine (3TC) and Abacavir (ABC). DTG is recommended once daily for adult patients infected with HIV-1 who do not have documented or clinically suspected resistance to INSTIs [18, 19]. In randomized controlled trials (RCTs) DTG had a higher barrier to resistance than RAL [15], was superior to once-daily EFV and once-daily DRV/r, and non-inferior to twice-daily RAL for the treatment of treatment-naïve patients with HIV-1 [20–23].

As a result of the 2016 NMA that compared INSTIs with EFV [23], the WHO now recommends a DTG-based regimen as a preferred first-line therapy for treatment-naïve patients with HIV-1 [17]. To assess the efficacy and safety of new DTG-based regimen was compared with old EFV-based regimen each one year from 2021 to 2022. Some studies found that a switch to a DTGbased therapy was not superior to the approved combination therapy [25, 26]. However, in other studies, statistical superiority of a DTG-based therapy over the approved combination therapy was also reported [27, 28]. Thus, the results of these studies are still inconclusive. This issue sparks our interesting to pool samples from RCTs and to get an enlarged sample size, which can make the evaluation more reliable.

METHOD AND MATERIALS

Study design and setting

This study is prospective cohort study at ART Center, Provincial Hospital, Madhesh Institute of Health Sciences, Janakpur, Madhesh Province, Nepal for a follow-up period one year.

Participant, sample size, and procedure

There are altogether 40 patients in each regimen before and after the use of Dolutegravir (DTG) regimen for one year in each regimen. Among 40 Patients, they were categorized into 7 high risk groups namely Migrants (18), Spouse of Migrants (15), Female sex worker-FSW (1), Mother to Child transmission-MTCT (1), Transgender-TG (2), Client of Sex workers (1), and Other (2). Here, an analysis of current evidence was conducted to assess the safety and efficacy of DTG in combination with other antiretroviral drugs. I.e. all core agents recommended at the time of the analysis.

Statistical analysis and data management

Descriptive statistics is studied to summarize baseline characteristics. Paired t-tests for pre- and post-treatment comparisons of hemoglobin and Creatinine levels are applied. Chi-square tests for associations between categorical variables (sex, age, QOL) are used. All the statistical calculations are performed using software R Core Team, 2022[32].

Ethical Consideration

For the purpose of the study, Institutional review board (IRB) approval was obtained from the authority. In addition, permission from the patients and ART centre of the hospital was obtained to provide consent.

RESULTS

Table 1 contains the effects of DTG on patient's hemoglobin level. The increase in hemoglobin levels from 10.867 g/dL to 12.321 g/dL suggests a clinically meaningful improvement in the patients' hematological status, especially for those who may have been anemic prior to treatment. The calculated t-value of 3.6488 indicates a significant difference in hemoglobin levels before and after treatment. That is, corresponding p-value (0.000394) is less than the significance level of 0.05, meaning the results are statistically significant. This suggests a high level of confidence that the observed increase in hemoglobin is not due to random chance.

Table 1| Effects on Hemoglobin before and after DTG-based treatment

HB Level	Number of patients	Average level of HB	Variation in HB
After DTG	40	12.321	2.297
Before DTG	40	10.867	1.962
Diff. in HB	40	+1.4538	2.4766

Table 2 displays the effect of DTG on patient's Creatinine level due the treatment. The average Creatinine level before treatment was 0.8276 mg/dL, which is within the normal range (typically around 0.6 to 1.2 mg/dL, depending on factors like age and gender). After treatment, the average Creatinine level decreased to 0.7565 mg/dL. The variation in Creatinine levels before treatment was 0.2135, while after treatment it was 0.22066, indicating a similar degree of variability in both cases. The average decrease in Creatinine after treatment is -0.07118 mg/dL, with a standard deviation of 0.25464. This indicates that while there is an observed reduction in Creatinine levels, the variation is relatively high, suggesting differing responses among patients. The calculated t-value 1.630

Table 2| Creatinine level before and after the DTG treatment

Creatinine Level	Number of patients	Average level of Creatinine	Variation in Creatinine
After DTG	34	0.7565	0.2206
Before DTG	34	0.8276	0.2135
Diff. in Creatinine	34	-0.0712	0.2546

Table 3. Sex – age cross table

Age	Sex		Total
	Male	Female	
0-20 years	3	0	3
20-40 years	12	12	24
40-60 years	7	6	13
Total	22	18	40
Chi square= 2.70; p value= 0.259			

indicates that while there is a change in Creatinine levels, the evidence is not strong enough to establish a significant difference. The p-value 0.113 is greater than the significance level of 0.05, suggesting that the change in Creatinine levels is not statistically significant. Therefore, we cannot confidently conclude that the reduction in Creatinine is a result of DTG treatment.

Although there is a decrease in Creatinine levels from 0.8276 mg/dL to 0.7565 mg/dL, the reduction is small and does not achieve statistical significance. This suggests that the clinical relevance of this decrease is uncertain.

Cross tabulation of sex versus age is shown in Table 3 and the chi square statistics is shown in Table 4. The null hypothesis for the Chi-square test posits that there is no association between sex and age group. In this case, a p-value greater than 0.05 (specifically, 0.259) indicates that we fail to reject the null hypothesis. This means that there is no statistically significant association between sex and age group within the sample. In other words, the distribution of males and females is similar across the different age categories. The likelihood ratio of 3.835 and its significance value of 0.147 further support the finding that there is no significant relationship between sex and age.

Table 4 shows the measures of some parameters after and before the DTG. We have also studied if there is any

Table 4| Average difference after and before the DTG and t- statistics

After DTG–Before DTG	Paired Differences					t	df	Sig. (2-tailed)
	Mean	SD	S.E(mean)	95% CI				
				Lower	Upper			
MCH- MCH	1.5481	3.9866	.7672	-.0289	3.1252	2.018	26	.054
MCV - MCV	7.1889	15.6427	3.0104	1.0009	13.3769	2.388	26	.024
SGPT - SGPT	-8.8757	15.5245	2.5522	-14.0518	-3.6995	-3.478	36	.001
SGOT - SGOT	6.1811	33.3032	5.4750	-4.9227	17.2849	1.129	36	.266
Urea - Urea	-1.6367	7.42405	1.40301	-4.51553	1.24196	-1.167	27	.254
Significant p-value < 0.05								

Table 5: QOL versus sex cross tabulation				
Characteristics		Sex		Total
		Male	Female	
QOL	Good	20	14	34
	Poor	2	4	6
Total		22	18	40
Chi square=1.33; p value= 0.247				

association between Sex and quality of life (QOL) after the DTG use in patients (Table 5).

Result shows that there is no statistically significant association between sex and QOL in this sample, suggesting that males and females report similar quality of life outcomes. The data shows that a majority of both males (20 out of 22) and females (14 out of 18) report a good quality of life. The small number of patients with poor QOL (6 total) indicates that overall, the patient population is relatively healthy or satisfied with their quality of life. The lack of significant differences in QOL based on sex suggests that both genders respond similarly to the treatment regarding their quality of life. This is important for ensuring equitable treatment outcomes across sexes in the context of DTG research.

DISCUSSIONS

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 [30,31].

Improving hemoglobin levels can have several positive health implications, including increased oxygen delivery to tissues, improved energy levels, and overall better quality of life for patients. The increase in hemoglobin could be attributed to DTG's role in enhancing overall health by controlling viral loads in HIV patients, which can, in turn, lead to better nutritional status and reduced inflammation. The results support the use of DTG-based regimens not only for viral load suppression but also for improving hematological parameters in patients who may present with anemia or low hemoglobin levels. The study demonstrates that DTG-based treatment significantly improves hemoglobin levels in patients, which is both statistically and clinically significant. The findings warrant further investigation into the mechanisms behind this improvement and whether this effect holds true across different populations and conditions.

Creatinine is a marker for renal function. While a decrease in Creatinine might generally be seen as favorable, the lack of statistical significance means we cannot definitively say that DTG treatment is improving renal function in the population studied. The results suggest that while DTG treatment might not adversely affect renal function (as indicated by the slight decrease in Creatinine), more research is needed to clarify its impact on kidney health. Continued monitoring of kidney function in patients on DTG is important, especially since some antiretroviral therapies can have renal implications. The findings indicate that while there is a trend towards decreased Creatinine levels, further studies with larger sample sizes or longer follow-up periods may be needed to establish clearer conclusions regarding the renal effects of DTG treatment.

The balanced distribution of males and females, especially in the 20-40 age group, suggests that both genders are represented similarly in the patient population undergoing DTG treatment. This is important for ensuring that treatment efficacy and safety profiles are applicable to both sexes. The lack of significant association implies that findings related to treatment outcomes or side effects of DTG are not confounded by age and sex in this sample. Researchers can analyze the efficacy and safety of DTG without needing to adjust for sex and age as potential confounding variables. 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.

Separate trial comparing DTG-based therapy with other approved regimens could not confirm the advantages or disadvantages of DTG-based therapy. 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, treatment-experienced patients outside of a clinical trial environment. Moreover, the endpoints reported in this meta-analysis are consistent with those used in randomized controlled trials and are widely used in clinical practice. It is also important to note that the lack of restrictions on inclusion criteria in real-world studies leads to substantial variations in patient populations, including multiple treatment backgrounds, different durations of treatment exposure, the presence of resistance mutations, experience of previous treatment failures and other characteristics that would normally exclude patients from randomized clinical trials, but may be more representative of real-world clinical setting.

More attention should be paid to the safety of a new drug, as it is possible to decrease patient adherence to treatments by increasing drug toxicities. Serious drug related adverse events were chosen as our primary outcome as a measure of the frequency of both clinically important and potentially life-threatening adverse drug events. The most common AEs with DTG

reported from the trials were nausea and headaches [20–23]. The forest plots for the clinical AEs suggest no statistically significant difference between DTG-based regimens and EFV-based regimens.

Future direction

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

CONCLUSIONS

These results show that the Dolutegravir (DTG)-based regimen is safe, effective, and improved quality of life (QOL), compared with the Efavirenz (EFV)–based regimen given daily to HIV Patients. Furthermore, viral suppression was not shown across patient populations and treatment histories of the individual studies included in this analysis.

ADDITIONAL INFORMATION AND DECLARATIONS

Acknowledgements Editorial support (in the form of writing assistance, assembling figures, collating author comments, grammatical editing and referencing) was provided by ART Center, MIHS, Nepal, and Asian Healthcare Foundation (AHF-Nepal). The authors would like to thank all individuals who provided their direct and indirect inputs and participation in this study.

Declaration of conflict: The authors declare no conflict of interest.

Author Contributions: Concept and design: RM; data collection and statistical analysis: RM and LBST; writing of the manuscript: RM, BKY, LBST, RC and VKS**;** monitoring and supervising the research finalizing the manuscript: RM, BKY, RC and all authors read and agreed with the contents of the final manuscript.

Data Availability: Data will be available upon request to corresponding authors after valid reason.

Funding: Self

:

REFERENCES

1. International C. Global report: UNAIDS report on the global AIDS epidemic 2013. *Geneva Switzerland Unaids*. 2013;(7):553–6.

2. Buzon MJ, Marfil S, Puertas MC, Garcia E, Clotet B, Ruiz L, et al. Raltegravir susceptibility and fitness progression of HIV type-1 integrase in patients on long-term antiretroviral therapy. *Antivir Ther.* 2008;13:881–93.

3. Blanco JL, Martinez-Picado J. HIV integrase inhibitors in ART-experienced patients. *Curr Opin HIV AIDS*. 2012;7:415–21.

4. Dorrucci M CL, Regine V, Giambenedetto SD, Perri GD, et al. Combined Antiretroviral Therapy (cART) Reduces AIDS-Related and Non- AIDS-Related Mortality: A Temporal Analysis from Time of Seroconversion (SC). *AIDS Clin Res*. 2015;6.

5. Rodger AJ, Lodwick R, Schechter M, Deeks S, Amin J, Gilson R, et al. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. *AIDS.* 2013;27(6):973–9.

6. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. *Lancet.* 2013;382(9903):1525–33.

7. Adih WK, Selik RM, Hu X. Trends in diseases reported on US death certificates that mentioned HIV infection, 1996-2006. *J Int Assoc Physicians AIDS Care (Chic).* 2011;10(1):5–11.

8. MacCarthy S, Hoffmann M, Ferguson L, Nunn A, Irvin R, Bangsberg D, et al. The HIV care cascade: models, measures and moving forward. *J Int AIDS Soc*. 2015;18:19395.

9. O'Brien ME, Clark RA, Besch CL, Myers L, Kissinger P. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr.* 2003;34(4):407–14.

10. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents Living with HIV. https://aidsinfo.nih.gov/ contentfiles/ lv guidelines/adult and adolescentgl. pdf.

11. Pommier Y, Johnson AA, Marchand C. Integrase inhibitors to treat HIV/ AIDS. *Nat Rev Drug Discov*. 2005;4:236–48.

12. European AIDS Clinical Society E. EACS Guidelines, Version 9.1, October 2018. 2018; [Available from: http://www.eacsociety.org/files/2018_ guidelines-9.1-english.pdf].

13. WHO. The use of antiretroviral drugs for treating and preventing HIV infection. http:// apps.who.int/ iris/bitstream/handle/10665/208825/ 9789241549684_eng. pdf?sequence=1; 2016.

14. Min S, Sloan L, DeJesus E, Hawkins T, McCurdy L, Song I, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of DTG as 10-day monotherapy in HIV-1-infected adults. *AIDS.* 2011;25:1737–45.

15. Hightower KE, Wang R, Deanda F, Johns BA, Weaver K, Shen Y, et al. DTG (S/GSK1349572) exhibits significantly slower dissociation than raltegravir and elvitegravir from wild-type and integrase inhibitorresistant HIV-1 integrase-DNA complexes. *Antimicrob Agents Chemother*. 2011;55:4552–9.

16. WHO. Updated recommendations on first-line and second-line Antiretroviral regimens and post-exposure prophylaxis and recommendations on early Infant diagnosis of HIV. http://apps.who.int/iris/bitstream/handle/10665/ 273632/WHO -CDS-HIV-18.18-eng.pdf ?ua=12018.

17. WHO. Updated recommendations on first-line and second-line Antiretroviral regimens and post-exposure prophylaxis and recommendations on early Infant diagnosis of HIV. http://apps.who.int/iris/bitstream/handle/10665/ 273632/WHO-CDS-HIV-18.18-eng.pdf?ua=12018.

18. Kanters S, Vitoria M, Doherty M, Socias ME, Ford N, Forrest JI, et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. *Lancet HIV.* 2016;3(11):e510–e20.

19.ViiV Healthcare. Dolutegravir (TIVICAY) Prescribing Information. https://www.

accessdata.fda.gov/drugsatfda_docs/label/2018/204790s016s018lbl.pdf; 2018.

20. Viiv Healthcare. Dolglutegravir (TIVICAY) Summary of product characteristics. 2019.

21. Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis.* 2013;13(11):927–35.

22. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviralnaive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet.* 2014;383(9936):2222–31.

23. Molina JM, Clotet B, van Lunzen J, Lazzarin A, Cavassini M, Henry K, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. *Lancet HIV.* 2015;2(4):e127–36.

24. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med.* 2013;369(19):1807–18.

25. van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, et al. Once daily DTG (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. *Lancet Infect Dis.* 2012;12:111–8.

26. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, et al. Once-daily DTG versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet.* 2013;381:735–43.

27. Walmsley S, Antela A, Clumeck N, et al. DTG (DTG, S/GSK1349572)+ abacavir/lamivudine once daily statistically superior to tenofovir/emtricitabine/efavirenz: 48-week results-SINGLE(ING114467). In: Abstract H-556b presented at the Fifty-second Inter-science Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA. Sept 9–12, 2012.

28. Cahn P, Pozniak AL, Mingrone H, Shuldyakov A, Brites C, AndradeVillanueva JF, et al. DTG versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet*. 2013;382:700–8.

29. Patel DA, Snedecor SJ, Tang WY, Sudharshan L, Lim JW, Cuffe R, et al. 48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naive HIV-1-infected patients: a systematic review and network meta-analysis. *PLoS One*. 2014;9(9):e105653.

30. Min S, Song I, Borland J, Chen S, Lou Y, Fujiwara T, et al. Pharmacokinetics and safety of S/GSK1349572, a next-generation HIV integrase inhibitor, in healthy volunteers. *Antimicrob Agents Chemother*. 2010;54:254–8.

31. Isentress(raltegravir)[packageinsert]. Whitehouse Station, NJ, Merck & Co, 2011.

32. R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.