AIDS Research and Therapy

RESEARCH

Open Access

Brief communication: Long-term treatment outcomes of transitioning to dolutegravir-based ART from efavirenz in HIV study participants in Mbeya, Tanzania

Revocatus T. Majula[1] and Clement N. Mweya[1*]

Abstract

Background The World Health Organization recommends dolutegravir-based antiretroviral therapy (ART) as the preferred first-line regimen for HIV treatment. This retrospective cohort study evaluated the long-term virologic outcomes and safety of transitioning from an efavirenz-based regimen (tenofovir, lamivudine, efavirenz [TLE]) to a dolutegravir-based regimen (tenofovir, lamivudine, dolutegravir [TLD]) among adult HIV participants in Mbeya, Tanzania.

Methods Medical records of 250 adult HIV participants who transitioned from TLE to TLD at Mbeya Zonal Referral Hospital were reviewed from August 2022 to December 2022. The primary outcome was virologic failure, defined as HIV RNA > 1000 copies/mL. Secondary outcomes included viral suppression (< 50 copies/mL) and adverse drug reactions (ADRs). Using appropriate statistical tests, participant characteristics and outcomes were compared before and six months after transitioning.

Results At baseline on TLE, 88% had viral suppression, and 3.6% had virologic failure. Six months after transitioning to TLD, viral suppression was 87.2% and virologic failure increased to 6.8%. Overall, 79.6% experienced ADRs with TLD, predominantly neurological effects and weight gain. No significant associations were found between viral load changes and participant characteristics like age, sex or treatment duration.

Conclusions Transitioning to dolutegravir maintained high rates of viral suppression comparable to efavirenz, albeit with a slight increase in virologic failure. Dolutegravir was well-tolerated overall despite a high ADR rate. Findings support the ongoing scale-up of dolutegravir in Tanzania and other resource-limited settings while highlighting the need for continued viral load monitoring and pharmacovigilance.

Keywords Efavirenz-based antiretroviral therapy, Dolutagravir-based antiretroviral therapy, Treatment outcomes, HIV-infected study participants, Retrospective evaluation, Tanzania

*Correspondence:
Clement N. Mweya
mweya.clement@udsm.ac.tz; mweyaclement@gmail.com
[1]Mbeya College of Health and Allied Sciences, University of Dar es Salaam, Mbeya, Tanzania

Introduction

The current preferred first-line regimen recommended by the World Health Organization (WHO) for managing HIV infection is a combination of tenofovir, lamivudine and dolutegravir (TLD) [1, 2]. Tanzania adopted this recommendation in 2019. Tanzania initiated a nationwide transition from tenofovir, lamivudine and efavirenz (TLE) to TLD in alignment with WHO recommendations [3]. This shift was driven by TLD's superior efficacy, reduced side effects, and a higher barrier to resistance, which were seen as critical to improving patient outcomes in a resource-limited setting [4]. The transition to TLD has been associated with challenges, including managing adverse drug reactions, ensuring patient adherence, and addressing socio-demographic factors that influence treatment outcomes [5]. These issues are particularly pertinent in the context of Tanzania's diverse HIV-affected populations.

While previous studies in high-income countries reported superior effectiveness of dolutegravir over efavirenz [6], there are questions about implementing dolutegravir in low- and middle-income countries like Tanzania, where genetics, nutrition and socio-demographics may impact treatment outcomes differently [7]. To our knowledge, there is limited published research on the outcomes of participants who transitioned from TLE to TLD in Tanzania. While some studies may be ongoing or unpublished, our study provides valuable insights into this transition in a Tanzania perspective.

This study, therefore, evaluated the virologic treatment outcomes and adverse drug reactions (ADRs) associated with transitioning from TLE to TLD in southwest Tanzania. The findings provide insights into the virologic outcomes and tolerability of dolutegravir in Tanzanian HIV study participants who transitioned from an efavirenz-based regimen, as well as contextual reasons for adopting dolutegravir-based ART in this setting. Results can enhance medication adherence and tolerability for dolutegravir regimens.

Methods

Study design and population

The descriptive retrospective study was conducted over a period of five months, from August 2022 to December 2022, to review the medical records of adult HIV participants at the HIV Care and Treatment Clinic (CTC) of Mbeya Zonal Referral Hospital (MZRH). Study participants who had been on a TLE regimen for at least six months before transitioning to a TLD regimen and had been on the TLD regimen for at least six months were included in the analysis. The study period was selected because, by 2022, the majority of people living with HIV (PLHIV) in the Mbeya region had transitioned to TLD, allowing for an evaluation of long-term outcomes within a stabilized treatment population.

The study utilized a hospital database of HIV-infected participants attending the CTC at MZRH. Inclusion criteria were: (1) participants who had been on a TLE regimen for at least six months before transitioning to a TLD regimen, (2) participants who had been on the TLD regimen for at least six months, and (3) adult participants (aged 18 years and above). Exclusion criteria were: (1) participants who had been on a TLE regimen for less than six months, (2) participants who had been on a TLD regimen for less than six months, and (3) participants below 18 years of age. These criteria ensured that we evaluated participants with sufficient exposure to both regimens to assess virologic outcomes and adverse reactions effectively. Mbeya is among the regions in Tanzania with a high prevalence of HIV infection, ranking third in the country with a prevalence of 9.3% [8, 9].

The initial sample size calculation indicated that 200 participants would be sufficient to achieve the desired statistical power. To account for potential issues such as incomplete medical records or missing data, we recruited 250 participants. This buffer helps ensure that the final dataset remains robust and statistically significant. The sample size was calculated using the Kish formula [10] obtained from the prevalence (p) of dolutegravir adverse effects in Germany, which is 7.6%, as it provided a reliable basis for ensuring the detection of significant differences in ADRs. This approach allowed us to also capture virologic outcomes with sufficient statistical power. The margin of error (Ɛ) allowed was 0.038%, and a 95% confidence interval (z = 1.96) was used. The sampling frame consisted of the medical records of HIV-infected participants attending the HIV Care and Treatment Clinic (CTC) at Mbeya Zonal Referral Hospital (MZRH). The sampling interval was determined by dividing the total number of eligible participants by the desired sample size. For this study, with a calculated sample size of 250 participants and an eligible population of approximately 1,000 participants, the sampling interval was set at every 4th participant (1,000/250).

Measurements

Data was collected from the CTC database at MZRH and recorded in Microsoft Excel. The following information was gathered: study participants sociodemographic details, TLE start date, TLD start date, months on regimens, current WHO stage, baseline viral load, six-month post-transition viral load and reported adverse drug reactions (ADRs). ADRs were defined as any unintended harmful response to a drug at normal doses. They were categorized according to pharmacovigilance data standards as captured in the CTC database. The primary outcome measured was virologic failure, defined as HIV

RNA > 1000 copies/mL. Secondary outcomes included viral suppression, defined as HIV RNA < 50 copies/mL, and the incidence of adverse drug reactions (ADRs). Additionally, the incidence of ADRs was recorded and analyzed to assess the safety profile of the TLD regimen.

Statistical analysis

Data were analyzed using SPSS version 23. Summary statistics were calculated. The data analysis involved comparing pre-transition and post-transition values for virologic outcomes and adverse drug reactions (ADRs). Specifically, we compared the viral load (measured as HIV RNA copies/mL) and the rate of viral suppression (defined as <50 copies/mL) as the primary outcome before transitioning from a TLE regimen to six months after transitioning to a TLD regimen. Additionally, we compared the incidence of virologic failure (defined as HIV RNA > 1000 copies/mL) and the frequency of reported ADRs between the two-time points. In this study, ADR is defined as any unintended or harmful response to a drug that occurs at normal doses used for prophylaxis, diagnosis, or therapy. The comparisons were made within the same group of participants, analyzing their clinical data before and after the transition to the TLD regimen. A p-value < 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of the study participants ($n = 250$)

Out of 250 HIV study participants included in the study, the majority were female (75.6%), with a mean age of 45.60 ± 11.48 years. 52.8% were aged 36–50 years, while only a small proportion (2.0%) were aged 0–18. Most participants were WHO stage 3 (69.2%), followed by stage 4 (23.2%), stage 1 (5.2%), and stage 2 (2.4%). Approximately two-thirds (67.2%) had been on a dolutegravir-based regimen for over 24 months, while 30.4% were on it for under 12 months. Over half (62.0%) were on an efavirenz-based regimen for over 72 months before transitioning. The majority (79.6%) experienced adverse drug reactions in dolutegravir. A viral load decrease was seen in 19.2% of study participants after transitioning to dolutegravir.

Study participant's virological suppression results

At baseline, 220 out of 250 study participants (88%) had viral suppression with <50 copies/ml, while the remaining 30 study participants (12%) had ≥ 50 copies/ml. After six months on the dolutegravir regimen, 218 study participants (87.2%) had < 50 copies/ml compared to 32 study participants (12.8%) with ≥ 50 copies/ml. A chi-square test was performed to assess the significance of the differences in viral suppression before and after switching to the dolutegravir regimen. The results showed a statistically significant difference between pre-switch and post-switch viral suppression rates, $\chi^2(1, n = 250) = 38.56$, $p < 0.001$. There was a slight decrease in the proportion of study participants with viral suppression < 50 copies/ml from 88% at baseline to 87.2% six months after the transition to dolutegravir. The proportion of study participants with a detectable viral load ≥ 50 copies/ml increased slightly from 12% at baseline to 12.8% at six months.

Virological failure after transitioning to a dolutegravir-based regimen

At baseline, 9 out of 250 study participants (3.6%) had virological failure with > 1000 copies/ml. The remaining 241 study participants (96.4%) had ≤ 1000 copies/ml. After six months on the dolutegravir regimen, the rate of virological failure increased −17 study participants (6.8%) now had > 1000 copies/ml compared to 233 study participants (93.2%) with ≤ 1000 copies/ml. There was an increase in the proportion of study participants experiencing virological failure from 3.6% at baseline to 6.8% at six months after transitioning to dolutegravir. The proportion of study participants with viral suppression (≤ 1000 copies/ml) decreased slightly from 96.4 to 93.2%.

Study participant characteristics and primary outcomes: post-transition viral load decrease

Table 1 shows the association between study participants characteristics and decreased viral load after transitioning to dolutegravir-based therapy. Only 19.2% of study participants experienced a viral load decrease post-transition. There were no significant differences based on sex, age group, WHO stage, adverse drug reactions, or duration of dolutegravir or efavirenz use. The proportions with decreased viral load were similar for females (19.05%) and males (19.67%) across age groups, WHO stages, presence or absence of adverse reactions, and durations of less than 12 months, 12–24 months, or more than 24 months on dolutegravir and efavirenz. Of the 250 study participants, approximately 19% were previously on an efavirenz-based regimen that showed a viral load decrease after transitioning to a dolutegravir-based regimen.

Potential adverse drug reactions

Of the 199 study participants with available adverse drug reaction (ADR) data, the most pronounced ADRs were neurological effects, especially neuropathy. Many study participants also experienced weight gain and increased appetite. Additional reported ADRs included neuropsychiatric symptoms (e.g., nightmares, insomnia, illusions, drowsiness, nervousness), dermatological effects, and gastrointestinal disturbances. None of the ADRs were severe, and no study participants discontinued dolutegravir due to ADRs (Fig. 1).

Table 1 Association between the study participant's characteristics and the decrease in viral load after transitioning from an efavirenz-based regimen to a dolutegravir-based regimen

Variable	Categories	Post-transition Viral Load Has Decreased		p-value
		No (%)	Yes (%)	
Sex	Female	153 (80.95)	36 (19.05)	1
	Male	49 (80.33)	12 (19.67)	
Age Groups	0–18 Years	4 (80.00)	1 (20.00)	0.6131
	19–35 Years	21 (61.76)	13 (38.24)	
	36–50 Years	110 (83.33)	22 (16.67)	
	51 + Years	67 (84.81)	12 (15.19)	
WHO Stage	Stage 1	11 (84.62)	2 (15.38)	0.5766
	Stage 2	6 (100.00)	0 (0.00)	
	Stage 3	137 (79.19)	36 (20.81)	
	Stage 4	48 (82.76)	10 (17.24)	
Study participant has ADR	No	39 (76.47)	12 (23.53)	0.4961
	Yes	163 (81.91)	36 (18.09)	
TLD Duration Category	Less than 12 months	56 (73.68)	20 (26.32)	0.1682
	12–24 months	5 (83.33)	1 (16.67)	
	More than 24 months	141 (83.93)	27 (16.07)	
EFV Duration Category	Less than 36 months	33 (89.19)	4 (10.81)	0.1862
	36–72 months	43 (74.14)	15 (25.86)	
	More than 72 months	126 (81.29)	29 (18.71)	
	Yes	34 (73.91)	12 (26.09)	

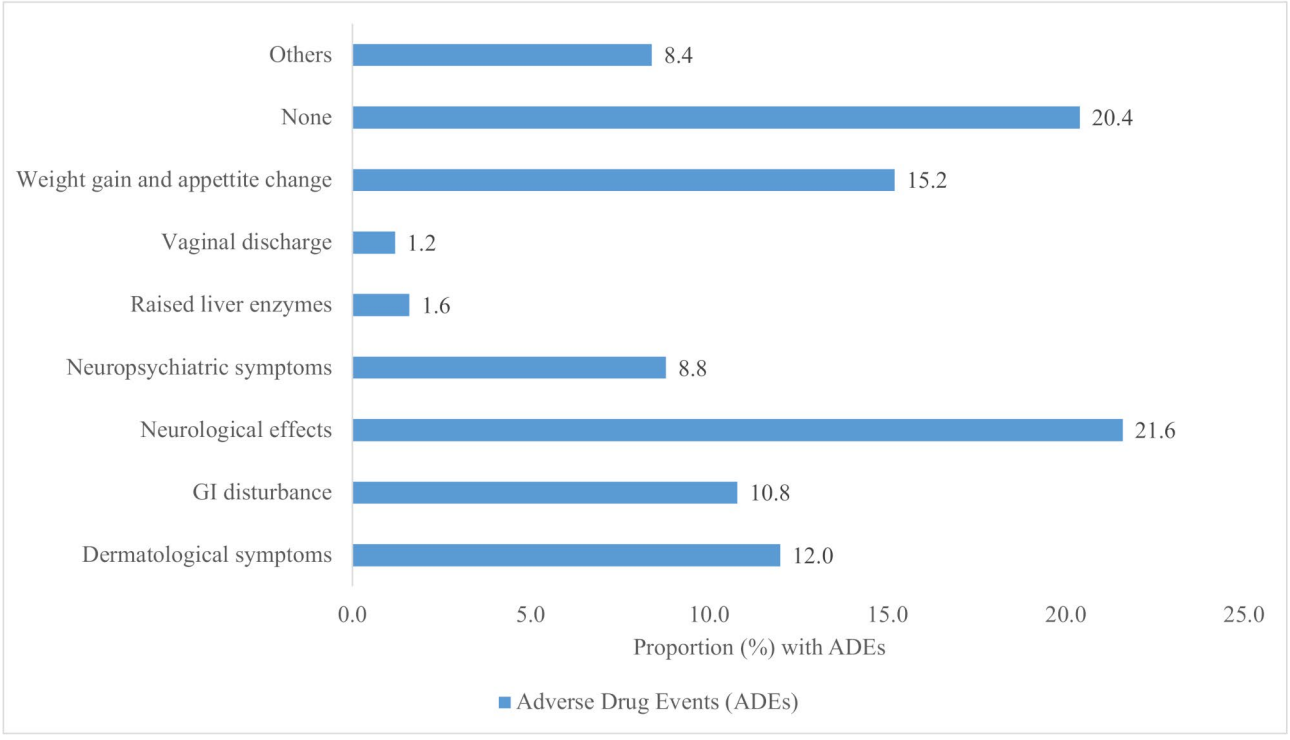

Fig. 1 Potential adverse drug reactions experienced by HIV study participants after transitioning from an efavirenz-based regimen to a dolutegravir-based regimen

Discussion

In our study of 250 participants, the demographic and clinical characteristics align with previous reports, comprising predominantly middle-aged females with stage 3 disease who were on efavirenz for lengthy durations before transitioning to dolutegravir regimens used for over 24 months. At the last measurement before transitioning from TLE, 88% had viral suppression (< 50

copies/mL), similar to 87.2% at six months after transitioning to the TLD regimen, indicating similar virologic outcomes between the two regimens, consistent with findings from a study in Cameroon [11]. However, only 10% suppressed in <36 months on efavirenz, 26.32% suppressed in <12 months after transitioning to dolutegravir, consistent with reports of higher dolutegravir efficacy over efavirenz [1, 12].

Virological failure increased slightly from 3.6% at baseline to 6.8% after transitioning to dolutegravir. While lower than 16.6% were reported elsewhere [13], this increase may relate to shorter dolutegravir use and poor adherence, as suggested by previous studies that link failure to these factors [13–15]. Regarding safety, 79.6% reported ADRs after transitioning, mainly neurological effects (27.1%) and weight gain (19.1%), aligning with known dolutegravir ADR profiles [16–19]. No ADRs were severe enough to discontinue dolutegravir [20].

We found no significant associations between viral load decrease after transitioning and factors like sex, age, WHO stage, adverse effects, or regimen durations ($p>0.05$ for all comparisons) (Table 1). This contrasts with some prior reports of associations with age and drug toxicity [14]. Our study had comparable viral suppression in females (19.1%) and males (19.7%). The youngest adults (19–35 years) had the highest suppression (38.2%) versus other ages. Among WHO stages, stage 3 showed the highest proportion (20.8%) with viral suppression compared to other stages, although staging was not significantly associated with suppression ($p=0.5766$).

This study has some important limitations to consider. Being a retrospective review of existing clinical data, we were limited to information recorded in the medical records, which may be incomplete or subject to documentation errors. Data on potential confounding factors like adherence, co-morbidity, and concomitant medications were not consistently available and could not be accounted for. Additionally, our analysis relied on a single viral load measurement at two time points, which may not fully capture the dynamics of virologic response over time. A prospective longitudinal study designed with systematic data collection would help overcome these limitations. Despite the methodological constraints inherent to retrospective studies, our findings provide valuable real-world insights into important clinical issues while transitioning to dolutegravir-based ART in resource-limited settings like Tanzania.

In conclusion, this study demonstrates the effectiveness of TLD in reducing viral load while maintaining good tolerability and adherence in HIV study participants. However, prospective studies are still needed, particularly in developing countries, to evaluate further the long-term benefits and safety profile of dolutegravir-based ART regimens. Continued active monitoring by regulatory bodies is also recommended to assess dolutegravir safety in real-world HIV/AIDS study participants population over time. Optimizing the implementation of effective and well-tolerated dolutegravir therapy represents a critical strategy for ending the HIV/AIDS epidemic worldwide.

Abbreviations

ADRs	adverse drug reactions
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CTC	Care and Treatment Clinic
HIV	human immunodeficiency virus
MCHAS	Mbeya College of Health and Allied Sciences
MZRH	Mbeya Zonal Referral Hospital
PLHIV	People Living with HIV
SPSS	Statistical Package for Social Sciences
TLD	tenofovir, lamivudine and dolutegravir
TLE	tenofovir, lamivudine and efavirenz
UDSM	University of Dar es Salaam
WHO	World Health Organization

Acknowledgements
We thank the administration of Mbeya Zonal Referral Hospital for permitting the use of data from the hospital. Finally, we thank the Tanzania Higher Education Student Loan Board (HESLB) for supporting this project financially.

Author contributions
RTM and CNM conceived and designed the study. RTM performed data collection and contributed to data analysis. RTM and CNM interpreted the data. CNM drafted the original manuscript. All authors contributed to subsequent revisions of the manuscript. All the authors have read and approved the final manuscript.

Funding
The authors received no external funding for the research, authorship or publication of this article. The study was conducted as part of a Doctor of Medicine (MD) research project by Revocatus T. Majula at the University of Dar es Salaam, Mbeya College of Health and Allied Sciences (UDSM-MCHAS). The project received internal financial support from the Tanzania Higher Education Student Loan Board (HESLB).

Data availability
The data presented in this study are available on reasonable request from the corresponding author.

Declarations

Ethical approval and consent to participate
This study received approval from the University of Dar es Salaam (UDSM), Mbeya College of Health and Allied Sciences (MCHAS) Research Ethical Clearance Sub-Committee (Ref No.: 2018-04-13276). The confidentiality and privacy of participants' information were protected during the record review. Identifying details such as names were excluded from the records to maintain anonymity. Since this retrospective study reviewed existing medical records, individual consent was unnecessary. However, MZRH administration granted a waiver of informed consent while ensuring appropriate protections were in place to safeguard participants' rights and privacy.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 5 February 2024 / Accepted: 1 October 2024
Published online: 23 December 2024

References

1. World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. 2021. https://www.who.int/publications-detail-redirect/9789240031593. Accessed 6 Aug 2023.
2. World Health Organization. United Republic of Tanzania: HIV Country Profile: 2017. World Health Organisation; 2020.
3. Ministry of Health. Community Development, gender, Elderly and Children (MoHCDGEC). National Guideline for the management of HIV and AIDS. National AIDS Control Programme; 2019.
4. Mutagonda RF, Mlyuka HJ, Maganda BA, Kamuhabwa AAR. Adherence, effectiveness and safety of Dolutegravir based antiretroviral regimens among HIV infected children and adolescents in Tanzania. J Int Assoc Provid AIDS Care. 2022;21:23259582221109613.
5. Mccluskey SM, Pepperrell T, Hill A, Venter WDF, Gupta RK. Adherence, resistance, and viral suppression on dolutegravir in sub-saharan Africa: implications for the TLD era. AIDS Lond Engl. 2021;35(Suppl 2):S127–35.
6. Zash R, Makhema J, Shapiro RL. Neural-tube defects with Dolutegravir Treatment from the Time of Conception. N Engl J Med. 2018;379:979–81.
7. Tsuchiya K, Ohuchi M, Yamane N, Aikawa H, Gatanaga H, Oka S et al. High-performance liquid chromatography-tandem mass spectrometry for simultaneous determination of raltegravir, dolutegravir and elvitegravir concentrations in human plasma and cerebrospinal fluid samples. Biomed Chromatogr BMC. 2018;32.
8. Kway A, Sabi I, Olomi W, Mcharo RD, Sanga E, William W, et al. HIV testing and linkage to care—A case of a mobile diagnostic and counseling service in Mbeya, Tanzania; a quantitative study. PLOS Glob Public Health. 2022;2:e0000448.
9. Sanga ES, Mukumbang FC, Mushi AK, Lerebo W, Zarowsky C. Understanding factors influencing linkage to HIV care in a rural setting, Mbeya, Tanzania: qualitative findings of a mixed methods study. BMC Public Health. 2019;19:383.
10. Wiegand H, Kish L: Survey Sampling. John Wiley, Sons I, York N. London 1965, IX + 643 S., 31 Abb., 56 Tab., Preis 83 s. Biom Z. 1968;10:88–9.
11. Calmy A, Tovar Sanchez T, Kouanfack C, Mpoudi-Etame M, Leroy S, Perrineau S, et al. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. Lancet HIV. 2020;7:e677–87.
12. NAMSAL ANRS 12313 Study Group, Kouanfack C, Mpoudi-Etame M, Omgba Bassega P, Eymard-Duvernay S, Leroy S, et al. Dolutegravir-based or low-dose efavirenz-based regimen for the treatment of HIV-1. N Engl J Med. 2019;381:816–26.
13. Nega J, Taye S, Million Y, Rodrigo C, Eshetie S. Antiretroviral treatment failure and associated factors among HIV patients on first-line antiretroviral treatment in Sekota, northeast Ethiopia. AIDS Res Ther. 2020;17:39.
14. Emagnu A, Abay Z, Bulti AB, Animut Y. Determinants of Virologic Failure among adult HIV patients on first-line antiretroviral therapy at Waghimra Zone, Northern Ethiopia: a case-control study. Adv Public Health. 2020;2020:e1929436.
15. Dorward J, Lessells R, Drain PK, Naidoo K, de Oliveira T, Pillay Y, et al. Dolutegravir for first-line antiretroviral therapy in low-income and middle-income countries: uncertainties and opportunities for implementation and research. Lancet HIV. 2018;5:e400–4.
16. Elzi L, Erb S, Furrer H, Cavassini M, Calmy A, Vernazza P, et al. Adverse events of raltegravir and dolutegravir. AIDS Lond Engl. 2017;31:1853–8.
17. Hoffmann C, Welz T, Sabranski M, Kolb M, Wolf E, Stellbrink H-J, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017;18:56–63.
18. Bourgi K, Rebeiro PF, Turner M, Castilho JL, Hulgan T, Raffanti SP, et al. Greater Weight Gain in treatment-naive persons starting Dolutegravir-based antiretroviral therapy. Clin Infect Dis off Publ Infect Dis Soc Am. 2020;70:1267–74.
19. World Health Organization. Dolutegravir (DTG) and the fixed dose combination (FDC) of tenofovir/lamivudine/dolutegravir (TLD) April 30 2018 Briefing note. Geneva, Switzerland; 2018.
20. van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, et al. Once daily dolutegravir (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.

Publisher's note