HIV/AIDS - Research and Palliative Care

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Prevalence and Patterns of Adverse Drug Events Among Adult Patients with Human Immune Virus Infection on Dolutegravir-Based Antiretroviral Drug Regimens in Amhara Comprehensive Specialized Hospitals, Northwest Ethiopia: A Multicenter Retrospective Follow-Up Study

Alemu Birara Zemariam[1], Yabibal Berie Tadesse[2], Abebe Tarekegn Kassaw[3]

[1]Department of Pediatrics and Child Health Nursing, School of Nursing, College of Medicine and Health Sciences, Woldia University, Woldia, Ethiopia; [2]Department of Pharmaceutical Chemistry, School of Pharmacy, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia; [3]Department of Pharmacy, College of Medicine and Health Sciences, Woldia University, Woldia, Ethiopia

Correspondence: Alemu Birara Zemariam, Tel +251913162327, Email alexb7298@gmail.com

Background: Antiretroviral therapy (ART) refers to any HIV treatment that uses a combination of two or more drugs to suppress viral load and preserve immunofunction. Despite the success of ART, adverse events persist, in particular in patients with baseline viral loads >100,000 copies/mL. Apart from premarketing surveillance, the safety and risk profile of dolutegravir has not been thoroughly researched in Ethiopia. Therefore, this study aimed to assess the prevalence and patterns of adverse drug events among HIV-infected adult patients on dolutegravir-based ART regimens at Amhara comprehensive specialized hospitals, northwest Ethiopia.

Methods: A retrospective follow-up study was conducted from January 1, 2019 to December 31, 2021 at Amhara comprehensive specialized hospitals, with a sample size of 423. Simple random sampling was employed and data collected using kobo tool box software by four trained BSc nurses from March to April, 2022. SPSS 25 was used for analysis. Descriptive summary statistics are used and data presented using tables and text.

Results: A total of 372 patient charts were included in the final analysis, and the prevalence of adverse events associated with dolutegravir was found to be 37.6% (95% CI 32.1%–42.1%). Nearly two-thirds (60.7%) of the participants had neuropsychiatric symptoms, followed by gastrointestinal symptoms (23.6%) and hepatic problems (7.14%). All recorded adverse events were mild.

Conclusion: Dolutegravir adverse events were relatively low compared to previous studies. Common adverse events reported were neuropsychiatric symptoms and gastrointestinal symptoms, followed by hepatic and renal events. All adverse events were mild and none was severe or life-threatening events. Therefore, we recommend the use of dolutegravir in clinical settings.

Keywords: adverse drug event, antiretroviral therapy, dolutegravir, HIV

Introduction

Antiretroviral therapy (ART) refers to any HIV treatment that uses a combination of two or more drugs to effectively suppress viral load and preserve immunofunction.[1] The initiation of ART has made HIV infection a chronic manageable disease for many patients.[2] Nowadays, patients receiving ART have access to a wide choice of therapeutic alternatives and have strong long-term survival chances. ART has unquestionably been successful, but there are still safety and efficacy issues with many medications, especially in individuals with baseline virus loads >100,000 copies/mL.[3]

Integrase strand-transfer inhibitor–based regimens are currently among the suggested and preferred first-line ARTs for the treatment of HIV1 infection, due to their benign side-effect profile, minimal drug–drug interactions, and virological

Received: 28 March 2023
Accepted: 28 May 2023
Published: 1 June 2023

efficacy. Dolutegravir (Dtg) is a new-generation integrase strand-transfer inhibitor that is recommended as the core first-line drug for the treatment of HIV patients due to its specific benefits over other antiretroviral medicines currently on the market.[4] It is anticipated that Dtg will have a strong barrier to resistance based on in vitro investigations and clinical trials in ART-naïve individuals.[3] Initiation of Dtg presents a significant opportunity for an efficient and longer-lasting treatment.[5]

All first-line regimens are now being switched over to this combination in a number of sub-Saharan African nations, including Ethiopia. Because levels of safety, efficacy, and associated factors vary across measures, patient subgroups, clinical stages, clinics, regions, and health-care systems, it is crucial to characterize these in each setting. As a result, measuring patient-reported outcomes like side-effect profile and positive outcomes is essential, especially in resource-limited countries.[6] Hence, weighing the advantages and disadvantages of a Dtg-based regimen is crucial in everyday clinical practice to assist, maintain, and increase patient well-being. Evidence on the new regimen is still required for low- and middle-income nations in order to make the best use of scarce resources.

In general, switching to a Dtg regimen necessitates careful monitoring of its therapeutic effectiveness. However, data on Dtg adverse drug events (ADEs) are limited in developing countries, such as Ethiopia. Therefore, the purpose of this study was to assess the prevalence and pattern of Dtg-based ART regimens among adult HIV patients. The study's conclusions may then help policymakers create interventions that are supported by the best available scientific evidence. This will also be advantageous to patients and the general public, aiding in the provision of health counseling and support by families and medical experts. It will also serve as a baseline for researchers who are interested in conducting in-depth studies.

Methods

Study Design, Period, and Setting

A multicenter retrospective follow-up study was conducted from January 1, 2019 to December 31, 2021. The study was conducted in Amhara region's comprehensive specialized hospitals. These include Debre Tabor, the University of Gondar, Felege Hiwot, and Debre Markos comprehensive specialized hospitals. These are located 592 km, 727 km, 492 km, and 300 km from Addis Ababa, respectively. The hospitals serve more than 2.7 million, 7 million, 5 million, and 3.5 million people from the catchment area, respectively. Apart from other services, all the comprehensive specialized hospitals have provided ART services for adult HIV-infected patients since 2005. From January 1, 2019 to December 31, 2021, a total of 530 HIV-infected adult patients were initiated on Dtg-based ART regimens.

Population

All HIV-infected patients aged ≥18 years who had initiated Dtg-based ART at Amhara region comprehensive specialized hospitals were considered the target population, and all HIV-infected patients aged ≥18 years who had initiated Dtg-based ART from January 1, 2019 to December 31 2021 in selected Amhara region comprehensive specialized hospitals were considered the study population.

Eligibility Criteria

All HIV-infected patients aged ≥18 years who had initiated and had been on treatment for at least 6 months were included, and adult HIV-infected patients who had incomplete charts or did not have a minimum of one follow-up visit were excluded from the study.

Sample-Size Determination

Sample size was determined by single proportion formula considering assumptions of confidence level of 95%, margin of error 5%, and 50% prevalence of ADEs):

$N = \frac{z^2 p(1-p)}{w^2}$ where n= number of samples, z= standard score at 95% CI which is 1.96.

The total sample size was 384. After adding 10% for incomplete charts, the final adequate sample size was 423.

Sampling Procedure

Initially, the numbers of adults ≥18 years of age initiated on Dtg-based ART from January 1, 2019 to December 31, 2021 were taken from the database of each hospital. After that, the sample size was proportionally allocated based on the number of patients who were receiving Dtg-based ART in each hospital: 140 of 175 from the University of Gondar Hospital, 88 of 110 from Felege Hiwot Hospital, 127 of 160 from Debre Markos Hospital, and 68 of 85 from Debre Tabor Hospital. A total of 423 medical charts were retrieved, of which 51 were excluded due to exclusion criteria. Finally, computer-generated simple random sampling was employed to select the study participants (Figure 1).

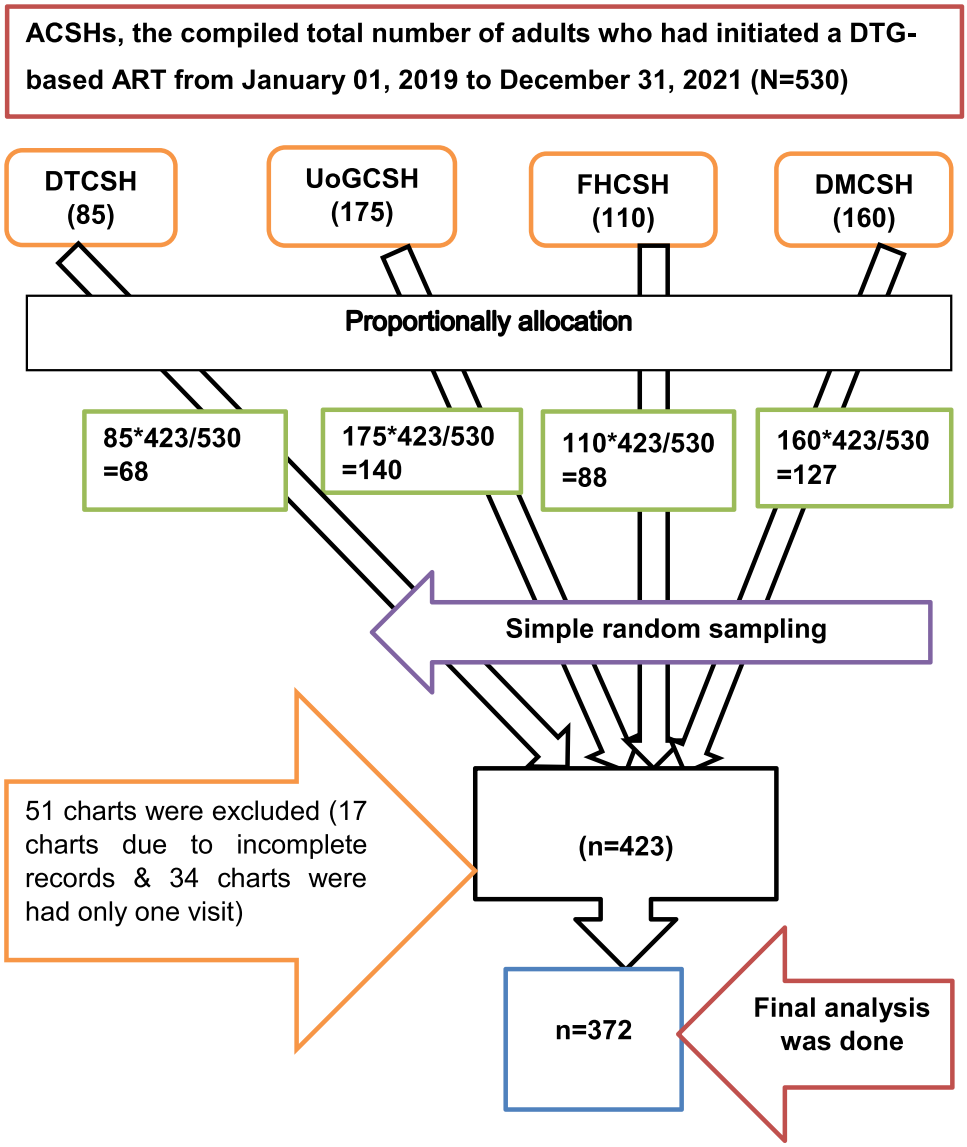

Figure 1 Schematic presentation of sampling procedure to assess prevalence and patterns of adverse drug events.
Abbreviations: ARCHs, Amhara region comprehensive specialized hospitals; ART, antiretroviral therapy; DMCSH, Debre Markos Comprehensive Specialized Hospital; DTCSH, Debre Tabor Comprehensive Specialized Hospital; Dtg, dolutegravir; FHCSH, Felege Hiwot Comprehensive Specialized Hospital; n, total sample size; N, total source population; UoGCSH, University of Gondar Comprehensive Specialized Hospital.

Data-Collection Tool and Procedures

A data-abstraction tool was adapted from an Ethiopian Federal Ministry of Health ART guideline. Charts were accessed based on medical record numbers. Then, data on sociodemographic variables, baseline clinical and laboratory-related factors, and treatment-related factors of HIV-infected children were collected using Kobo Toolbox software after designing all of the questionnaires in this software and installing them on smartphones. The data were collected by four trained BSc nurses from March to April 2022. Data were extracted from the charts using the data-abstraction tool.

Study Variable

- Occurrence of ADEs (yes/no).

Operational Definition

According to the World Health Organization, an ADE is defined as a list of patient-reported symptoms recorded on their charts as a result of Dtg use that must be confirmed by a physician as being due to Dtg use and also including all available laboratory test results.[7–9]

Data Quality Assurance

A pretest was conducted on 10 patients and their charts at the University of Gondar Hospital before the actual data collection. After that, the necessary amendments were made. Data quality was also guaranteed with proper recruitment, and 1 day's training was also given to data collectors in each hospital concerning the use of software, the data-abstraction tool, and the data-collection process. The principal investigator and supervisor closely supervised the data-collection process on-site and/or on the server and gave prompt feedback to the data collector. At the end of each data-collection day, data completeness and consistency were cross-checked by both the principal investigator and the supervisor. All four data collectors had basic and comprehensive HIV care-and-treatment training and the supervisor had ART mentoring certificates.

Data Processing and Analysis

Data were checked, coded, and cleaned, then exported to SPSS 25 for analysis. The prevalence of ADE was estimated using simple descriptive summary statistics, such as frequency and proportion. Tables and text are used to present the results of the analyzed data.

Ethics

Ethics clearance was obtained from the University of Gondar College of Medicine and Health Sciences School of Nursing Ethical Clearance Review Committee (January 9, 2022, ECRC 245/2022). A consent waiver was obtained from the ethics committee. Then, the data were collected after getting a permission letter from each hospital. Since the study was done through the review of medical records, the individual patients would not be subjected to harm as long as confidentiality were kept. To keep confidentiality, the patients' clinical records were reviewed anonymously and names and unique ART numbers were not included in data collection. Information obtained from patient medical records was kept confidential and used merely for this particular study. This study was in compliance with the Declaration of Helsinki.

Results

Sociodemographic and Baseline Clinical and Laboratory Characteristics of the Participants

A total of 423 medical records of adult patients who were on Dtg-based antiretroviral regimens were retrieved. After excluding 51 charts due to exclusion criteria, we had 372 charts for the final analysis. Of these, nearly two-third s 247 (63.4%) were female and the mean age was 29.28±11.6 years. A majority of the participants(220, 59.1%), were urban dwellers, and 117 (31.5%) hadhad a primary school education. At the timet of the survey, the mean

Table 1 Socio-demographic, baseline clinical and laboratory characteristic of participants (n=372)

		n	%
Sex	Male	125	33.6
	Female	247	63.4
Residence	Urban	220	59.1
	Rural	152	40.9
Age, years	18–31	164	44.1
	32–44	169	45.4
	45+	39	10.5
Education	None	57	15.3
	Primary	117	31.5
	Secondary	101	27.1
	College and above	97	26.1
CD4 count baseline	Below the threshold (<200/mm^3 or <15%)	110	29.6
	Above the threshold (≥200/mm^3 or ≥ 15%)	262	70.4
WHO stage	I and II	302	81.2
	III and IV	70	18.8
Viral load	Suppressed (<1000 copies/mL)	276	74.2
	Unsuppressed (>1000 copies/mL)	96	25.8
Functional status	Working	297	79.8
	Ambulatory	51	13.7
	Bedridden	24	6.5
Adherence	Good	276	74.2
	Fair/poor	96	25.8
Duration on Dtg-based ART regimen	<1 year	54	14.5
	≥1 year	318	85.5

overall duration on Dtg-based ART was 1.9±0.6 years, more than two-thirds of the participants 262 (70.4%) had a baseline CD4 count above the threshold, and a majority of the participants were classified as WHO clinical stage I and II (Table 1).

Physician-Confirmed Symptoms from Patient Reports and Laboratory Test Results of Dtg-Related Adverse Events

The prevalence of at least one ADE was 37.6% (95% CI 32.1%–42.1%). Nearly two-thirds (60.7%) of the participants had neuropsychiatric symptoms, followed by gastrointestinal symptoms (23.6%) and hepatic problems (7.14%). Among the neuropsychiatric symptoms recorded by physicians was insomnia (21.4%), and diarrhea had also been reported, confirmed, and recorded by the physicians as a gastrointestinal AED in 12.1% of patients. All ADEs recorded by physicians were mild, and none was severe, life-threatening, or led to hospitalization or death (Table 2).

Table 2 Patient-reported and laboratory test results of Dtg-related adverse events

		n	%
Adverse event	Yes	140	37.6
	No	232	62.4
Neuropsychiatric	Insomnia	30	21.4
	Depression	12	8.6
	Anxiety and mood disorders	17	12.1
	Dizziness/headache	21	15
	Bilateral visual change	5	3.6
Gastrointestinal	Diarrhea	17	12.1
	Nausea/vomiting	11	7.9
	Heartburn/stomach pain	5	3.6
Renal		9	6.4
Hepatic		10	7.14
Diabetes		3	2.14

Discussion

Despite the optimal efficacy and safety profile of Dtg-based regimens demonstrated in clinical trials, recent studies have questioned the tolerability of Dtg because of a high incidence of discontinuation reporting due to toxicity, mainly related to neuropsychiatric events associated with Dtg.[10–16] Even with the upcoming widespread use of Dtg as part of dual regimens in ART-naïve and -experienced patients, as well as being the first-line option in resource-constrained countries like Ethiopia, additional studies are required to accurately estimate the ADE prevalence and tolerability profile of Dtg-based regimens in real-world settings.[15,17,18] This study was intended to assess the prevalence and patterns of Dtg-associated ADEs among adult HIV-infected patients on Dtg-based ART regimens in Amhara comprehensive specialized hospitals, northwest Ethiopia.

The prevalence of at least one ADE among adult patients on Dtg was 37.6% (95% CI 32.1%–42.1%). This finding was in line with a study conducted in Uganda,[19] which reported a prevalence of 33.1% of ADEs among patients on Dtg-based regimens. The similarity might be due to the same study design, outcome measurement, and study population used in the studies. The current study's figure was higher than in a study conducted in Brazil,[20] which revealed that the prevalence of ADEs was 10%. This could be due to a variance in population characteristics and study periods.

A majority of the participants had neuropsychiatric followed by gastrointestinal symptoms. Among the neuropsychiatric ADEs, insomnia was the most commonly reported. This symptom might contribute to poor patient adherence to drug treatment. The current finding is supported by studies from Italy and Brazil,[14,20] but incongruent with former findings[21,22] where insomnia along with depression and mood disorders were the commonest neuropsychiatric symptoms associated with Dtg and resulting in treatment discontinuation and switching.

Nevertheless, the rate of Dtg discontinuation due to ADEs like neuropsychiatric events observed in this study was analogous to several previous studies,[6,14,16] with the highest occurrence reported in a Dutch cohort.[14] In a large-cohort study, although the rates of ADEs leading to treatment discontinuation were similar between Dtg and elvitegravir (7.6% at 12 months), the risk of discontinuing treatment due to neuropsychiatric events was consistently higher for the former (5.6% vs 0.7% at 12 months),[17,18] although the deployment of Dtg in resource-constrained nations is anticipated to be both economical and effective, especially in light of the rising prevalence of pretreatment NNRTI resistance.[23]

Strengths and Limitations

This study has described the real-life setting of Dtg-based ADEs by physician-confirmed and patient reports and laboratory findings. We used a 3-year retrospective design, which helped in assessing both short- and long-term ADEs associated with the use of Dtg. However, the study has its limitations, eg, we used merely descriptive statistics, and some variables were excluded due to incompleteness as the data source was secondary (chart review).

Conclusion and Recommendation

ADEs were relatively low compared to previous studies. This commonest ADEs in laboratory test results and reported by patients were neuropsychiatric symptoms and gastrointestinal symptoms, followed by hepatic and renal. The findings also revealed that all the recorded ADEs were mild and none severe or life-threatening events leading to hospitalization or death. Therefore, we recommend the use of Dtg in clinical settings. Furthermore, a prospective cohort or experimental study shall be conducted to generate more evidence and build a cause–effect relationship regarding symptoms and use of Dtg, and inferential statistics shall be considered by future researchers.

Abbreviations

ADEs, adverse drug events; ART, antiretroviral therapy; Dtg, dolutegravir; HIV, human immunodeficiency virus; UoGCSH, University of Gondar Comprehensive Specialized Hospital.

Data Sharing

The datasets generated during the current study will be available upon reasonable appeal from the corresponding author.

Acknowledgments

We are highly obliged to University of Gondar College of Medicine and Health Science Institutional Review Board for its ethics approval. The authors also acknowledge ART clinic staff, supervisors, data collectors, and card room workers for their commendable efforts and participation in this study. We are also grateful to administrative bodies at all levels who permitted us to undertake this study.

Author Contributions

All authors made a significant contribution to the conception, study design, execution, acquisition, analysis and interpretation of data, drafting, revising, or critically reviewing the article, gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Funding

There was no funding for this work.

Disclosure

The authors declare that they have no competing interests.

References

1. Famil K. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents; 2005.
2. Dikman AE, Schonfeld E, Srisarajivakul NC, Poles MA. Human immunodeficiency virus-associated diarrhea: still an issue in the era of antiretroviral therapy. *Dig Dis Sci*. 2015;60(8):2236–2245. doi:10.1007/s10620-015-3615-y
3. Orkin C, Llibre J, Gallien S, Antinori A, Behrens G, Carr A. Nucleoside reverse transcriptase inhibitor-reducing strategies in HIV treatment: assessing the evidence. *HIV Med*. 2018;19(1):18–32. doi:10.1111/hiv.12534
4. Cruciani M, Parisi SG. Dolutegravir based antiretroviral therapy compared to other combined antiretroviral regimens for the treatment of HIV-infected naive patients: a systematic review and meta-analysis. *PLoS One*. 2019;14(9):e0222229. doi:10.1371/journal.pone.0222229
5. Snedecor SJ, Radford M, Kratochvil D, Grove R, Punekar YS. Comparative efficacy and safety of dolutegravir relative to common core agents in treatment-naïve patients infected with HIV-1: a systematic review and network meta-analysis. *BMC Infect Dis*. 2019;19(1):1–14. doi:10.1186/s12879-019-3975-6

6. Drummond MF, Schwartz JS, Jönsson B, et al. Key principles for the improved conduct of health technology assessments for resource allocation decisions. *Int J Technol Assess Health Care*. 2008;24(3):244–258. doi:10.1017/S0266462308080343
7. Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N. Adverse effects of highly active antiretroviral therapy in developing countries. *Clin Infect Dis*. 2007;45(8):1093–1101. doi:10.1086/521150
8. Teklay G, Legesse B, Legesse M. Adverse effects and regimen switch among patients on antiretroviral treatment in a resource limited setting in Ethiopia. *J Pharmacovigilance*. 2013;1(4):115. doi:10.4172/2329-6887.1000115
9. Tamirat T, Woldemichael K, Tewelde T, Laelago T. Anti-retro viral therapy adverse drug reaction and associated factors among human immuno deficiency virus infected adult patients at Nigist Eleni Mohammed memorial hospital, South Ethiopia. *Afr Health Sci*. 2020;20(2):560–567. doi:10.4314/ahs.v20i2.3
10. Punekar Y, Parks D, Joshi M, et al. Effectiveness and safety of dolutegravir two-drug regimens in virologically suppressed people living with HIV: a systematic literature review and meta-analysis of real-world evidence. *HIV Med*. 2021;22(6):423–433. doi:10.1111/hiv.13050
11. Chen I-W, Sun H-Y, Hung -C-C. Meta-analysis of efficacy and safety of coformulated bictegravir, emtricitabine, and tenofovir alafenamide among people living with HIV. *Infect Dis Ther*. 2021;10(3):1331–1346. doi:10.1007/s40121-021-00449-z
12. Sculier D, Wandeler G, Yerly S, et al. Efficacy and safety of dolutegravir plus emtricitabine versus standard ART for the maintenance of HIV-1 suppression: 48-week results of the factorial, randomized, non-inferiority SIMPL'HIV trial. *PLoS Med*. 2020;17(11):e1003421. doi:10.1371/journal.pmed.1003421
13. Del Mar Gutierrez M, Mateo MG, Vidal F, Domingo P. Drug safety profile of integrase strand transfer inhibitors. *Expert Opin Drug Saf*. 2014;13(4):431–445. doi:10.1517/14740338.2014.897327
14. Mondi A, Cozzi-Lepri A, Tavelli A, et al. Effectiveness of dolutegravir-based regimens as either first-line or switch antiretroviral therapy: data from the Icona cohort. *J Int AIDS Soc*. 2019;22(1):e25227. doi:10.1002/jia2.25227
15. Ciccullo A, Baldin G, Borghetti A, Di Giambenedetto S. Dolutegravir plus lamivudine for the treatment of HIV-1 infection. *Expert Rev Anti Infect Ther*. 2020;18(4):279–292. doi:10.1080/14787210.2020.1729742
16. Goh OQ, Colby DJ, Pinyakorn S, et al. Switch to dolutegravir is well tolerated in Thais with HIV infection. *J Int AIDS Soc*. 2019;22(7):e25324. doi:10.1002/jia2.25324
17. Peñafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. *J Antimicrob Chemother*. 2017;72(6):1752–1759. doi:10.1093/jac/dkx053
18. Patel R, Evitt L, Mariolis I, et al. HIV treatment with the two-drug regimen dolutegravir plus lamivudine in real-world clinical practice: a systematic literature review. *Infect Dis Ther*. 2021;10(4):2051–2070. doi:10.1007/s40121-021-00522-7
19. Namulindwa A, Wasswa JH, Muyindike W, Tamukong R, Oloro J. Prevalence and factors associated with adverse drug events among patients on dolutegravir-based regimen at the Immune Suppression Syndrome Clinic of Mbarara Regional Referral Hospital, Uganda: a mixed design study. *AIDS Res Ther*. 2022;19(1):1–8. doi:10.1186/s12981-022-00442-7
20. Correa A, Monteiro P, Calixto F, Batista J, de Alencar Ximenes RA, Montarroyos UR. Dolutegravir: virologic response and tolerability of initial antiretroviral regimens for adults living with HIV. *PLoS One*. 2020;15(8):e0238052. doi:10.1371/journal.pone.0238052
21. Bruzzese E, Lo Vecchio A, Smarrazzo A, et al. Dolutegravir-based anti-retroviral therapy is effective and safe in HIV–infected paediatric patients. *Ital J Pediatr*. 2018;44(1):1–5. doi:10.1186/s13052-018-0469-x
22. Baldin G, Ciccullo A, Rusconi S, et al. Long-term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multi-centre cohort of HIV-1-infected, virologically suppressed patients. *Int J Antimicrob Agents*. 2019;54(6):728–734. doi:10.1016/j.ijantimicag.2019.09.002
23. Hauser A, Kusejko K, Johnson LF, et al. Impact of scaling up dolutegravir on antiretroviral resistance in South Africa: a modeling study. *PLoS Med*. 2020;17(12):e1003397. doi:10.1371/journal.pmed.1003397