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ORIGINAL RESEARCH ARTICLE

The Potential Teratogenicity Alert for Women Conceiving on Dolutegravir-Based Regimens: An Assessment of Risk Communication by an Urban HIV Clinic in Uganda and Choices made by Women

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Abstract

Introduction and Objective In May 2018, the World Health Organization and other regulatory authorities released a safety alert for dolutegravir related to a risk of neural tube defects among women exposed to dolutegravir at the time of conception. Models of how drug safety information can be shared effectively in the shortest time are necessary to prevent interruptions of public health programs. We sought to describe an implementation process to inform and support women already on dolutegravir-based regimens at the time of conception to make informed choices following the safety alert of a potential teratogenicity risk. We describe the choices made by women, as well as determine the factors associated with women's choices to switch off dolutegravir.

Methods A clinic response plan was developed in the first week following the alert and clinic staff were trained on safety guidance. All women aged < 55 years taking dolutegravir were identified from the clinic database and contacted by phone for earlier appointments. Non-menopausal and non-surgically sterilized women were referred for urine pregnancy testing and evaluation of pregnancy intentions in the following 12 months and effective family planning was offered. We describe the coverage of women who received the communication as well as the fidelity to the outlined plan from 21 May to 12 September, 2018. We used modified a Poisson regression analysis to determine factors associated with switching off dolutegravir.

Results Of all active patients in the clinic, 9% (690/7963) were identified as female aged < 55 years taking dolutegravir. Ninety-five percent (656/690) were reviewed by September 2018 and informed of the safety alert, implying a high level of uptake. Fidelity to standard operating procedures was also high at 72%. Twenty-two percent (146/656) of patients were menopausal or surgically sterilized. Five hundred and ten women were of reproductive potential with a median age (interquartile range) of 37 years (30–42 years). Five percent (23/510) were human chorionic gonadotrophin positive and all initial ultrasound reports revealed no deformities. Twenty-one percent (108/510) had intentions to conceive and opted to stop taking dolutegravir with 90% (97/108) switching to efavirenz. Seventy-nine percent (402/510) opted to remain taking dolutegravir. However, only 40% (160/402) chose effective contraceptive methods and 60% (242/402) opted for condoms only/no contraceptive method.

Conclusions A rapid well-coordinated response ensured prompt communication of the dolutegravir safety warning. The process developed by the clinic can act as a model for response during drug safety alerts. Women made informed decisions with most opting to remain taking dolutegravir; however, effective contraception uptake was low.

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Extended author information available on the last page of the article

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Key Points

Effective and quick communication about drug safety concerns ensures that the population remains confident in healthcare delivery.

Models of how this can be achieved in resource limited settings are scarce.

Use of patient telephone contacts and reorganization of clinic activities allowed information on a dolutegravir safety alert to be quickly relayed and most women chose to continue using dolutegravir.

1 Introduction

Africa has seen the growth of one of the largest public health responses to the human immunodeficiency virus (HIV) epidemic with 65% of HIV-infected individuals receiving antiretroviral therapy (ART) by 2017 [1]. Key to the success of the response is the use of effective and tolerable antiretroviral drugs with frequent recommendations for new and better drugs to be introduced. In 2017, the World Health Organization recommended dolutegravir (DTG) as a preferred first-line regimen for countries whose pre-treatment resistance levels to non-nucleoside reverse transcriptase inhibitors had exceeded 10% [2]. With a pre-treatment non-nucleoside reverse transcriptase inhibitor resistance of 18.1%, Uganda was considered eligible to transition to first-line DTG-containing regimens. In 2017, the Uganda Ministry of Health (MoH) initiated the roll-out of DTG, commencing in HIV treatment centers of excellence alongside the development of new HIV treatment guidelines.

In May 2018, preliminary results from the Tsepamo study in Botswana identified a potential safety risk with DTG [3]. The observational study reported an increased risk (0.9% vs 0.1%) of neural tube defects among infants born to women who took DTG at the time of conception (4/429) compared with other ARTs. Consequently, the World Health Organization issued a recommendation for DTG for all individuals including women of childbearing age. Women planning a pregnancy and women not using consistent contraception should use DTG with caution especially during the period of potential risk for developing neural tube defects and women who take DTG should be fully informed about the potential risks of neural tube defects to make the decision on the choice of ART [4].

For low- and middle-income countries with public health models of HIV care, there are few examples of how to quickly and efficiently communicate risk without causing unnecessary anxiety, misconception, and interrupting routine services. Ineffective or delayed risk communication has caused misconceptions about drugs and fueled public mistrust in governments and health systems, for example, slowing down or halting polio vaccination and mass treatment programs after schistosomiasis [5]. Even in high-income countries, there have been withdrawals of otherwise safe drugs from the market because of ineffective communications of risk when identified [6]. Even as increasingly more new drugs are introduced in public health programs both for HIV and other illnesses such as tuberculosis, vaccinations, and neglected tropical diseases, models of how drug safety information can be shared effectively in the shortest time are necessary [7].

Effective risk communication empowers patients to make decisions based on their own perceived understanding of the risk-benefit ratio. Patient decisions might not always be clinicians' preferences; however, they must be respected in view of the ethical principles of autonomy. We report the choices made by women on whether to remain taking DTG or be switched and what factors were associated with these decisions. In addition, women who chose to use DTG also made decisions on whether to use effective contraceptives.

We describe one of the first experiences from sub-Saharan Africa on implementing a standard operating procedure to inform and support women taking DTG to make informed choices on available ART and contraception options at the Infectious Diseases Institute, a center of excellence selected by the Uganda MoH to roll out DTG as a first-line ART option.

2 Materials and Methods

2.1 Study Site

The Infectious Diseases Institute adult clinic is a center of excellence that offers specialized HIV services in Kampala, Uganda and follows the public health model of care for HIV [8]. In 2017, over 7000 HIV-infected patients were enrolled and actively in care.

The Infectious Diseases Institute was selected by the MoH for early adoption of DTG as first-line treatment in Uganda to generate preliminary safety data on DTG in treated patients. Between June 2017 and March 2018, DTG was only offered to patients experiencing toxicity to first-line ART regimens containing non-nucleoside reverse transcriptase inhibitors, particularly efavirenz (EFV). From March 2018, following further guidance from the MoH, DTG was offered to all patients starting or already receiving first-line ART with suppressed viral loads.

2.2 Ethical Statement

Routinely collected clinic data were approved for analysis and reporting by the Faculty of Medicine, Makerere University Research and Ethics Committee (approval number: 120-2009) and the Uganda National Council for Science and Technology (approval number: HS 683) [9]. All data were de-identified to maintain patients' anonymity.

2.3 Development of Clinic Operating Procedures

On 21 May, 2018, 3 days after the release of the alert, the Infectious Diseases Institute clinical management and senior staff developed draft operating procedures in consultation with the MoH for further guidance. Other clinical staff also reviewed the procedures and provided feedback. A working group was constituted to oversee the process, and comprised a pharmacist to support pharmacovigilance, physicians, counselors, clinical officers, a quality manager, and peer support officers. Operating procedures were piloted in the first week following the alert. Women scheduled for a clinic visit that week were seen in a routine manner by a nurse and doctor. A standard message was used to communicate to the women the content of the DTG safety alert (Electronic Supplementary Material [ESM]). Separate training sessions were held for different cadres and general staff training was conducted to obtain buy-in, facilitate understanding, and to address concerns about the process. The training sessions included a review of the findings from the Tsepamo study, the standard message, and the screening checklist (ESM) and were conducted during the routine early morning continuous medical education sessions as well as scheduled meetings.

2.3.1 Staffing

To allow the other functions in the clinic to continue, some staff were dedicated to informing the women, including a clinical officer to triage, assess for fertility desire, and provide contraceptive information. Two groups comprising a counsellor and a doctor held the talks interchangeably. The clinic manager also supported the talks when needed. The pregnant women were reviewed by the clinic radiographer and a medical doctor who oversees the sexual and reproductive health clinic or an obstetrician when available.

2.4 Identification of Women Taking Dolutegravir

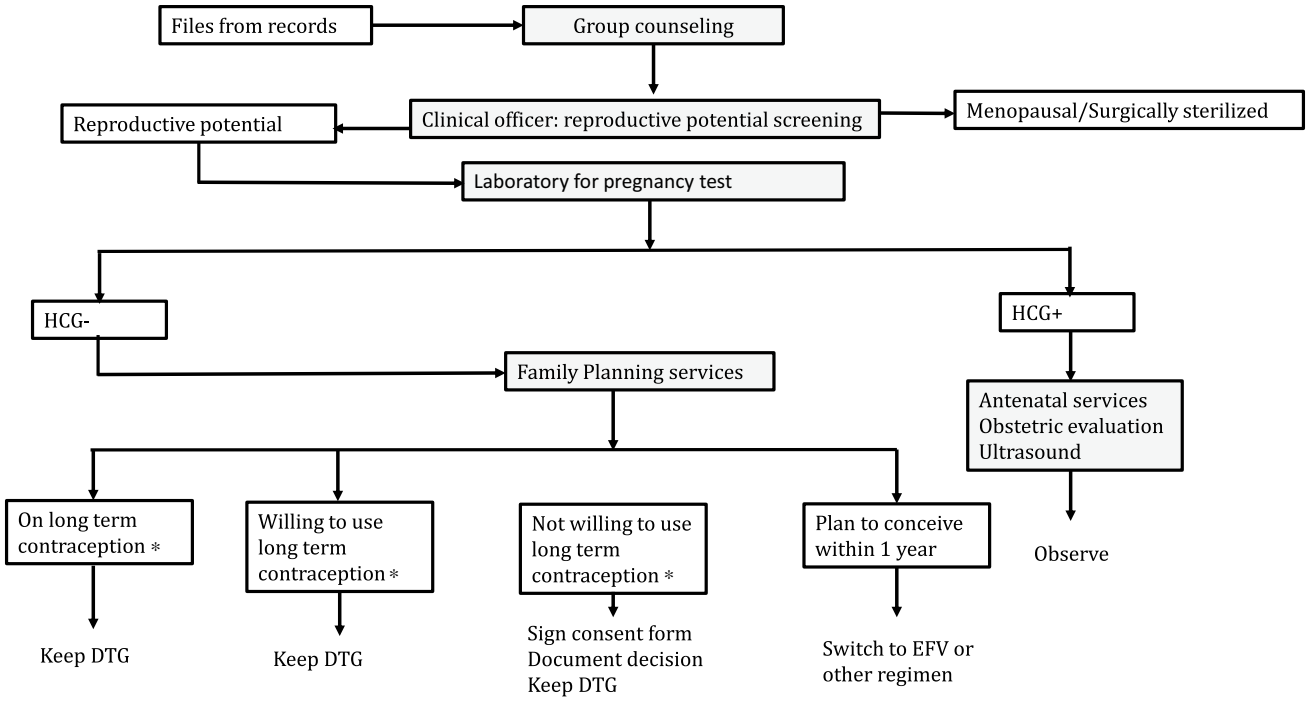
A list of women already taking DTG was generated from the clinic database including age, contact information, and family planning use. Priority was given to women aged below 55 years and with no evidence of contraceptive use; phone calls using a standard message were made by trained counselors to reschedule clinic appointments. Telephone costs were kept low by using promotional mobile phone voice bundles and this cost was incurred by the clinic. Approximately 30 patients were scheduled each clinic day. For those who were not reachable by phone, their files were tagged to remind doctors to have a conversation with them during their routine visits.

2.5 Clinic Flow

To avoid interference with patients with usual clinic appointments, a separate flow for women taking DTG recalled to the clinic was designed (Fig. 1). Following clinic registration by a peer support officer, the women were counseled in groups not exceeding 15, using standard messaging from a doctor and a counselor. An opportunity was provided for questions and responses.

All women underwent screening by two clinical officers to establish eligibility to continue DTG using a screening checklist (ESM). All women were to be screened for pregnancy using urine a human chorionic gonadotropin pregnancy test at the first encounter at the clinic. Women using or choosing to commence effective long-term contraception were retained on DTG. Effective contraception was defined as condoms plus hormonal implants or intrauterine devices but this was subsequently expanded to also include condoms plus oral contraceptives or injectable contraceptives. Treatment-experienced menopausal (defined as 45 years of age or older plus a history of amenorrhea for the previous 12 months) and surgically sterilized women were also offered DTG as a first-line option in accordance with the national roll-out guidance.

Women starting contraceptives for the first time were referred to the contraceptive corner, where they were provided with information on the different types available as well as their advantages and disadvantages. Pregnant women, women intending to become pregnant within 1 year, or women who were unwilling to use effective contraception were offered to switch to an EFV-based regimen. Ritonavir-boosted atazanavir was offered as an alternative if women could not tolerate EFV. The women had previously received information on the benefits of using a DTG-based regimen at the time they commenced the regimen, though it had been highlighted to them at that time that there was not sufficient information on its use in pregnancy. Therefore, the discussions referred to new evidence that had originated from the Tsepamo study. If women declined to discontinue DTG but did not agree to use effective contraception, they were referred to a doctor for further advice. Women declining contraception were asked to sign a declaration of informed consent (ESM). Women who needed more time to make a decision including those who needed to discuss with partners were also allowed this opportunity. Folic acid



HCG: Human chorionic gonadotropin DTG: dolutegravir; EFV: efavirenz Long term contraception: intrauterine device, and hormonal implants

Fig. 1 Clinic process flow for women on dolutegravir

supplementation was offered to all pregnant women and to women planning to become pregnant.

All pregnant women exposed to DTG were counseled, offered an ultrasound scan, and referred to the clinic obstetrician for review. The pharmacy team collected information on pregnancy exposures for submission to the Uganda National Drug Authority and the International Antiretroviral Pregnancy Registry [10].

2.6 Monitoring Progress

A trained clinical officer reviewed files for the women daily including the screening checklist to ensure clinicians followed procedures correctly and feedback was provided where gaps were identified. Weekly progress reports were reviewed by the clinic leadership team.

3 Analyses

We described fidelity to clinic operating procedures expressed as proportions and the uptake of clinic recommendations for contraception and ART. We used descriptive statistics to characterize the population and a modified Poisson regression analysis to determine factors associated with switching off DTG. All analyses were performed using STATA 15.3 (StataCorp; Texas, USA). We also explored associations between the independent variables and the choice to switch off DTG completion at an unadjusted level using a modified Poisson regression with robust standard errors. Linearity of quantitative covariates was also tested. Variables with p values < 0.2 at the unadjusted analysis were then modeled in an adjusted modified Poisson regression with robust standard errors, which was used to determine associations with switching off DTG. Statistical significance was set at the 95% level.

4 Results

4.1 Uptake and Fidelity

Of 7963 active patients enrolled in care in the period 21 May to 12 September, 2018, 9% (690/7963) were identified to be female taking DTG and 95% (656/690) were reviewed in clinics and provided with DTG safety information (Fig. 2). Twenty-two percent (146/656) were menopausal or surgically sterilized. The remaining 510 (78%) women were of reproductive potential with a median age of 37 years (interquartile range 30–42 years) and a mean treatment duration of DTG of 4 months (interquartile range 3–5 months) (Fig. 3).

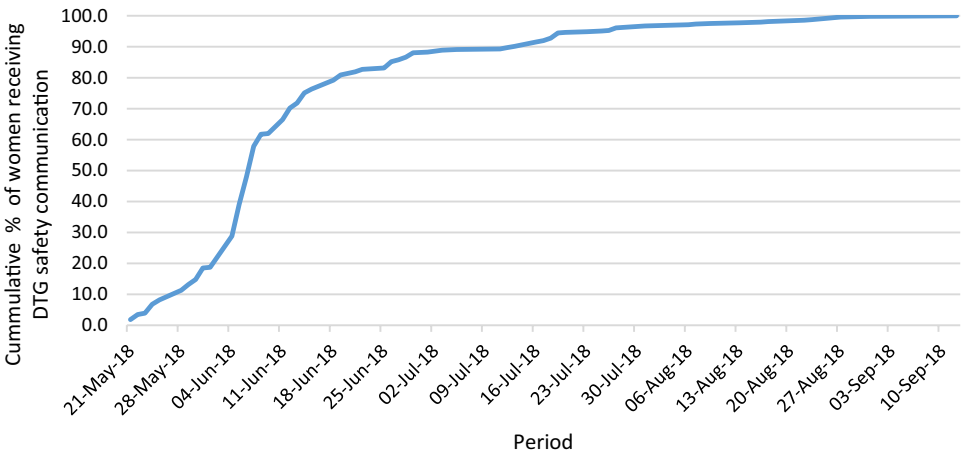


Fig. 2 Coverage of dolutegravir (DTG) safety communication from 12 May to 12 September, 2018 among women aged less than 55 years at the Infectious Diseases Institute in Kampala, Uganda

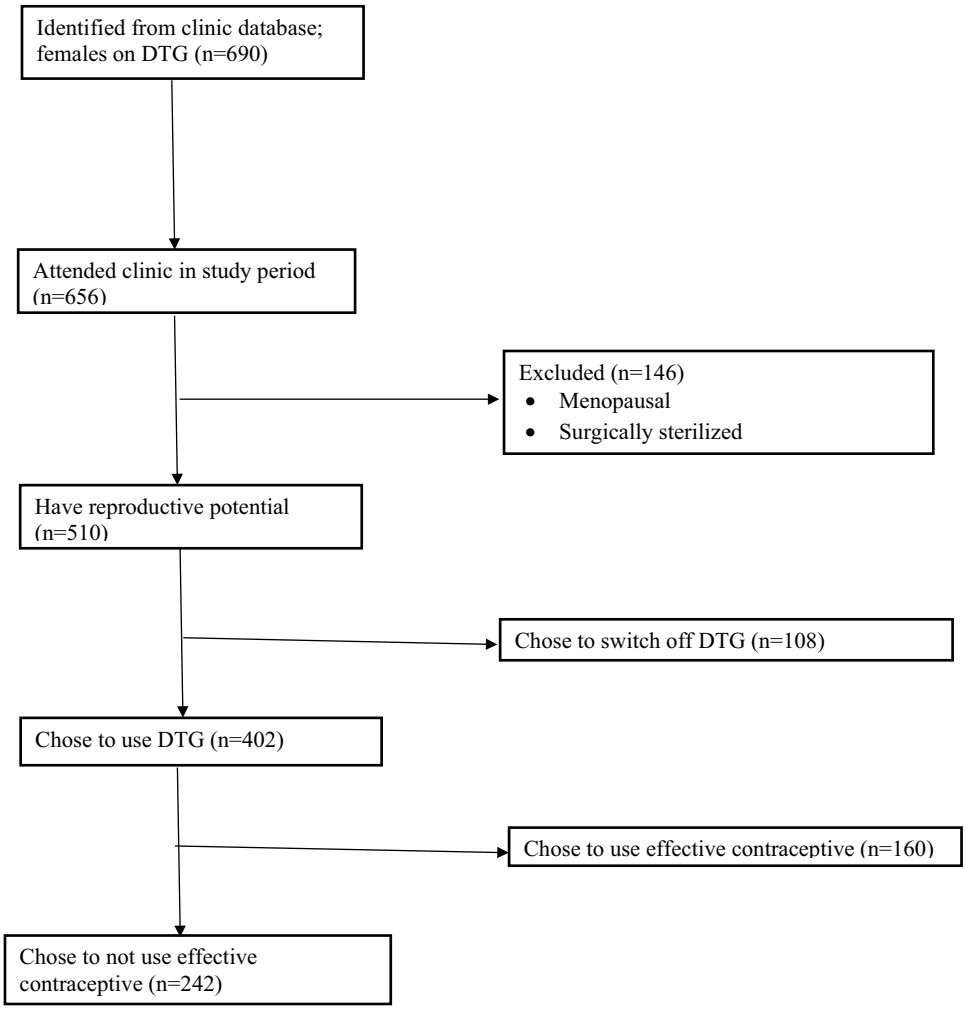


Fig. 3 Screening process and the choices made by women. *DTG* dolutegravir

4.2 Women's Choices

Of the 510 women of reproductive potential who had visited the clinic by the date of censorship, 402 chose to remain taking DTG; 242/402 (60%) chose not to use an effective contraception method [condoms and/or intra-uterine devices, implants, oral contraceptives, injectable contraceptives (Fig. 4)], and opted for condoms only, of which 72% had a signed declaration of informed consent. Five percent (23/510) tested positive for beta human chorionic

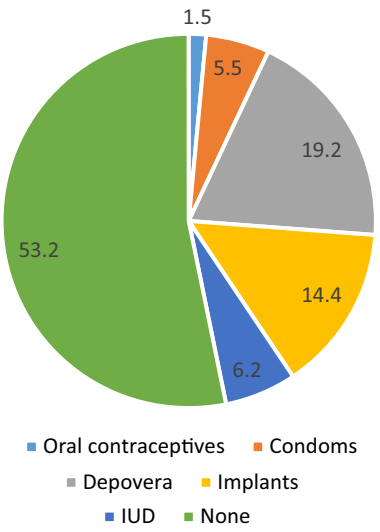


Fig. 4 Percentage of contraceptive choices for 402 women who remained taking dolutegravir at the Infectious Diseases Institute clinic in Kampala, Uganda. Effective contraception (oral contraceptives, injectable contraceptives, implants, intra-uterine device [IUD]) and non-effective contraception (condoms, none)

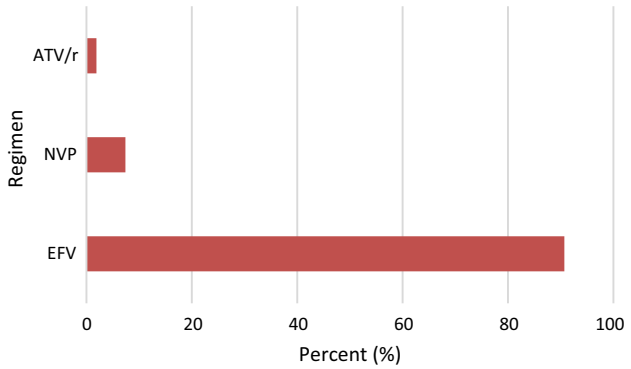


Fig. 5 Regimen choices for women who chose to be switched off dolutegravir at the Infectious Diseases Institute clinic in Kampala, Uganda. *ATV/r* ritonavir-boosted atazanavir, *EFV* efavirenz, *NVP* nevirapine

gonadotrophin. All initial ultrasound reports revealed no deformities. Twenty-one percent (108/510) had intentions to conceive and chose to switch from DTG to other antiretroviral drugs. The regimens they chose to be switched to are shown in Fig. 5 with 90% (97/108) switching to EFV, 79% (402/510) opting to remain taking DTG. The decision to allow pregnant women to choose whether to continue using DTG or be switched off was because most were still young and might want to conceive in the short term. Factors associated with switching off DTG at the unadjusted level were age, duration on DTG, being pregnant, and using an effective contraceptive before the DTG safety alert as well using an effective contraceptive after the DTG safety alert. Having used an effective contraceptive before the DTG safety alert was significant ($p < 0.009$) at the adjusted level but because it was highly correlated with using effective contraception after the safety alert, it was not moved to the unadjusted level (Table 1). Older women (aged > 36 years) were less likely to switch off DTG (prevalence ratio 0.61, 95% confidence interval 0.39–0.96, $p = 0.031$) and those using effective contraceptives after the DTG safety alert (prevalence ratio 0.08, 95% CI 0.03–0.21, $p < 0.001$).

5 Discussion

Following the release of the DTG safety alert on the potential risk for neural tube defects, we report the approach of a large ART clinic in Uganda to rapidly communicate the potential risk to women of child-bearing potential who were already using DTG. Our clinic succeeded in reaching most women using a combination of innovative approaches including mass rescheduling, group counseling, new clinic flows, and dedicated tracking of the process. Having a reliable and easily accessible database of telephone contacts in a setting where an increasing number of people have access to mobile phones is vital for quick dissemination of a safety alert [5]. We used a woman-centered approach but this required significant inputs including clinical officers dedicated to screening women and counselors and trained medical personnel to provide accurate information on the DTG safety alert as well as answer queries. In many ART clinics with lower provider-to-patient ratios, such a strategy would have been impractical without additional investment in staffing, access to electronic medical records, and dedicated pharmacovigilance staff.

The fidelity to standard operating procedures measured by the number of women of reproductive potential who chose not to use effective contraception but had signed informed consent was high at 72%; this was because there was consistent review of the clinic files by the quality manager with feedback for improvement to the clinical team. Most women chose to remain taking DTG but less than half of the women on DTG agreed to use effective contraception. Some of these women had previously used EFV, and a high prevalence of persistent central nervous system side effects related to EFV was recently reported at the site [11]. It is likely that women who had prior toxicity to EFV would be unwilling to change their regimen if their symptoms were relieved with DTG. This has also been described as a potential limitation of the willingness to use EFV even among women who desire to conceive and highlights the need for more options including boosted atazanavir [1].

Older women (aged > 36 years) and women who were using contraception were less likely to switch from DTG to another regimen, ostensibly because of less fertility desire in

Table 1 Demographic and clinical factors associated with switching from dolutegravir (DTG) to other antiretroviral therapy regimens

Characteristics	$N=510$ (%)	Unadjusted PR (95% CI)	p value	Adjusted PR (95% CI)	p value
Age (years)					
16–25	64 (12.6)			1.00	
26–35	169 (33.1)	0.86 (0.54–1.39)	0.541	1.04 (0.67–1.62)	0.869
> 36	277 (54.3)	0.63 (0.39–1.00)	0.052	0.61 (0.39–0.96)	0.031
Duration taking DTG, months; median (IQR)	4 (3–5)	0.92 (0.83–1.01)	0.093	0.92 (0.84–1.01)	0.078
Pregnant[a]					
No	486 (95.5)	1.00		1.00	
Yes	23 (4.5)	1.92 (1.12–3.30)	0.018	1.06 (0.61–1.83	0.834
Effective contraceptive after alert					
No	345 (67.7)	1.00		1.00	
Yes	165 (32.3)	0.10 (0.04–0.24)	< 0.001	0.08 (0.03–0.21)	< 0.001
Effective contraceptive method before alert					
No FP before	311 (61.0)	1.00		–	–
Had FP	199 (39.0)	0.60 (0.41–0.88)	0.009	–	–

CI confidence interval, *FP* Family Planning method, *IQR* interquartile range, *PR* prevalence ratio

[a]Missing: pregnant, 1 (0.20%)

the short term. Injectable contraceptives were used by 19% of women opting to remain taking DTG.

The low uptake of contraceptives among women of reproductive potential despite the safety risk communicated alludes to the preposition made by Edwards and Elwyn that the professional goals of communication should be to make informed choices and not modify behavior [12]. Sometimes patients' choices/preferences might not result in a standardized healthcare provision, this is a dilemma for public healthcare models. The DTG safety alert draws on the delicacy of the balance between a public healthcare model and what might be best for the individual based on his/her own choices as was evidenced by public outcries from women demanding to be given the rights to make their own choices on whether to use DTG [13].

5.1 Limitations

We were not able to conduct an in-depth interview with healthcare providers and the women we interacted with in this process. This would have provided more information on the challenges of the approach we took to communicate this risk. More qualitative work around risk communication will better inform choices of processes and strategies. It would also be important to explore for any beliefs/perceptions rational or not that might have been created during the process and whether this undermined confidence in DTG.

Whilst we were able to use a woman-centered approach to communicate the risk, it would be necessary to adopt routine screening for fertility intentions—a practice that is not common even in HIV clinic settings in higher income countries. It would be recommended that clinics be supported with both training materials and electronic reminders to adopt this routine screening of fertility intentions [14–17].

Since July 2019, new data released form the Tsepamo study indicate that the risk of DTG-associated teratogenicity might not be as high as earlier reported (0.03% for DTG vs 0.01% for other ARTs) [18]. These data are reassuring for programs and countries to resume the roll out of a preferred DTG-based regimen as has been advised by the World Health Organization [19].

6 Conclusions

Our experience shows that a rapid comprehensive response to the DTG safety alert was feasible in a specialised HIV facility in Uganda. However, this required the development of clear guidelines and a dedicated team. We provide a model for risk communication that can be employed for public health programs.

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Declarations

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Conflict of interest Mohammed Lamorde reports grants and non-financial support from ViiV, grants and personal fees from Mylan, and grants from Janssen Pharmaceuticals, outside the submitted work. Eva Agnes Odongpiny Laker, Arnold Arinaitwe, Noela Owarwo, Annet Onzia, Benson Nasasira, Abdullah Wailagala, Ivan Kalule, Godwin Anguzu, Agnes Kiragga, Kay Seden, Isaac Lwanga, Barbara Castelnuovo, and Rachel Musomba have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval Analysis and publication of data obtained from the Infectious Diseases Institute Adult Clinic are approved and annually renewed by the School of Medicine Research and Ethics Committee, Makerere University Medical School (reference no. 2009-120) and the Uganda National Council for Science and Technology. All information is analyzed after removing unique personal identifiers.

Consent to Participate Patients provided written or oral consent to participate in the study.

Consent for Publication Not applicable.

Availability of Data and Material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Author Contributions EL had final responsibility for the decision to publish. AA, NO, OA, NB, WA, AG, KS, RM, AG, IL, RM, BC, and ML all contributed to the design, data analysis, and interpretation of results. AG and AK were responsible for data extraction from the clinic database. EL, AA, NO, OA, NB, WA, KS, RM, AG, IL, RM, BC, and ML contributed to the drafting of the manuscript, reviewed the paper for substantial intellectual content, and approved the final manuscript.

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