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Disparities in Dolutegravir Uptake Affecting Females of Reproductive Age With HIV in Low- and Middle-Income Countries After Initial Concerns About Teratogenicity: An Observational Study

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International epidemiology Databases to Evaluate AIDS (IeDEA)*

Abstract

Background: The transition to dolutegravir-containing antiretroviral therapy (ART) in low- and middle-income countries (LMICs) was complicated by an initial safety signal in May 2018 suggesting that exposure to dolutegravir at conception was possibly associated with infant neural

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tube defects. On the basis of additional evidence, in July 2019, the World Health Organization recommended dolutegravir for all adults and adolescents living with HIV.

Objective: To describe dolutegravir uptake and disparities by sex and age group in LMICs.

Design: Observational cohort study.

Setting: 87 sites that began using dolutegravir in 11 LMICs in the Asia-Pacific; Caribbean, Central and South America network for HIV epidemiology (CCASAnet); and sub-Saharan African regions of the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium.

Patients: 134 672 patients aged 16 years or older who received HIV care from January 2017 through March 2020.

Measurements: Sex, age group, and dolutegravir uptake (that is, newly initiating ART with dolutegravir or switching to dolutegravir from another regimen).

Results: Differences in dolutegravir uptake among females of reproductive age (16 to 49 years) emerged after the safety signal. By the end of follow-up, the cumulative incidence of dolutegravir uptake among females 16 to 49 years old was 29.4% (95% CI, 29.0% to 29.7%) compared with 57.7% (CI, 57.2% to 58.3%) among males 16 to 49 years old. This disparity was greater in countries that began implementing dolutegravir before the safety signal and initially had highly restrictive policies versus countries with a later rollout. Dolutegravir uptake was similar among females and males aged 50 years or older.

Limitation: Follow-up was limited to 6 to 8 months after international guidelines recommended expanding access to dolutegravir.

Conclusion: Substantial disparities in dolutegravir uptake affecting females of reproductive age through early 2020 are documented. Although this disparity was anticipated because of country-level restrictions on access, the results highlight its extent and initial persistence.

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Introduction

Dolutegravir, an integrase strand transfer inhibitor, was first recommended in the World Health Organization (WHO) antiretroviral therapy (ART) guidelines in 2016, and in 2018, it was conditionally recommended as part of the preferred first- and second-line regimens for adults and adolescents living with HIV (1, 2). The ongoing transition to dolutegravir in low- and middle-income countries (LMICs) represents a landmark shift in the public health approach to global HIV treatment. For the past 2 decades, a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen containing either nevirapine or efavirenz was the recommended first-line treatment and has been used for millions of people living with HIV (3, 4). The reach of dolutegravir-containing ART is anticipated to be extensive and it is projected to be the most commonly used regimen among people living with HIV in LMICs by 2025 (4). Robust evidence indicates that dolutegravir-containing ART is associated with improved viral suppression, less drug resistance, and fewer discontinuations compared with the previous preferred first-line regimen of efavirenz-containing ART (5).

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Despite the promise of dolutegravir, its widespread use has not been without controversy. In May 2018, an interim analysis of the Tsepamo cohort in Botswana found a possible association between dolutegravir exposure at conception and infant neural tube defects (NTDs) (6). The WHO subsequently cautioned against dolutegravir use among females of reproductive age for whom consistent contraception could not be assured and emphasized the importance of ongoing surveillance (7). Many countries and organizations issued their own policies about dolutegravir use, largely restricting access for most females of reproductive age (8–12). This development especially affected the dolutegravir transition in sub-Saharan Africa where females of reproductive age are the population most affected by HIV (13) and more broadly in LMICs where there are limited options for antiretroviral drugs (4).

In July 2019, the WHO fully recommended dolutegravir-containing ART for all adults and adolescents living with HIV, including females of reproductive age regardless of contraception (14). This was informed by a weaker association of NTDs in expanded data through March 2019 from the Tsepamo cohort (15) and a more holistic understanding of the risks versus benefits. Modeling studies supported the use of dolutegravir because its benefits (for example, fewer deaths and HIV transmissions) outweighed even a potentially higher risk for NTDs (16, 17). Many countries, such as Kenya, which initially restricted dolutegravir use for females of reproductive age, revised their policies to recommend its use in accordance with the WHO recommendation (9, 18). Other countries that began implementing dolutegravir more recently have had a less restrictive trajectory of dolutegravir use (19–24).

Because of the known benefits of dolutegravir, a disparity in uptake for females of reproductive age, particularly a sustained one, could result in excess HIV-related morbidity and mortality. Therefore, we sought to describe dolutegravir uptake and disparities by sex and age group in LMICs in the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium.

Methods

Data Sources

The IeDEA is an international research consortium of HIV care sites that collects and harmonizes clinical data across 7 geographic regions (www.iedea.org). This analysis used data from the Asia-Pacific; Caribbean, Central and South America network for HIV epidemiology (CCASAnet); and Central, East, and Southern Africa regions. During clinical encounters at the sites, patient data are collected either on paper forms, which are later extracted into local databases, or directly into the local electronic medical record. Data are deidentified before transmission to a regional data management center. Site-level data are collected through surveys completed by local staff. Institutional review boards or research ethics committees at each site and regional data management center provided ethical oversight and approved the use of deidentified data for this analysis. Informed consent requirements were deferred to the local approving bodies.

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Sites

We included sites in LMICs in the participating regions that had begun to prescribe dolutegravir. We excluded sites with a database closure date before January 2020. We further restricted the analysis to sites with 50 or more patients in care and 1% or more with documented dolutegravir use since the earliest date of dolutegravir use at the site.

Patients

We included patients who were 16 years or older at the time of enrollment into HIV care, had at least 1 visit on or after the date that their site began to use dolutegravir, and were newly initiating or already receiving ART. The age minimum of 16 years was chosen because globally this is the most common legal age to consent to medical treatment (25). On the basis of WHO guidelines, ART was defined as receiving a regimen containing an NNRTI, integrase strand transfer inhibitor, or protease inhibitor (1, 2, 14). We excluded persons who had missing data for sex, were unknown to be ART naive or experienced at the start of follow-up, or had incomplete information for an ART regimen (Appendix Figure).

Measures

Our main outcome was dolutegravir uptake, which we defined as newly initiating ART with a dolutegravir-containing regimen or switching to dolutegravir from another regimen. Start dates for medications were based on clinician documentation of a new prescription or pharmacy dispensing records, depending on the site. Our main exposures were sex and age group. Age group was based on age at start of follow-up and was categorized into 2 groups based on the reproductive age for females (that is, 15 to 49 years [7]): 16 to 49 years and 50 years or older. We also examined subgroups within each age category.

Other variables of interest were ART experience at the start of follow-up; year of ART initiation among ART-experienced patients; ART regimen base (that is, dolutegravir, efavirenz, nevirapine, protease inhibitor, other integrase strand transfer inhibitor or other NNRTI); pregnancy status, which was only available for this analysis from sites in Kenya, Tanzania, and Uganda and was defined as presenting pregnant at a visit; site urbanicity; site level of care; and country start of dolutegravir implementation, either before or after the safety signal in May 2018, based on each country's earliest date of dolutegravir use in our cohort (Appendix Table 1).

Statistical Analysis

The observation period of the study was from January 2017 through March 2020. Follow-up for individual patients began on the date at which their site began to use dolutegravir or when they started ART, whichever occurred later. Follow-up ended on the date of dolutegravir uptake or, for those not initiating dolutegravir treatment, it ended on the date after the last recorded contact among those who were lost to follow-up (that is, no recorded contacts for ≥7 months immediately preceding the date of site database closure) or known to have left care, date of death among those known to have died, or date of site database closure among those who remained alive and in care.

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We computed descriptive statistics for sample characteristics and ART regimen information, including dolutegravir use among ART-naive and ART-experienced patients. Among females aged 16 to 49 years, we computed the proportion who newly initiated ART on a visit with a documented pregnancy and ART regimens among this group. We also computed the proportion who were receiving dolutegravir before their earliest visit with a pregnancy and the proportion who started dolutegravir treatment on a visit with a documented pregnancy.

We used the Aalen–Johansen estimator (26) to compute cumulative incidence function estimates for dolutegravir uptake, considering any reason for dropout to be a competing event. We first computed and graphed cumulative incidence proportions at the end of each month during the observation period of the study, overall and stratified by sex and age group. We then computed cumulative incidence proportions with 95% CIs overall and by sex and age group at 3 time points: before the safety signal (until 18 May 2018), after the safety signal (until 22 July 2019), and after the WHO recommended dolutegravir for all (until 31 March 2020). We further stratified sex- and age-group specific estimates by ART experience, year of starting ART (among ART-experienced patients), and country start of dolutegravir implementation. Because more than half of our data were from Kenya, we did a sensitivity analysis excluding patients in Kenya to see how our results changed.

To gain a preliminary understanding of how disparities in dolutegravir uptake changed before and after WHO recommended dolutegravir for all in July 2019, we computed and graphed ratios of cumulative incidence proportions for the 2 periods (that is, until 22 July 2019 and until 31 March 2020) to compare females with males by age strata. At database closure, we computed descriptive statistics for latest ART regimen among all patients alive and engaged in care, including among patients who left the cohort after initiating dolutegravir treatment. All analyses were done using SAS, version 9.4 (SAS Institute).

Role of the Funding Source

The funder was not involved in the design of the study; the collection, analysis, and interpretation of the data; or the decision to approve publication of the finished manuscript.

Results

Sample Disposition and Characteristics

We included 134 672 persons at 87 facilities in 11 countries, from the earliest site use of dolutegravir in January 2017 to site database closure from January through March 2020 (Appendix Table 1). Overall, 138 198 patients were assessed for eligibility, and 3% were excluded (Appendix Figure). By the end of follow-up, 14% of patients had prematurely left the cohort because of death, loss to follow-up, or a known reason for leaving care. Median follow-up was 14 months (interquartile range, 7 to 23 months). Overall, 52% of patients were females aged 16 to 49 years, 25% were males aged 16 to 49 years, 13% were females aged 50 years or older, and 10% were males aged 50 years or older (Table 1). About half (52%) of patients accessed care at rural sites, 42% at sites with a primary level of care, 58% at sites in Kenya, and 76% were in countries that began implementing dolutegravir before the safety signal.

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Dolutegravir Use by ART Experience and Among Pregnant Women

Overall, 22 100 (16%) patients newly initiated ART, and among these patients, 8160 (37%) started a dolutegravir-containing regimen (Table 2). Initiating ART with dolutegravir occurred among 20% of females aged 16 to 49 years, 57% of males aged 16 to 49 years, 55% of females aged 50 years or older, and 55% of males aged 50 years or older. Among the 13 940 patients who newly initiated ART with a non–dolutegravir-containing regimen, 3108 (22%) eventually switched to dolutegravir. Later switching to dolutegravir occurred among 12% of females aged 16 to 49 years, 40% of males aged 16 to 49 years, 51% of females aged 50 years or older, and 50% of males aged 50 years or older.

Overall, 112 572 (84%) patients were already receiving ART when their site began to use dolutegravir, and 76% of these patients started ART before 2016 (Table 1). Among ART-experienced patients, 46 231 (41%) switched to a dolutegravir-containing regimen. Switching to dolutegravir among the ART-experienced patients occurred among 27% of females aged 16 to 49 years, 52% of males aged 16 to 49 years, 60% of females aged 50 years or older, and 62% of males aged 50 years or older (Table 2). When considering all patients who switched to dolutegravir regardless of ART experience at the start of follow-up (n = 49 339), 60% did so from an efavirenz-containing regimen and 38% from a nevirapine-containing regimen.

Among 49 074 females aged 16 to 49 years in Kenya, Tanzania, and Uganda, 4873 (10%) were pregnant at some time during follow-up, among whom 619 (13%) newly initiated ART on a visit with a documented pregnancy (data not shown in the tables). Of those initiating ART, 568 (92%) started an efavirenz-containing regimen, 45 (7%) started a dolutegravir-containing regimen, and 6 (1%) started another regimen. Among the 4254 patients already on ART, 268 (6%) were already receiving dolutegravir before their first visit with a pregnancy. Overall, 143/4873 (3%) started a dolutegravir-containing regimen on a visit with a pregnancy.

Cumulative Incidence of Dolutegravir Uptake and Differences by Sex and Age Group

By the time of the safety signal, 3.2% (95% CI, 3.1% to 3.3%) of patients had initiated dolutegravir treatment (Table 3), and differences by sex and age group emerged thereafter (Figure 1). By the time the WHO recommended dolutegravir for all, the cumulative incidence of dolutegravir uptake was 16.2% (CI, 15.9% to 16.5%) among females aged 16 to 49 years and 40.4% (CI, 39.8% to 40.9%) among males aged 16 to 49 years. By the end of follow-up, cumulative incidence was 29.4% (CI, 29.0% to 29.7%) among females aged 16 to 49 years and 57.7% (CI, 57.2% to 58.3%) among males aged 16 to 49 years (Table 3). Disparities in overall cumulative incidence were greatest when comparing females aged 16 to 29 years (14.2% [CI, 13.6% to 14.8%]) with males aged 16 to 29 years (54.1% [CI, 52.7% to 55.6%]) and females aged 30 to 39 years (21.3% [CI, 20.8% to 21.9%]) with males aged 30 to 39 years (56.8% [CI, 55.9% to 57.6%]). Cumulative incidence was similar among females aged 50 years or older and males aged 50 years or older.

Disparities in uptake among females aged 16 to 49 years compared with males aged 16 to 49 years were present when stratifying by ART experience and year of starting ART

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(Table 4). In countries that began implementing dolutegravir treatment before the safety signal, the cumulative incidence of dolutegravir uptake among females and males aged 16 to 49 years was 31.1% (CI, 30.6% to 31.6%) and 65.8% (CI, 65.2% to 66.4%), respectively. In countries that began implementing dolutegravir treatment after the safety signal, the cumulative incidence of dolutegravir uptake among females and males aged 16 to 49 years was 20.3% (CI, 19.7% to 20.9%) and 27.9% (CI, 26.9% to 28.9%), respectively. In our sensitivity analysis excluding patients in Kenya, cumulative incidence proportions were lower in magnitude, but there were similar disparities affecting females aged 16 to 49 years (Appendix Table 2).

The disparity in dolutegravir uptake affecting females aged 16 to 49 years began to attenuate after the July 2019 WHO recommendation of dolutegravir for all (Figure 2). The ratio of cumulative incidence proportions (females aged 16 to 49 years to males aged 16 to 49 years) before the recommendation was 0.40, and this increased to 0.51 after the recommendation. The largest changes were among ART-naive patients (0.27 before, 0.48 after) and ART-experienced patients starting ART in 2016 or later (0.22 before, 0.40 after). Ratios for females aged 50 years or older and males aged 50 years or older were close to 1 before and after the recommendation, which is consistent with a lack of disparity.

Antiretroviral Therapy Regimens at Database Closure

From January through March 2020, 45% of patients alive and engaged in care were receiving dolutegravir, 43% were receiving efavirenz, and 9% were receiving a protease inhibitor (Table 2). Efavirenz-containing regimens were most common among females aged 16 to 49 years (60%), whereas dolutegravir-containing regimens were most common for males aged 16 to 49 years (62%), females aged 50 years or older (62%), and males aged 50 years or older (66%).

Discussion

This study describes the initial rollout of dolutegravir in 11 LMICs in the IeDEA consortium through the trajectory of a safety signal. Dolutegravir uptake was lowest for females of reproductive age, among whom use of efavirenz prevailed. This disparity was anticipated because of country-level restrictions on access; however, our study highlights the extent and initial persistence of disparities despite recommendations to expand access to dolutegravir. If sustained, this disparity could have implications for HIV treatment outcomes because of the superior efficacy and tolerability of dolutegravir (5) and its anticipated population health benefits (16, 17, 27, 28).

The implications of dolutegravir use at scale are not known, and future research should examine the effect of disparities in dolutegravir uptake on clinical outcomes, considering the real-world context and potential risks. Although the superior efficacy of dolutegravir can be inferred from the breadth of the evidence, some clinical trials in resource-constrained settings have reported similar long-term viral suppression compared with efavirenz (29, 30). Drug resistance mutations in reverse transcriptase are widespread (31) and may have a role in treatment failure associated with first-line dolutegravir-containing ART (32). Dolutegravir has also been associated with greater excess weight gain than efavirenz, especially among

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women (29, 30, 33), the consequences of which are not yet fully understood when dolutegravir is used at scale.

Although dolutegravir was recommended by the WHO for all adults and adolescents living with HIV in July 2019 (14), additional evidence has emerged since the completion of follow-up in our study in early 2020 that further supports that all women living with HIV should have unrestricted access to dolutegravir. Data from the Tsepamo cohort through April 2020 indicated no statistically significant association between dolutegravir exposure at conception and NTDs (34), and this finding has been corroborated by studies in other settings (35–38). Randomized trials of dolutegravir treatment started during pregnancy have demonstrated its superior virologic efficacy compared with efavirenz, showing the potential to reduce vertical transmission (39, 40). In our study, few patients initiating ART during pregnancy started dolutegravir treatment. These women were likely initiating ART after neural tube closure, so 1 possible explanation for this low use of dolutegravir could be that health care providers were not fully aware of the time window of risk for NTDs. With the recent data, however, we would anticipate that dolutegravir-containing ART becomes a standard of care for pregnant women living with HIV.

The differential effect of sex and age group on dolutegravir uptake by country start of implementation suggests that initial policies and communications about the safety of dolutegravir may have an enduring effect on uptake among females of reproductive age. Countries that began implementing dolutegravir before the safety signal had more restrictive initial policies about the provision of dolutegravir to females of reproductive age, either largely or entirely excluding them (8–12). In contrast, countries with a later rollout after the safety signal had more inclusive, mostly choice-based policies (19–24), which may be a reflection of implementing dolutegravir at a time when more global experience had been gained and more data were available about the risks versus benefits.

To mitigate the anticipated negative downstream effects of lower dolutegravir uptake among females of reproductive age, HIV treatment programs and policymakers at community, national, and international levels should reaffirm the safety of dolutegravir and actively educate women, health care providers, and other stakeholders about the current evidence. In addition, education for providers about shared decision making and integration of contraception and pregnancy planning into HIV care is needed to ensure that patients can make informed decisions about their ART (41). Women living with HIV must be engaged to understand their beliefs, opinions, and needs about the policies and practices that govern the provision of dolutegravir or any other antiretroviral drug to them. Data in the context of the dolutegravir rollout have highlighted how women have felt the acute need for their voices to be heard before policy decisions are made at national and international levels (42, 43).

There are some parallels between the situation of dolutegravir and that of efavirenz more than a decade earlier. After case reports of NTDs among infants exposed to efavirenz at conception (44, 45), the WHO in guidelines in 2006 recommended against the use of efavirenz in females of reproductive age without contraception (46). It was not until several years later that sufficient evidence could be accumulated to show that the risk for fetal harm was limited and the benefits of efavirenz outweighed any potential harms (47). On

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the basis of the updated data, efavirenz was recommended for all adults and adolescents in the 2013 WHO guidelines (48). During the many years it took to resolve safety concerns, women were undoubtedly denied access to efavirenz-containing regimens, which were more effective and safer than the alternative, nevirapine-containing first-line regimen at the time. Although the initial safety signal with dolutegravir was resolved faster than that of efavirenz, the emergence of safety signals with both drugs highlight the need for a rapid and comprehensive response to simultaneously protect and promote public health (49). A critical component of such a response is robust pharmacovigilance systems, which remain limited in LMICs (50).

Our results should be interpreted in the context of some limitations. Sites and patients within the IeDEA consortium may not be fully representative of a country or region. However, patients included in this analysis received care from public HIV programs that follow local guidelines, so our findings are likely reflective of these programs in general. The data used in this study were originally collected for clinical purposes rather than research and are thus subject to limitations related to data entry error and missingness. However, data in IeDEA conform to a rigorous data exchange standard (51), and for this analysis, few patients were excluded because of missing or erroneous data. We examined females of reproductive age without information on their fertility potential or intent. Although this precluded examining the effect of contraceptive use on dolutegravir uptake, data from an HIV treatment program in Kenya that contributed data to this study found that noncondom contraceptive use was uncommon among women initiating dolutegravir treatment (43). Follow-up of our cohort was limited through early 2020 and therefore, changes in guidance to expand access to dolutegravir may not be fully reflected at the patient level. Even after changes in clinical guidance, additional time must be anticipated for increased procurement and distribution (52). Because antiretroviral drugs are ordered in large quantities and are not wasted, increasing dolutegravir uptake among women of reproductive age may be partly dependent on supply chain factors, such as existing stock of efavirenz. Germane to the discussion of timing of follow-up is that our study largely predates the COVID-19 pandemic, which has negatively affected the delivery of HIV care (53). We can only hypothesize that the COVID-19 public health crisis has further negatively affected the rollout of dolutegravir and expansion of its access to all adults and adolescents.

In conclusion, our study found that profound disparities in the uptake of dolutegravir-containing ART affecting females of reproductive age emerged after the initial safety signal and persisted through early 2020, despite recommendations to expand its use to all adults and adolescents living with HIV. Policymakers need to carefully consider the risks versus benefits of restricting access to an antiretroviral drug, even in the context of a possible safety issue, and should include the population affected in formulating relevant policies and recommendations—in this case women living with HIV. Further monitoring of the global dolutegravir rollout is needed as it relates to use among females of reproductive age. Equitable access to the most effective ART through alignment of clinical practice with evidence is an essential component to ending the HIV epidemic as a public health threat.

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Appendix

Appendix Table 1.

Number of Sites, Dates of Follow-up, and Initial Policies About Dolutegravir Use for Females of Reproductive Age, by Country

Country	Sites, *n*	Earliest Date of Dolutegravir Use in Our Sample	Database Closure Date	Initial Policy About Dolutegravir Use for Females of Reproductive Age After Safety Signal*
Start of country dolutegravir implementation before the May 2018 safety signal				
Brazil	1	January 2017†	January 2020	Women who intend to become pregnant or who are pregnant should not receive dolutegravir. Women of reproductive age must use a contraceptive method preferably not dependent on adherence, e.g., implant or intrauterine device, to access dolutegravir (8).
Kenya	23	July 2017	January 2020–February 2020	Dolutegravir is not recommended for women of childbearing age (15–49 y) and those already receiving it should transition to efavirenz. Pregnant and breastfeeding women who are currently receiving dolutegravir should continue their current regimen until complete cessation of breastfeeding (9).
Cambodia	1	January 2018	March 2020	Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive dolutegravir together with consistent and reliable contraception. An efavirenz-based regimen is recommended for women desiring pregnancy or women with childbearing potential who do not wish to take contraception (10).
Rwanda	10	February 2018	March 2020	Dolutegravir is contraindicated for all females <50 y (11).
Uganda	1	February 2018	March 2020	Women of reproductive age (15–49 y) are only eligible for dolutegravir if they have long-term contraception (i.e., tubal ligation, implant, intrauterine device). Dolutegravir is recommended for pregnant women starting ART (12).
Start of country dolutegravir				

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Country	Sites, *n*	Earliest Date of Dolutegravir Use in Our Sample	Database Closure Date	Initial Policy About Dolutegravir Use for Females of Reproductive Age After Safety Signal*
implementation after the May 2018 safety signal				
Haiti	1	October 2018	March 2020	The transition to dolutegravir is inclusive of all women. Programme National de Lutte contre le Sida issued a memo in April 2019 stating that women of reproductive age may choose dolutegravir even in the absence of contraception after counseling on risks and benefits and with informed consent (19).
Zimbabwe	33	February 2019	March 2020	Adolescent girls and women of childbearing potential should be given adequate information to make informed choices about their treatment options. A dolutegravir-containing regimen is recommended if the person has effective contraception (intrauterine device, intrauterine system, implant, injection); otherwise, efavirenz-containing ART is recommended. Women who are pregnant and receiving ART should switch to dolutegravir after their first trimester and continue it while breastfeeding with provision of effective contraception (20).
Democratic Republic of the Congo	1	February 2019	March 2020	The transition to dolutegravir will include women of childbearing potential (21).
Mozambique	8	May 2019	March 2020	Dolutegravir recommended for all adults living with HIV. Efavirenz should be offered to women of reproductive potential age who are planning a pregnancy at the time of starting ART. Women of reproductive age should be offered long-term contraceptive methods (e.g., implant, injection, intrauterine device) (22). Note, earlier in 2019, dolutegravir was only recommended for specific populations (e.g., tuberculosis coinfection) as part of "phase I" of the rollout.
Tanzania	1	June 2019	March 2020	Dolutegravir recommended for all adults and adolescents with HIV, but efavirenz is available for women who choose not to use dolutegravir. A women-centered approach is adopted and women of childbearing potential, including those who are using long-term effective contraception, will be given adequate information to enable them to make informed decision and informed choice consent to using dolutegravir (23).
Lesotho	7	June 2019	March 2020	All women and adolescent girls of childbearing potential should be counseled on the risks and benefits of dolutegravir versus efavirenz and allowed to decide which regimen best suits her needs. Women who do not wish to become pregnant should be offered and encouraged to use consistent and reliable contraception (24).

ART = antiretroviral therapy.

*Earliest policies after the safety signal (May 2018) that pertained to dolutegravir use among females of reproductive age were identified. The terminology used reflects that of the source.

†Twenty patients started a dolutegravir-containing regimen in 2016; however, the earliest use date was revised to January 2017 to reflect when dolutegravir was initially recommended as the first-line regimen in national guidelines.

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Appendix Table 2.

Sensitivity Analysis Excluding Patients in Kenya: Cumulative Incidence of Dolutegravir Uptake by Sex and Age Group, Overall and by Antiretroviral Therapy Experience, Year of Starting Antiretroviral Therapy, and Country Timing of Dolutegravir Implementation

Variable	Summary of Outcomes				Dolutegravir Uptake, Cumulative Incidence Proportion (95% CI)		
	Total Patients, *n*	Patients Initiating Dolutegravir, *n*	Patients Who Dropped Out, *n*	Patients Censored, *n*	Before the Safety Signal (Until 18 May 2018)	After the Safety Signal (Until 22 July 2019)	After the WHO Recommended Dolutegravir for All (Until 31 March 2020)
Entire sample	57 126	16 751	6310	34 065	0.7 (0.6–0.7)	10.8 (10.5–11.0)	30.1 (29.7–30.5)
Sex and age group							
Females aged 16–49 y	29 196	5545	3110	20 541	0.2 (0.1–0.2)	3.8 (3.6–4.0)	19.8 (19.3–20.3)
Males aged 16–49 y	15 738	6408	2188	7142	1.8 (1.6–2.0)	20.2 (19.6–20.8)	41.6 (40.1–42.3)
Females aged ≥50 y	6963	2584	482	3897	0.2 (0.1–0.3)	12.7 (12.0–13.5)	37.5 (36.4–38.7)
Males aged ≥50 y	5229	2214	530	2485	0.8 (0.6–1.1)	18.7 (17.7–19.8)	42.9 (41.6–44.3)
Experience with ART at start of follow-up							
Naive							
Females aged 16–49 y	3537	1317	487	1733	0.7 (0.5–1.0)	9.2 (8.3–10.2)	39.4 (37.7–41.1)
Males aged 16–49 y	2655	1877	235	543	7.8 (6.9–8.9)	33.8 (32.0–35.6)	71.9 (70.1–73.6)
Females aged ≥50 y	312	201	12	99	1.3 (0.4–3.1)	23.1 (18.6–27.9)	65.1 (59.4–70.2)
Males aged ≥50 y	337	231	31	75	4.8 (2.8–7.4)	33.8 (28.8–38.9)	69.6 (64.2–74.3)
Experienced							
Females aged 16–49 y	25 659	4228	2623	18 808	0.1 (0.05–0.1)	3.0 (2.8–3.2)	17.2 (16.7–17.6)
Males aged 16–49 y	13 083	4531	1953	6599	0.6 (0.4–0.7)	17.4 (16.8–18.1)	35.3 (34.5–36.2)
Females aged ≥50 y	6651	2383	470	3798	0.1 (0.06–0.2)	12.3 (11.5–13.1)	36.2 (35.1–37.4)

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Variable	Summary of Outcomes				Dolutegravir Uptake, Cumulative Incidence Proportion (95% CI)		
	Total Patients, *n*	Patients Initiating Dolutegravir, *n*	Patients Who Dropped Out, *n*	Patients Censored, *n*	Before the Safety Signal (Until 18 May 2018)	After the Safety Signal (Until 22 July 2019)	After the WHO Recommended Dolutegravir for All (Until 31 March 2020)
Males aged ≥50 y	4892	1983	499	2410	0.5 (0.3–0.7)	17.7 (16.7–18.8)	41.1 (39.7–42.5)
Year of starting ART (among ART-experienced patients)							
2010 or prior							
Females aged 16–49 y	4414	1181	530	2703	0.1 (0.04–0.3)	7.6 (6.8–8.4)	27.8 (26.4–29.2)
Males aged 16–49 y	2127	877	454	796	0.5 (0.2–0.8)	22.8 (21.0–24.6)	42.0 (39.9–44.1)
Females aged ≥50 y	2643	1131	243	1269	0.1 (0.03–0.3)	17.7 (16.3–19.2)	43.3 (41.4–45.2)
Males aged ≥50 y	1959	915	264	780	0.6 (0.3–1.0)	24.9 (23.0–26.9)	47.4 (45.1–49.6)
2011–2015							
Females aged 16–49 y	12 263	2001	1104	9158	0.1 (0.1–0.2)	2.8 (2.5–3.1)	17.4 (16.7–18.1)
Males aged 16–49 y	5910	2322	825	2763	0.8 (0.6–1.0)	20.9 (19.8–21.9)	40.6 (39.3–41.9)
Females aged ≥50 y	2622	968	141	1513	0.2 (0.1–0.4)	10.8 (9.7–12.1)	37.5 (35.6–39.3)
Males aged ≥50 y	2000	800	150	1050	0.5 (0.3–0.9)	14.8 (13.3–16.4)	40.7 (38.5–42.8)
2016 or later							
Females aged 16–49 y	8982	1046	989	6947	0.02 (0.01–0.1)	1.1 (0.9–1.3)	11.9 (11.2–12.6)
Males aged 16–49 y	5046	1332	674	3040	0.3 (0.2–0.5)	11.1 (10.3–12.0)	26.7 (25.5–27.9)
Females aged ≥50 y	1386	284	86	1016	0.1 (0.1–0.4)	4.6 (3.5–5.7)	20.6 (18.5–22.8)
Males aged ≥50 y	933	268	85	580	0.4 (0.1–1.1)	8.8 (7.1–10.7)	29.0 (26.1–31.9)
Time country started implementing dolutegravir regimen							
Before the May 2018 safety signal *							

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Variable	Summary of Outcomes				Dolutegravir Uptake, Cumulative Incidence Proportion (95% CI)		
	Total Patients, *n*	**Patients Initiating Dolutegravir, *n***	**Patients Who Dropped Out, *n***	**Patients Censored, *n***	**Before the Safety Signal (Until 18 May 2018)**	**After the Safety Signal (Until 22 July 2019)**	**After the WHO Recommended Dolutegravir for All (Until 31 March 2020)**
Females aged 16–49 y	12 169	2090	2182	7897	0.4 (0.3–0.5)	6.7 (6.3–7.2)	18.1 (17.4–18.9)
Males aged 16–49 y	8342	4347	1779	2216	3.4 (3.0–3.8)	35.8 (34.7–36.8)	53.2 (52.0–54.3)
Females aged ≥50 y	2174	1167	333	674	0.6 (0.3–0.9)	37.9 (35.9–39.9)	53.8 (51.7–55.9)
Males aged ≥50 y	2266	1284	421	561	1.8 (1.3–2.4)	40.8 (38.8–42.8)	57.1 (55.0–59.1)
After the May 2018 safety signal[†]							
Females aged 16–49 y	17 027	3455	928	12 644	NA	1.7 (1.5–1.9)	20.3 (19.7–20.9)
Males aged 16–49 y	7396	2061	409	4926	NA	2.6 (2.3–3.0)	27.9 (26.9–28.9)
Females aged ≥50 y	4789	1417	149	3223	NA	1.3 (1.0–1.7)	29.6 (28.3–30.9)
Males aged ≥50 y	2963	930	109	1924	NA	1.9 (1.5–2.4)	31.4 (29.8–33.1)

ART = antiretroviral therapy.

[*] Brazil, Cambodia, Rwanda, and Uganda.

[†] Democratic Republic of the Congo, Haiti, Lesotho, Mozambique, Tanzania, and Zimbabwe. Because this category does not include Kenya, results are the same as the main analysis.

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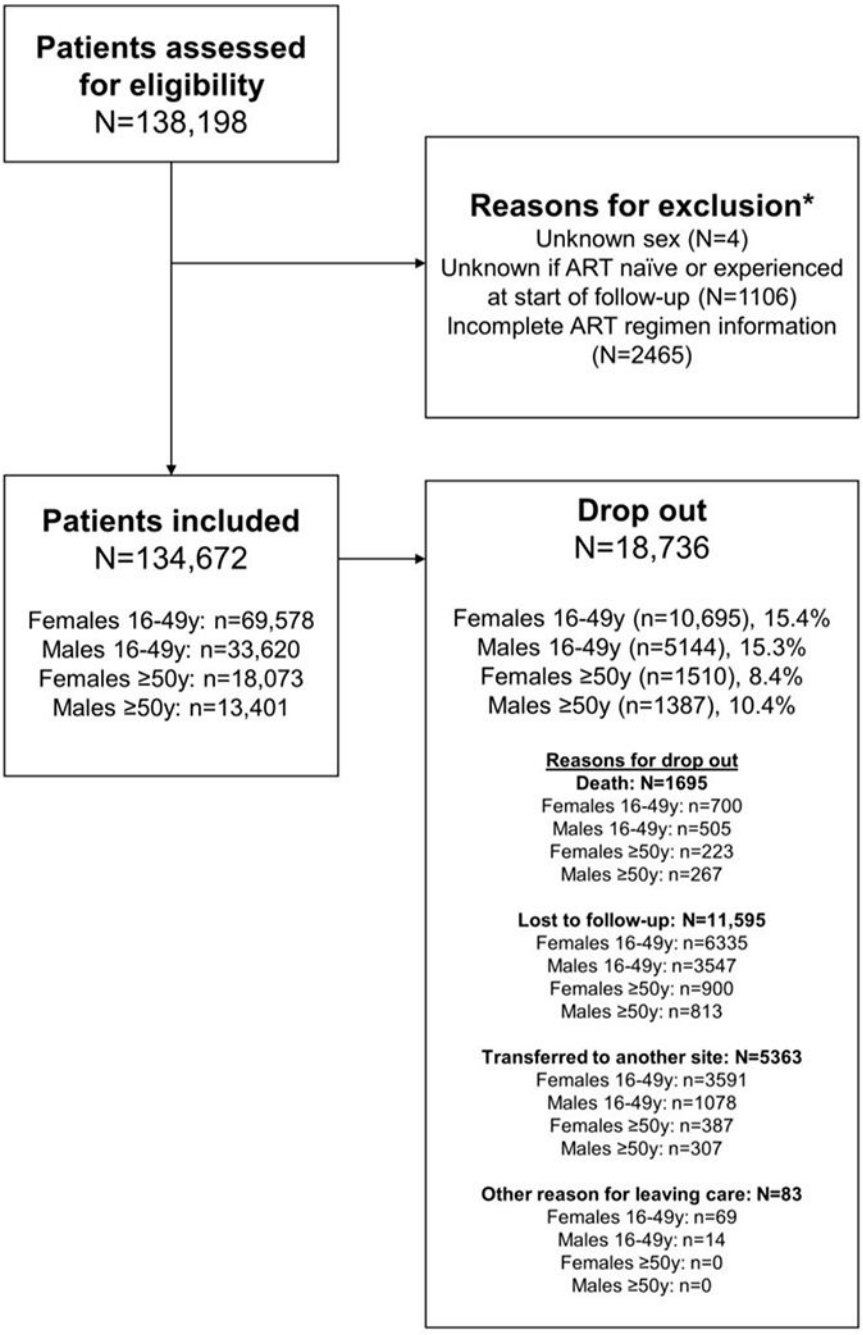

Appendix Figure. Patient assessment for eligibility, reasons for exclusion, sample included at the start of follow-up, and drop out.

*Reasons for exclusion are not mutually exclusive. ART = antiretroviral therapy.

References

1. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Accessed at https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1 on 27 August 2021.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2. World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Accessed at https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf on 27 August 2021.
3. Vitoria M, Hill A, Ford N, et al. The transition to dolutegravir and other new antiretrovirals in low-income and middle-income countries: what are the issues? AIDS. 2018;32:1551–1561. doi:10.1097/QAD.0000000000001845 [PubMed: 29746295]
4. Gupta A, Juneja S, Vitoria M, et al. Projected uptake of new antiretroviral (ARV) medicines in adults in low- and middle-income countries: a forecast analysis 2015-2025. PLoS One. 2016;11:e0164619. doi:10.1371/journal.pone.0164619 [PubMed: 27736953]
5. Kanters S, Vitoria M, Zoratti M, et al. Comparative efficacy, tolerability and safety of dolutegravir and efavirenz 400mg among antiretroviral therapies for first-line HIV treatment: a systematic literature review and network meta-analysis. EClinicalMedicine 2020;28:100573. doi:10.1016/j.eclinm.2020.100573 [PubMed: 33294805]
6. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception [Letter]. N Engl J Med. 2018;379:979–981. doi:10.1056/NEJMc1807653 [PubMed: 30037297]
7. World Health Organization. Potential safety issue affecting women living with HIV using dolutegravir at the time of conception. Accessed at www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf on 27 August 2021.
8. Departamento de Vigilância, Prevenção e Controle das IST, do HIV/AIDS e das Hepatites Virais (Brazil). Nota informativa Nº 10/2018-.DIAHV/SVS/MS Recomendações sobre o uso do dolutegravir. 18 May 2018. Accessed at www.aids.gov.br/pt-br/legislacao/nota-informativa-no-102018-diahvsvsms on 27 August 2021.
9. Ministry of Health (Kenya). Statement on the use of dolutegravir in women of child bearing age (15-49 yrs), ref: MOH/NASCOP/DPPH/C&T/002; 22 June 2018.
10. National Center for HIV/AIDS, Dermatology, and STD. Operational guidance: use of dolutegravir (DTG) for adults and adolescents in Cambodia. Accessed at www.nchads.org/documents_post/operational-guidance-use-of-dolutegravir-dtg-for-adults-and-adolescents-in-cambodia/ on 27 August 2021.
11. Ministry of Health (Rwanda). Transmission of circular on changes in HIV prevention and management guidelines. Accessed at https://rbc.gov.rw/fileadmin/user_upload/guide/Circular%202018.pdf on 27 August 2021.
12. Ministry of Health (Uganda). Consolidated guidelines for prevention and treatment of HIV in Uganda. Accessed at http://library.health.go.ug/publications/hivaids/consolidated-guidelines-prevention-and-treatment-hiv-uganda-1 on 27 August 2021.
13. Hegdahl HK, Fylkesnes KM, Sandøy IF. Sex differences in HIV prevalence persist over time: evidence from 18 countries in sub-Saharan Africa. PLoS One. 2016;11:e0148502. doi:10.1371/journal.pone.0148502 [PubMed: 26841112]
14. World Health Organization. Policy brief: update of recommendations on first- and second-line antiretroviral regimens. Accessed at https://apps.who.int/iris/handle/10665/325892 on 27 August 2021.
15. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. N Engl J Med. 2019;381:827–840. doi:10.1056/NEJMoa1905230 [PubMed: 31329379]
16. Dugdale CM, Ciaranello AL, Bekker LG, et al. Risks and benefits of dolutegravir- and efavirenz-based strategies for south African women with HIV of child-bearing potential: a modeling study. Ann Intern Med. 2019;170:614–625. doi:10.7326/M18-3358 [PubMed: 30934067]
17. Phillips AN, Venter F, Havlir D, et al. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. Lancet HIV. 2019;6:e116–e127. doi:10.1016/S2352-3018(18)30317-5 [PubMed: 30503325]
18. Ministry of Health (Kenya). Updated statement on use of dolutegravir in adolescent girls and women of child-bearing potential in Kenya, ref: MOH/ADM/1/1/2; 25 July 2019.

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19. U.S. President's Emergency Plan for AIDS Relief (PEPFAR). Haiti country operational plan: 2019. Strategic direction summary. 11 June 2019. Accessed at www.state.gov/wp-content/uploads/2019/09/Haiti_COP19-Strategic-Directional-Summary_public.pdf on 27 August 2021.
20. National Medicines and Therapeutics Policy Advisory Committee (NMTPAC) and The AIDS and TB Directorate, Ministry of Health and Child Care (Zimbabwe). Addendum to the 2016 guidelines for antiretroviral therapy for the prevention of and treatment of HIV in Zimbabwe. 29 March 2019.
21. U.S. President's Emergency Plan for AIDS Relief (PEPFAR). Democratic Republic of the Congo country operational plan 2019: strategic direction summary. 12 April 2019. Accessed at www.state.gov/wp-content/uploads/2019/09/DRC_COP19-Strategic-Directional-Summary_public.pdf on 27 August 2021.
22. Ministério da Saúde (Mozambique). Normas clínicas actualizadas para o seguimento do paciente HIV positivo. Circular n°: 04/2103/DNSP/019. 30 October 2019.
23. Ministry of Health, Community Development, Gender, Elderly, and Children (Tanzania), National AIDS Control Programme. National guidelines for the management of HIV and AIDS. 7th ed. April 2019. Accessed at https://differentiatedservicedelivery.org/Portals/0/adam/Content/NqQGryocrU2RTj58iR37uA/File/NATIONAL_GUIDELINES_FOR_THE_MANAGEMENT_OF_HIV_AND_AIDS_2019.pdf on 27 August 2021.
24. Ministry of Health (Lesotho). Addendum to the national guidelines on the use of antiretroviral therapy for HIV prevention and treatment. July 2019.
25. UNAIDS, UNICEF. A progress report: all in to end the adolescent AIDS epidemic. Accessed at www.unaids.org/sites/default/files/media_asset/ALLIN2016ProgressReport_en.pdf on 27 August 2021.
26. Aalen OO, Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. Scand J Stat. 1978;5:141–150.
27. Phillips AN, Bansi-Matharu L, Venter F, et al. Updated assessment of risks and benefits of dolutegravir versus efavirenz in new antiretroviral treatment initiators in sub-Saharan Africa: modelling to inform treatment guidelines. Lancet HIV. 2020;7:e193–e200. doi:10.1016/S2352-3018(19)30400-X [PubMed: 32035041]
28. 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:e1003397. doi:10.1371/journal.pmed.1003397 [PubMed: 33315863]
29. Calmy A, Tovar Sanchez T, Kouanfack C, et al. ; New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-Income Countries (NAMSAL) ANRS 12313 Study Group. 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–e687. doi:10.1016/S2352-3018(20)30238-1 [PubMed: 33010241]
30. Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. Lancet HIV. 2020;7:e666–e676. doi:10.1016/S2352-3018(20)30241-1 [PubMed: 33010240]
31. World Health Organization. HIV drug resistance report 2019. Accessed at www.who.int/publications/i/item/WHO-CDS-HIV-19.21 on 27 August 2021.
32. Siedner MJ, Moorhouse MA, Simmons B, et al. Reduced efficacy of HIV-1 integrase inhibitors in patients with drug resistance mutations in reverse transcriptase. Nat Commun. 2020;11:5922. doi:10.1038/s41467-020-19801-x [PubMed: 33262331]
33. Caniglia EC, Shapiro R, Diseko M, et al. Weight gain during pregnancy among women initiating dolutegravir in Botswana. EClinicalMedicine. 2020;29-30:100615. doi:10.1016/j.eclinm.2020.100615 [PubMed: 33437946]
34. Zash R, Holmes L, Diseko M, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. Presented at 23rd International AIDS Conference (AIDS 2020), 6–10 July 2020. Oral late breaker abstract OAXLB0102.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

35. Pereira GFM, Kim A, Jalil EM, et al. ; National Cohort Study of Dolutegravir and Pregnancy Outcomes in Brazil. Dolutegravir and pregnancy outcomes in women on antiretroviral therapy in Brazil: a retrospective national cohort study. Lancet HIV. 2021;8:e33–e41. doi:10.1016/S2352-3018(20)30268-X [PubMed: 33387477]
36. Money D, Lee T, O'Brien C, et al. ; Canadian Perinatal HIV Surveillance Program. Congenital anomalies following antenatal exposure to dolutegravir: a Canadian surveillance study. BJOG. 2019;126:1338–1345. doi:10.1111/1471-0528.15838 [PubMed: 31188522]
37. Chouchana L, Pariente A, Pannier E, et al. Dolutegravir and neural tube defects: a new insight [Letter]. Lancet Infect Dis. 2020;20:405–406. doi:10.1016/S1473-3099(20)30117-1
38. Raesima MM, Ogbuabo CM, Thomas V, et al. Dolutegravir use at conception - additional surveillance data from Botswana [Letter]. N Engl J Med. 2019;381:885–887. doi:10.1056/NEJMc1908155 [PubMed: 31329378]
39. Kintu K, Malaba TR, Nakibuka J, et al. ; DolPHIN-2 Study Group. Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial. Lancet HIV. 2020;7:e332–e339. doi:10.1016/S2352-3018(20)30050-3 [PubMed: 32386721]
40. Lockman S, Brummel SS, Ziemba L, et al. ; IMPAACT 2010/VESTED Study Team and Investigators. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet. 2021;397:1276–1292. doi:10.1016/S0140-6736(21)00314-7 [PubMed: 33812487]
41. Bernard C, Thorne J, Humphrey J, et al. Chaguo Langu—My Choice: counseling and shared decision-making about antiretroviral therapy and reproductive health options in western Kenya. Poster presented at 23rd International AIDS Conference (AIDS 2020), 6–10 July 2020. Poster PEB 0286.
42. Alhassan Y, Twimukye A, Malaba T, et al. Community acceptability of dolutegravir-based HIV treatment in women: a qualitative study in South Africa and Uganda. BMC Public Health. 2020;20:1883. doi:10.1186/s12889-020-09991-w [PubMed: 33287795]
43. Humphrey J, Omodi V, Bernard C, et al. Viral suppression and contraceptive use among women initiating dolutegravir-containing antiretroviral therapy in Kenya: The Chaguo Langu study. Presented at 23rd International AIDS Conference (AIDS 2020), 6–10 July 2020.
44. Fundarò C, Genovese O, Rendeli C, et al. Myelomeningocele in a child with intrauterine exposure to efavirenz [Letter]. AIDS. 2002;16:299–300. [PubMed: 11807320]
45. De Santis M, Carducci B, De Santis L, et al. Periconceptional exposure to efavirenz and neural tube defects. Arch Intern Med. 2002;162:355.
46. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2006 revision. Accessed at https://apps.who.int/iris/handle/10665/43554 on 27 August 2021.
47. Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. AIDS. 2014;28 Suppl 2:S123–31. doi:10.1097/QAD.0000000000000231 [PubMed: 24849471]
48. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (2013): recommendations for a public health approach. Accessed at www.who.int/publications/i/item/9789241505727 on 27 August 2021.
49. Mofenson LM, Pozniak AL, Wambui J, et al. Optimizing responses to drug safety signals in pregnancy: the example of dolutegravir and neural tube defects. J Int AIDS Soc. 2019;22:e25352. doi:10.1002/jia2.25352 [PubMed: 31298496]
50. Kant A, de Vries L, Rolfes L. Surveillance of drug safety during pregnancy: insight in current international activities, future intentions and need for support of national pharmacovigilance centres. Drug Saf 2019;42:35–43. doi:10.1007/s40264-018-0729-0 [PubMed: 30284215]
51. Duda SN, Musick BS, Davies M-A, et al. The IeDEA Data Exchange Standard: a common data model for global HIV cohort collaboration. medRxiv. Preprint posted online 25 July 2020. doi:10.1101/2020.07.22.20159921

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52. Tippett Barr BA. Assessing the capacity and findings of routine programmatic data in Kenya to guide decision-making around contraceptives and antiretroviral therapy [Letter]. BMC Med. 2021;19:192. doi:10.1186/s12916-021-02066-6 [PubMed: 34384455]

53. Dorward J, Khubone T, Gate K, et al. The impact of the COVID-19 lockdown on HIV care in 65 South African primary care clinics: an interrupted time series analysis. Lancet HIV. 2021;8:e158–e165. doi:10.1016/S2352-3018(20)30359-3 [PubMed: 33549166]

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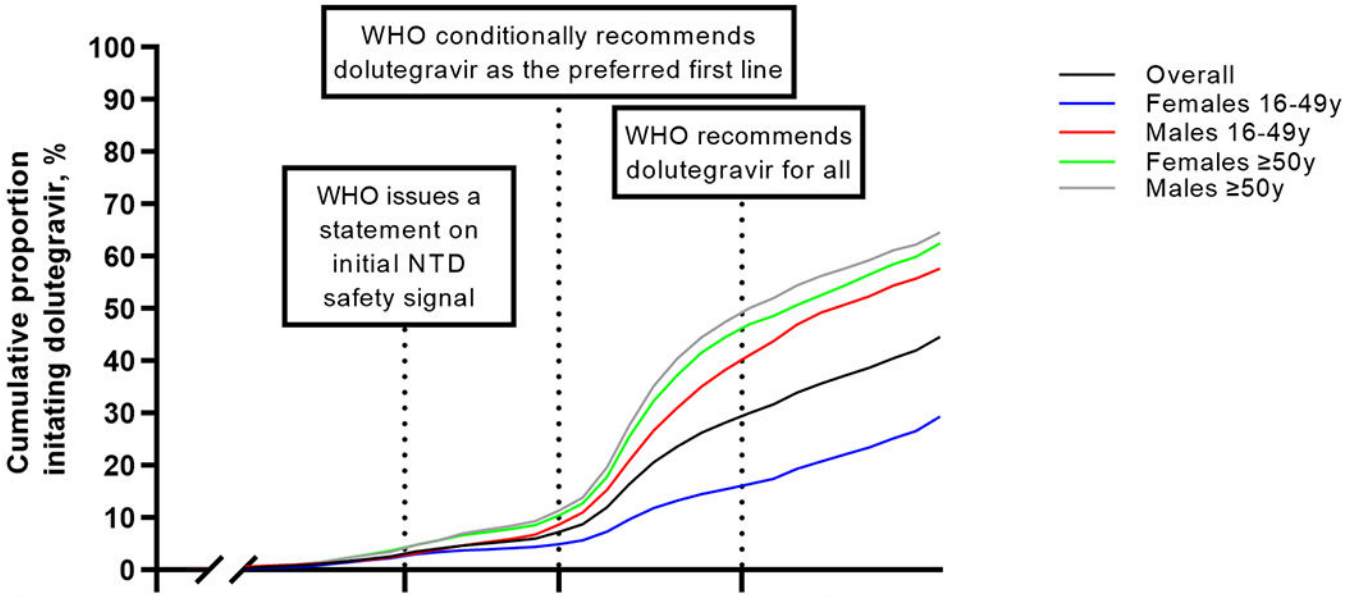

	May 18, 2018	December 1, 2018	July 22, 2019
Number of patients at risk			
Overall	125,869	116,248	79,298
Females 16-49y	65,166	61,423	49,695
Males 16-49y	31,354	28,161	15,559
Females ≥50y	16,875	15,435	8438
Males ≥50y	12,474	11,229	5606

Figure 1. Cumulative incidence of dolutegravir uptake, overall and by sex and age group, January 2017 through March 2020.

The graph shows the cumulative incidence of dolutegravir uptake at the end of the calendar month in the observation period. Each tick on the x-axis corresponds to dates of the events described in the graph. NTD = neural tube defect; WHO = World Health Organization.

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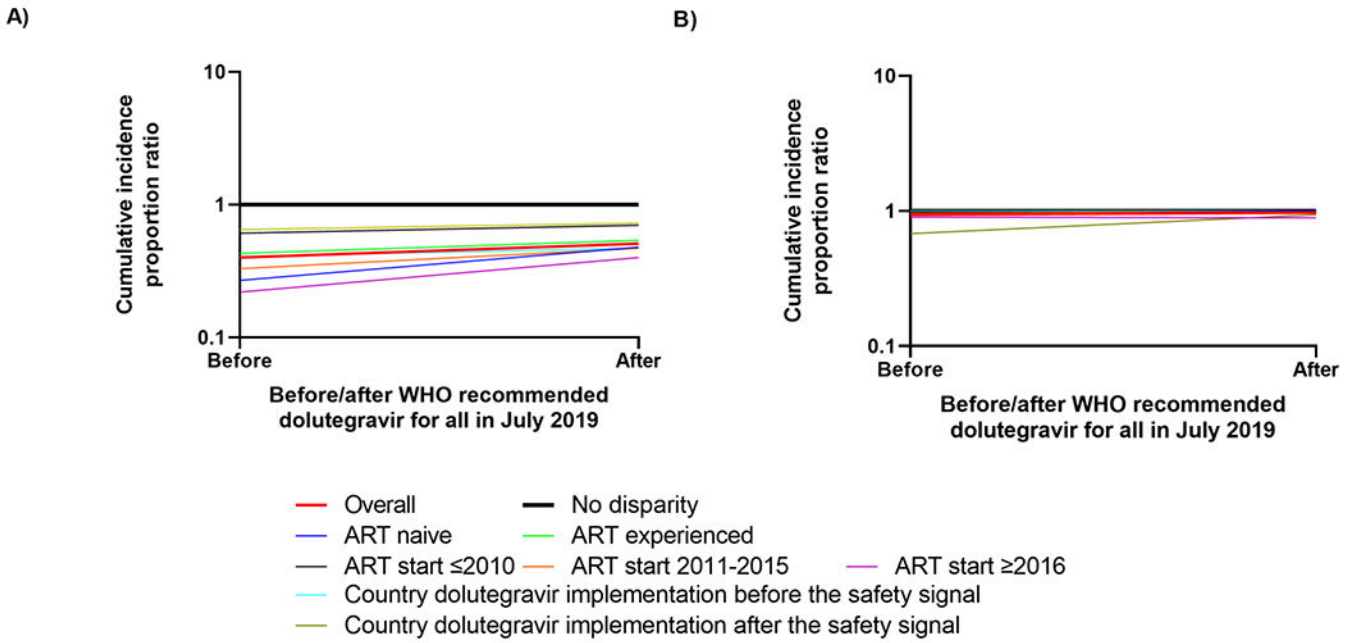

Figure 2. Ratios of cumulative incidence proportions before and after WHO recommended dolutegravir for all, overall and stratified by other variables.

The graphs show ratios of cumulative incidence proportions from Table 3 comparing females with males in age strata. Year of starting ART is among ART-experienced patients. ART = antiretroviral therapy; WHO = World Health Organization. **Left (A).** Females aged 16–49 y to males aged 16–49 y. **Right (B).** Females aged ≥50 y to males aged ≥50 y.

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Table 1.

Sample Characteristics of Patients Receiving Care at Sites That Began Using Dolutegravir, Overall and Stratified by Sex and Age Group

Characteristic	All Patients	Females Aged 16–49 y	Males Aged 16–49 y	Females Aged ≥50 y	Males Aged ≥50 y
Total, *n* (%)	134 672 (100)	69 578 (51.7)	33 620 (25.0)	18 073 (13.4)	13 401 (10.0)
Mean age (SD), *y*	41 (12)	36 (8)	38 (7)	57 (6)	58 (6)
Experience with ART at start of follow-up, *n* (%)					
Naive	22 100 (16.4)	11 818 (17.0)	7507 (22.3)	1417 (7.8)	1358 (10.1)
Experienced	112 572 (83.6)	57 760 (83.0)	26 113 (77.7)	16 656 (92.2)	12 043 (89.9)
Year of starting ART (among ART-experienced patients), *n* (%)					
2010 or prior	38 214 (34.0)	17 649 (30.6)	6398 (24.5)	8117 (48.7)	6050 (50.2)
2011–2015	47 522 (42.2)	25 365 (43.9)	11 641 (44.6)	6120 (36.7)	4396 (36.5)
2016 or later	26 836 (23.8)	14 746 (25.5)	8074 (30.9)	2419 (14.5)	1597 (13.3)
Site urbanicity, *n* (%) *					
Rural	69 264 (52.3)	36 359 (53.1)	16 629 (50.2)	9631 (54.7)	6645 (50.6)
Urban	63 060 (47.7)	32 056 (46.9)	16 527 (49.9)	7981 (45.3)	6496 (49.4)
Site level of care, *n* (%) *					
Primary	54 889 (41.5)	28 175 (41.2)	13 398 (40.4)	7859 (44.6)	5457 (41.5)
Secondary	45 420 (34.3)	24 032 (35.1)	10 588 (31.9)	6432 (36.5)	4368 (33.2)
Tertiary	32 015 (24.2)	16 208 (23.7)	9170 (27.7)	3321 (18.9)	3316 (25.2)
Country, *n* (%)					
Brazil	1991 (1.5)	337 (0.5)	1394 (4.2)	74 (0.4)	186 (1.4)
Cambodia	323 (0.2)	114 (0.2)	182 (0.5)	7 (0.04)	20 (0.2)
Democratic Republic of the Congo	440 (0.3)	288 (0.4)	49 (0.2)	61 (0.3)	42 (0.3)
Haiti	682 (0.5)	331 (0.5)	239 (0.7)	56 (0.3)	56 (0.4)
Kenya	77 546 (57.6)	40 382 (58.0)	17 882 (53.2)	11 110 (61.5)	8172 (61.0)
Lesotho	6305 (4.7)	3053 (4.4)	1262 (3.8)	1242 (6.9)	748 (5.6)

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Characteristic	All Patients	Females Aged 16–49 y	Males Aged 16–49 y	Females Aged ≥50 y	Males Aged ≥50 y
Mozambique	7847 (5.8)	4736 (6.8)	2066 (6.2)	652 (3.6)	393 (2.9)
Rwanda	9313 (6.9)	4244 (6.1)	2947 (8.8)	1081 (6.0)	1041 (7.8)
Tanzania	2221 (1.7)	1218 (1.8)	662 (2.0)	192 (1.1)	149 (1.1)
Uganda	13 324 (9.9)	7474 (10.7)	3819 (11.4)	1012 (5.6)	1019 (7.6)
Zimbabwe	14 680 (10.9)	7401 (10.6)	3118 (9.3)	2586 (14.3)	1575 (11.8)
Time country started implementing dolutegravir regimen, *n* (%)					
Before the May 2018 safety signal[†]	102 497 (76.1)	52 551 (75.5)	26 224 (78.0)	13 284 (73.5)	10 438 (77.9)
After the May 2018 safety signal[‡]	32 175 (23.9)	17 027 (24.5)	7396 (22.0)	4789 (26.5)	2963 (22.1)

ART = antiretroviral therapy.

[*] Missing data for 2348 patients.

[†] Brazil, Cambodia, Kenya, Rwanda, and Uganda.

[‡] Democratic Republic of the Congo, Haiti, Lesotho, Mozambique, Tanzania, and Zimbabwe.

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Table 2.

Antiretroviral Therapy Regimens and Dolutegravir Use, Overall and Stratified by Sex and Age Group

Variable	All Patients	Females Aged 16–49 y	Males Aged 16–49 y	Females Aged ≥50 y	Males Aged ≥50 y
Regimen bases among patients newly initiating ART, *n/N (%)*					
Dolutegravir	8160/22 100 (36.9)	2377/11 818 (20.1)	4262/7507 (56.8)	773/1417 (54.6)	748/1358 (55.1)
Efavirenz	13 424/22 100 (60.7)	9168/11 818 (77.6)	3088/7507 (41.1)	602/1417 (42.5)	566/1358 (41.7)
Nevirapine	278/22 100 (1.3)	158/11 818 (1.3)	71/7507 (1.0)	26/1417 (1.8)	23/1358 (1.7)
Protease inhibitor	190/22 100 (0.9)	101/11 818 (0.9)	61/7507 (0.8)	15/1417 (1.1)	13/1358 (1.0)
Other	48/22 100 (0.2)	14/11 818 (0.1)	25/7507 (0.3)	1/1417 (0.1)	8/1358 (0.6)
Initially ART-naive patients who later switched to dolutegravir, *n/N (%)*	3108/13 940 (22.3)	1161/9441 (12.3)	1311/3245 (40.4)	328/644 (50.9)	308/610 (50.5)
ART-experienced patients who switched to dolutegravir, *n/N (%)*	46 231/112 572 (41.1)	15 311/57 760 (26.5)	13 464/26 113 (51.6)	9996/16 656 (60.0)	7460/12 043 (61.9)
All patients who switched to dolutegravir from another regimen, *n/N (%)*	49 339/126 512 (39.0)	16 472/67 201 (24.5)	14 775/29 358 (50.3)	10 324/17 300 (59.7)	7768/12 653 (61.4)
Previous regimen bases among all patients who switched to dolutegravir, *n/N (%)*					
Efavirenz	29 748/49 339 (60.3)	9649/16 472 (58.6)	10 210/14 775 (69.1)	5640/10 324 (54.6)	4249/7768 (54.7)
Nevirapine	18 482/49 339 (37.5)	6352/16 472 (38.6)	4237/14 775 (28.7)	4533/10 324 (43.9)	3360/7768 (43.3)
Protease inhibitor	1010/49 339 (2.1)	442/16 472 (2.7)	283/14 775 (1.9)	144/10 324 (1.4)	141/7768 (1.8)
Other	99/49 339 (0.2)	29/16 472 (0.2)	45/14 775 (0.3)	7/10 324 (0.1)	18/7768 (0.2)
Latest regimen bases among all patients alive and engaged in care at database closure, *n/N (%)*					
Dolutegravir	50 308/112 426 (44.8)	15 956/57 877 (27.6)	16 718/26 919 (62.1)	10 019/16 108 (62.2)	7615/11 522 (66.1)
Efavirenz	48 680/112 426 (43.3)	34 786/57 877 (60.1)	7370/26 919 (27.4)	4103/16 108 (25.5)	2421/11 522 (21.0)
Nevirapine	3432/112 426 (3.1)	1894/57 877 (3.3)	544/26 919 (2.0)	625/16 108 (3.9)	369/11 522 (3.2)
Protease inhibitor	9971/112 426 (8.9)	5225/57 877 (9.0)	2275/26 919 (8.5)	1357/16 108 (8.4)	1114/11 522 (9.7)
Other	35/112 426 (0.03)	16/57 877 (0.03)	12/26 919 (0.04)	4/16 108 (0.02)	3/11 522 (0.03)

ART = antiretroviral therapy.

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Table 3.

Cumulative Incidence of Dolutegravir Uptake, by Sex and Age Group

Variable	Summary of Outcomes				Dolutegravir Uptake, Cumulative Incidence Proportion (95% CI)		
	Total Patients, *n*	Patients Initiating Dolutegravir, *n*	Patients Who Dropped Out, *n*	Patients Censored, *n*	Before the Safety Signal (Until 18 May 2018)	After the Safety Signal (Until 22 July 2019)	After the WHO Recommended Dolutegravir for All (Until 31 March 2020)
Entire sample	134 672	57 499	18 736	58 437	3.2 (3.1–3.3)	29.6 (29.3–29.8)	44.6 (44.3–44.9)
Sex and age group							
Females aged 16–49 y	69 578	18 849	10 695	40 034	2.8 (2.7–3.0)	16.2 (15.9–16.5)	29.4 (29.0–29.7)
Males aged 16–49 y	33 620	19 037	5144	9439	2.9 (2.7–3.0)	40.4 (39.8–40.9)	57.7 (57.2–58.3)
Females aged ≥50 y	18 073	11 097	1510	5466	4.3 (4.0–4.6)	46.4 (45.6–47.1)	62.6 (61.8–63.3)
Males aged ≥50 y	13 401	8516	1387	3498	4.3 (3.9–4.6)	49.4 (48.5–50.2)	64.7 (63.8–65.5)
Sex and age subgroup							
Females aged 16–29 y	16 056	2002	3727	10 327	0.9 (0.8–1.1)	3.3 (3.0–3.6)	14.2 (13.6–14.8)
Males aged 16–29 y	4881	2583	899	1399	4.2 (3.7–4.8)	33.8 (32.5–35.1)	54.1 (52.7–55.6)
Females aged 30–39 y	28 110	5315	4452	18 343	2.4 (2.3–2.6)	9.1 (8.8–9.5)	21.3 (20.8–21.9)
Males aged 30–39 y	13 142	7325	2066	3751	2.1 (1.9–2.4)	39.2 (38.3–40.0)	56.8 (55.9–57.6)
Females aged 40–49 y	25 412	11 532	2516	11 364	4.5 (4.2–4.8)	32.1 (31.5–32.7)	47.6 (47.0–48.3)
Males aged 40–49 y	15 597	9129	2179	4289	3.1 (2.8–3.3)	43.4 (42.6–44.2)	59.7 (58.9–60.5)
Females aged 50–59 y	12 991	8165	1053	3773	4.5 (4.1–4.9)	48.7 (47.9–49.6)	64.0 (63.1–64.8)
Males aged 50–59 y	9216	5912	978	2326	4.3 (3.9–4.8)	50.8 (49.8–51.8)	65.3 (64.2–66.3)
Females aged ≥60 y	5082	2932	457	1693	4.0 (3.4–4.5)	40.4 (39.0–41.7)	58.8 (57.4–60.2)
Males aged ≥60 y	4185	2604	409	1172	4.1 (3.5–4.7)	46.2 (44.7–47.7)	63.3 (61.8–64.8)

WHO = World Health Organization.

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Table 4.

Age- and Sex-Group Specific Cumulative Incidence of Dolutegravir Uptake, by Antiretroviral Therapy Experience, Year of Starting Antiretroviral Therapy, and Country Timing of Dolutegravir Implementation

Variable	Summary of Outcomes				Dolutegravir Uptake, Cumulative Incidence Proportion (95% CI)		
	Total Patients, *n*	Patients Initiating Dolutegravir, *n*	Patients Who Dropped Out, *n*	Patients Censored, *n*	Before the Safety Signal (Until 18 May 2018)	After the Safety Signal (Until 22 July 2019)	After the WHO Recommended Dolutegravir for All (Until 31 March 2020)
Experience with ART at start of follow-up							
Naive							
Females aged 16–49 y	11 818	3538	2865	5415	1.6 (1.4–1.9)	11.7 (11.1–12.2)	36.3 (35.1–37.5)
Males aged 16–49 y	7507	5573	1157	777	4.1 (3.6–4.5)	43.6 (42.5–44.7)	75.7 (74.7–76.7)
Females aged ≥50 y	1417	1101	174	142	1.8 (1.2–2.6)	46.4 (43.8–48.9)	78.6 (76.3–80.7)
Males aged ≥50 y	1358	1056	193	109	3.0 (2.1–4.0)	49.7 (47.0–52.3)	78.7 (76.4–80.8)
Experienced							
Females aged 16–49 y	57 760	15 311	7830	34 619	3.1 (3.0–3.2)	17.1 (16.8–17.4)	28.4 (28.0–28.8)
Males aged 16–49 y	26 113	13 464	3987	8662	2.5 (2.3–2.7)	39.4 (38.8–40.0)	52.5 (51.9–53.1)
Females aged ≥50 y	16 656	9996	1336	5324	4.6 (4.2–4.9)	46.4 (45.6–47.1)	61.2 (60.4–62.0)
Males aged ≥50 y	12 043	7460	1194	3389	4.4 (4.0–4.8)	49.3 (48.4–50.2)	63.1 (62.2–64.0)
Year of starting ART (among ART-experienced patients)							
2010 or prior							
Females aged 16–49 y	17 649	7044	1900	8705	5.6 (5.2–5.9)	31.3 (30.6–32.0)	43.3 (42.4–44.2)
Males aged 16–49 y	6398	3882	866	1650	3.9 (3.4–4.4)	51.5 (50.3–52.7)	62.3 (61.0–63.6)
Females aged ≥50 y	8117	5261	636	2220	5.7 (5.2–6.2)	53.3 (52.2–54.4)	66.5 (65.4–67.6)
Males aged ≥50 y	6050	4036	590	1424	5.1 (4.5–5.6)	56.6 (55.4–57.9)	68.2 (66.9–69.4)
2011–2015							
Females aged 16–49 y	25 365	6038	3282	16 045	2.8 (2.6–3.0)	13.7 (13.3–14.1)	26.1 (25.5–26.7)
Males aged 16–49 y	11 641	6365	1668	3608	2.8 (2.5–3.1)	41.2 (40.3–42.1)	56.0 (55.1–57.0)
Females aged ≥50 y	6120	3704	452	1964	4.4 (3.9–4.9)	43.9 (42.7–45.1)	61.7 (60.4–62.9)
Males aged ≥50 y	4396	2659	408	1329	4.3 (3.8–5.0)	45.5 (44.0–47.0)	61.6 (60.1–63.0)
2016 or later							

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Variable	Summary of Outcomes				Dolutegravir Uptake, Cumulative Incidence Proportion (95% CI)		
	Total Patients, *n*	**Patients Initiating Dolutegravir, *n***	**Patients Who Dropped Out, *n***	**Patients Censored, *n***	**Before the Safety Signal (Until 18 May 2018)**	**After the Safety Signal (Until 22 July 2019)**	**After the WHO Recommended Dolutegravir for All (Until 31 March 2020)**
Females aged 16–49 y	14 746	2229	2648	9869	0.7 (0.5–0.8)	6.0 (5.6–6.4)	16.0 (15.4–16.7)
Males aged 16–49 y	8074	3217	1453	3404	1.0 (0.8–1.3)	27.3 (26.3–28.2)	40.3 (39.2–41.4)
Females aged ≥50 y	2419	1031	248	1140	1.2 (0.8–1.7)	29.2 (27.4–31.1)	43.0 (41.0–45.0)
Males aged ≥50 y	1597	765	196	636	2.0 (1.4–2.8)	32.3 (30.0–34.6)	48.3 (45.8–50.8)
Time country started implementing dolutegravir regimen							
Before the May 2018 safety signal [*]							
Females aged 16–49 y	52 551	15 394	9767	27 390	3.8 (3.6–3.9)	20.9 (20.5–21.2)	31.1 (30.6–31.6)
Males aged 16–49 y	26 224	16 976	4735	4513	3.7 (3.4–3.9)	51.0 (50.4–51.6)	65.8 (65.2–66.4)
Females aged ≥50 y	13 284	9680	1361	2243	5.9 (5.5–6.3)	62.6 (61.8–63.4)	73.4 (72.6–74.2)
Males aged ≥50 y	10 438	7586	1278	1574	5.5 (5.0–5.9)	62.9 (61.9–63.8)	73.3 (72.4–74.2)
After the May 2018 safety signal [†]							
Females aged 16–49 y	17 027	3455	928	12 644	NA	1.7 (1.5–1.9)	20.3 (19.7–20.9)
Males aged 16–49 y	7396	2061	409	4926	NA	2.6 (2.3–3.0)	27.9 (26.9–28.9)
Females aged ≥50 y	4789	1417	149	3223	NA	1.3 (1.0–1.7)	29.6 (28.3–30.9)
Males aged ≥50 y	2963	930	109	1924	NA	1.9 (1.5–2.4)	31.4 (29.8–33.1)

ART = antiretroviral therapy; NA = not applicable.

[*] Brazil, Cambodia, Kenya, Rwanda, and Uganda.

[†] Democratic Republic of the Congo, Haiti, Lesotho, Mozambique, Tanzania, and Zimbabwe.

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