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Risks and Benefits of Dolutegravir- and Efavirenz-Based Strategies for South African Women With HIV of Child-Bearing Potential

A Modeling Study

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Background: Dolutegravir is superior to efavirenz for HIV antiretroviral therapy (ART) but may be associated with an increased risk for neural tube defects (NTDs) in newborns if used by women at conception.

Objective: To project clinical outcomes of ART policies for women of child-bearing potential in South Africa.

Design: Model of 3 strategies: efavirenz for all women of child-bearing potential (EFV), dolutegravir for all women of child-bearing potential (DTG), or World Health Organization (WHO)-recommended efavirenz without contraception or dolutegravir with contraception (WHO approach).

Data Sources: Published data on NTD risks (efavirenz, 0.05%; dolutegravir, 0.67% [Tsepamo study]), 48-week ART efficacy with initiation (efavirenz, 60% to 91%; dolutegravir, 96%), and age-stratified fertility rates (2 to 139 per 1000 women).

Target Population: 3.1 million South African women with HIV (aged 15 to 49 years) starting or continuing first-line ART, and their children.

Time Horizon: 5 years.

Perspective: Societal.

Intervention: EFV, DTG, and WHO approach.

Outcome Measures: Deaths among women and children, sexual and pediatric HIV transmissions, and NTDs.

Results of Base-Case Analysis: Compared with EFV, DTG averted 13 700 women's deaths (0.44% decrease) and 57 700 sexual HIV transmissions, but increased total pediatric deaths by 4400 because of more NTDs. The WHO approach offered some benefits compared with EFV, averting 4900 women's deaths and 20 500 sexual transmissions while adding 300 pediatric deaths. Overall, combined deaths among women and children were lowest with DTG (358 000 deaths) compared with the WHO approach (362 800 deaths) or EFV (367 300 deaths).

Results of Sensitivity Analysis: Women's deaths averted with DTG exceeded pediatric deaths added with EFV unless dolutegravir-associated NTD risk was 1.5% or greater.

Limitation: Uncertainty in NTD risks and dolutegravir efficacy in resource-limited settings, each examined in sensitivity analyses.

Conclusion: Although NTD risks may be higher with dolutegravir than efavirenz, dolutegravir will lead to many fewer deaths among women, as well as fewer overall HIV transmissions. These results argue against a uniform policy of avoiding dolutegravir in women of child-bearing potential.

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Dolutegravir-based antiretroviral therapy (ART) for persons with HIV offers superior efficacy and tolerability compared with efavirenz-based ART, which has long been recommended by the World Health Organization (WHO) as the preferred first-line regimen (1–3). Recent cost negotiations yielding a price of approximately $75 per person per year make dolutegravir more affordable in resource-limited settings; thus, its global rollout has been widely anticipated (1, 4, 5). Enthusiasm for dolutegravir was tempered for women of child-bearing potential in May 2018, when preliminary data from the Tsepamo study revealed a higher risk for neural tube defects (NTDs) (4 in 426 infants, 0.94%) in infants born to women who conceived while receiving dolutegravir than in those born to women receiving efavirenz (0.05%) (6–8). Soon thereafter, the WHO released interim guidance that included dolutegravir-based ART as preferred first-line therapy; however, it recommended efavirenz as a safe and effective alternative for women of child-bearing potential desiring pregnancy or lacking access to "consistent and reliable contraception" (1).

Neural tube defects result in substantial morbidity and 75–100% mortality in resource-limited settings (9). From a public health perspective, but also from clinical and patient perspectives, the risk for NTDs potentially attributable to dolutegravir should be weighed against the benefits conveyed by dolutegravir over efavirenz. Dolutegravir is likely to increase sustained virologic suppression,

See also:

Editorial comment 1

Web-Only
Supplement

thereby improving outcomes for women and reducing HIV transmission (3, 10, 11). Although recommending dolutegravir for women using contraception would increase access to this therapy for some women, inadequate access to reproductive health services will be a barrier for others (12–14). Policymakers in resource-limited settings may face challenges in implementing the WHO guidance, including increased demand for reproductive health services, drug procurement difficulties with several first-line ART options, and providers who lack adequate time and training to help women make an informed ART choice. Therefore, guidelines in some countries (such as Kenya and Malawi) may continue to recommend efavirenz for all women of child-bearing potential, whereas others (such as Zimbabwe) may allow women to choose dolutegravir (15). To inform this important discussion, we examined clinical tradeoffs of ART policies for women of child-bearing potential in South Africa by using published and validated mathematical models of HIV disease (16–20).

METHODS

We conducted a series of model-based analyses in South Africa over a 5-year horizon, examining several outcomes: clinical and sexual transmission outcomes for women of child-bearing potential receiving or initiating first-line ART; anticipated live births among these women, including the projected number of children with NTDs; and clinical outcomes of the children, including overall and HIV-free survival and rates of HIV infection. Together, these outcomes provide a picture of the public health tradeoffs of a countrywide policy of efavirenz, dolutegravir for all women of child-bearing potential, or WHO guideline–concordant use of both, depending on access to and intended use of effective contraception (WHO approach).

Published data sources were used to derive model inputs (**Supplement Tables A2** and **A3**, available at Annals.org). We reviewed the published literature (PubMed, EMBASE [Elsevier], and Web of Science [Clarivate Analytics] from 1 January 1995 to 25 September 2018) and conference abstracts (from the 2017 and 2018 Conference on Retroviruses and Opportunistic Infections, International AIDS Society Meeting, and IDWeek) to identify randomized clinical trials that reported 48- or 96-week virologic suppression (HIV RNA <50 copies/mL) with dolutegravir or efavirenz combined with 2 nucleoside reverse transcriptase inhibitors (**Supplement Table A3**, available at Annals.org). Studies that enrolled only persons with tuberculosis co-infection, used stavudine or didanosine, did not exclude women with pretreatment drug resistance (PTDR), or omitted reasons for study withdrawal were excluded. Estimates were pooled and weighted by study size to inform 48- and 96-week ART efficacy and discontinuation due to adverse events. Participants who were lost to follow-up, died, or withdrew from the study because of adverse events were censored to avoid double counting these events, which are simulated elsewhere in the model (**Supplement**, available at Annals.org). We assumed that an adverse event occurring in a patient receiving first-line ART would prompt an immediate switch to a protease inhibitor–based regimen without viral rebound, and we tested this assumption in sensitivity analyses.

Modeled Cohort Definition

The modeled cohort of women included 3 subcohorts reflecting present-day HIV treatment status: ART-naive women initiating ART (new ART starts), women currently receiving first-line efavirenz-based ART with virologic suppression (ART-experienced-suppressed), and women currently receiving first-line efavirenz-based ART without virologic suppression (ART-experienced–not suppressed) (**Supplement Figures A1** and **A2**, available at Annals.org). Estimates from the Joint United Nations Programme on HIV/AIDS for South Africa in 2017 informed the number of women of child-bearing potential (aged 15 to 49 years) in each subcohort: 219 300 new ART starts (in each year of the simulation), 1 562 600 ART-experienced-suppressed, and 440 700 ART-experienced–not suppressed, for a total of 3 099 800 women estimated to ever be receiving first-line ART over the next 5 years (**Supplement Table A1**, available at Annals.org) (21). In all subcohorts, 24% to 40% of women were modeled as using long-acting contraception, with an annual contraceptive failure rate of 0.05% to 6%, depending on the method (22, 23).

Modeled Strategies

We compared 3 strategies: initiation or continuation of first-line efavirenz-based ART (EFV), initiation of (for new ART starts) or switch to (for ART-experienced women) first-line dolutegravir-based ART (DTG), and WHO guideline–concordant initiation or continuation of efavirenz-based ART for women not using long-acting contraception and initiation of or switch to dolutegravir-based ART for women using long-acting contraception (WHO approach) (1, 15). Outcomes for the WHO approach were calculated as a weighted average of the DTG and EFV strategies based on contraceptive use.

Projecting Outcomes for Women of Child-Bearing Potential

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International model of HIV disease to simulate a cohort of women with HIV of child-bearing potential (**Supplement**) (16–18). Women in the model are assigned health states depending on the degree of immunologic suppression or ART-related reconstitution (CD4) and virologic suppression or rebound (HIV RNA). Women start the model in 1 of the 3 subcohorts: new ART starts (mean CD4, 0.354×10^9 cells/L), ART-experienced-suppressed (mean CD4, 0.634×10^9 cells/L), and ART-experienced–not suppressed (mean CD4, 0.634×10^9 cells/L), each with distinct ART efficacy parameterization (**Table 1**) (24, 25). All modeled women undergo viral load monitoring in accordance with WHO guidelines (26) (**Supplement**). In all subcohorts, upon diagnosed viremia, women have 1 opportunity for "resuppression" on first-line ART after

adherence counseling, followed by a switch to a second-line protease inhibitor–based ART regimen if viremia persists (**Supplement Figure A2**).

Antiretroviral therapy efficacy and adverse event rates varied by strategy and subcohort (**Table 1** and **Supplement Tables A2** to **A6**, available at Annals.org). We modeled 10.7% nonnucleoside reverse transcriptase inhibitor (NNRTI) PTDR, leading to reduced efficacy of efavirenz in South Africa, where resistance testing is not uniformally performed (27). We calculated first-order sexual transmissions by using projected monthly estimates of the number of women in each HIV RNA stratum, multiplied by stratum-specific transmission rates (range, 0.16 to 9.03 transmissions per 100

Table 1. Input Parameters for an Analysis of Clinical Outcomes of Women and Children, Comparing Efavirenz- and Dolutegravir-Based ART for First-Line Treatment of HIV in South Africa

Parameters	Base Case	Range Examined	References
Women			
Mean starting CD4 count, new ART starts/ART-experienced, × 10^9 *cells/L*	0.354/0.634	–	24, 25*
NNRTI PTDR, %	10.7	0–30	27
ART discontinuation due to early adverse events, %†‡			
EFV	0–8	4–19	2, 28–30
DTG	2–4	0–4	2, 31–34
ART efficacy, virologic suppression at 48 wk, %§‖			
New ART starts without NNRTI PTDR†			
EFV	91	76–100	2, 28–30, 35
DTG	96	95–98	2, 32, 33, 36
New ART starts with NNRTI PTDR†			
EFV	60	20–80	37–40
DTG	96	95–98	2, 32, 33, 36
ART-experienced-suppressed			
EFV	100¶	–	Assumption
DTG	97	96–97	31, 34
ART-experienced–not suppressed			
EFV	0	–	Assumption
DTG	84	78–90	41, 42
Second-line protease inhibitor–based ART	75	–	43
Resuppression after first-line treatment failure, %	45	19–88	44–48
Sexual transmissions per 100 person-years (by HIV RNA stratum)	0.16–9.03	0.5 to 2 times	10, 23, 49
Use of long-acting contraception (range by age), %**	24–40	–	23
Failure rates of long-acting contraception (range by contraceptive method), %††	0.05–6.00	–	22
Children			
Breastfed infants, %	80	–	50–52
Breastfeeding duration, mean (SD), *mo*	6 (6)	–	52
NTDs in live births, %			
EFV	0.05	–	6, 8
DTG	0.67	0.1–2.0	6, 8
Mortality with NTD, %	100	–	Assumption based on reference 9
Pediatric HIV infection risks†			
IU/IP–receiving ART, with virologic suppression	0.25%	0.5–2 times	11, 53, 54
IU/IP–receiving ART, without virologic suppression	4.64%	0.5–2 times	11, 53, 54
IU/IP–not receiving ART (range by CD4 count)	17%–27%	–	55–57
PP–receiving ART, with virologic suppression	0.05% per mo	0.5–2 times	58, 59
PP–receiving ART, without virologic suppression	0.29% per mo	0.5–2 times	58, 59
PP–not receiving ART (range by CD4 count)	0.24%–1.28% per mo	–	56, 57, 60

ART = antiretroviral therapy; CEPAC = Cost-Effectiveness of Preventing AIDS Complications; DTG = dolutegravir for all women of child-bearing potential; EFV = efavirenz for all women of child-bearing potential; IP = intrapartum; IU = intrauterine; NNRTI = nonnucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PP = postpartum; PTDR = pretreatment drug resistance.

* The mean CD4 count at model start for ART-experienced women was from CEPAC-generated CD4 count projections of women who had been receiving efavirenz-based ART for a mean of 34 mo (25).

† Additional studies informing these inputs are detailed in the **Supplement** (available at Annals.org).

‡ Adverse events prompt transition from first-line ART to a protease inhibitor–based regimen without intervening viral rebound.

§ Most publications of clinical trials count loss to follow-up, protocol deviation, consent withdrawal, and discontinuation due to mortality as virologic failures. However, these events are accounted for separately in the model. Therefore, we extract these parameters from our calculation of virologic suppression to calculate as-treated values of HIV RNA suppression to <50 copies/mL and avoid double counting in the model. See the **Supplement** for details.

‖ The 48-wk ART efficacy in the subcohort of DTG new ART starts was informed by trials involving ART-naive participants; ART efficacy data for ART-experienced persons were taken from switch studies (ART-experienced-suppressed) and from studies of second-line dolutegravir-based ART among treatment-experienced persons (ART-experienced–not suppressed).

¶ In the EFV strategy, women in the ART-experienced-suppressed subcohort who continued receiving efavirenz-based ART started with 100% probability of virologic suppression by definition, but then were immediately eligible for a monthly risk for late treatment failure. See the **Supplement** for details.

** Long-acting contraception includes female or male sterilization, IU devices, injectable contraceptives, and implants.

†† Failure rates reflect the percentage of women who have an unintended pregnancy within the first year of typical use (22).

Table 2. Projected 5-Year Outcomes for Approximately 3.1 Million Women of Child-Bearing Potential Who Ever Receive First-Line ART and Their Children

Outcomes	EFV	DTG	WHO	DTG-EFV Outcome*	WHO-EFV Outcome*	DTG-WHO Outcome*
Women						
Women virologically suppressed on ART	1 830 800	1 901 300	1 855 800	+70 400^{D}	+24 900^{W}	+45 500^{D}
Severe OIs among women†	658 900	619 100	644 800	−39 700^{D}	−14 100^{W}	−25 700^{D}
Deaths among women‡	276 500	262 800	271 700	−13 700^{D}	−4900^{W}	−8900^{D}
Sexual transmissions to partners	251 800	194 000	231 300	−57 700^{D}	−20 500^{W}	−37 300^{D}
Children						
Children born to women with HIV	1 030 400	1 033 400	1 030 600	+3000	+200	+2800
Non-NTD-related pediatric deaths	90 300	88 300	90 200	−2100^{D}	−100^{W}	−1900^{D}
NTDs	500	6900	900	+6400^{E}	+400^{E}	+6000^{W}
Pediatric HIV infections	29 800	22 600	29 300	−7100^{D}	−400^{W}	−6700^{D}
Children alive and HIV-free	921 800	924 700	921 900	+3000^{D}	+200^{W}	+2800^{D}
Cumulative pediatric deaths§	90 800	95 200	91 100	+4400^{E}	+300^{E}	+4100^{W}
Combined						
Cumulative deaths among women and children	367 300	358 000	362 800	−9300^{D}	−4500^{W}	−4800^{D}

ART = antiretroviral therapy; DTG = dolutegravir for all women of child-bearing potential; EFV = efavirenz for all women of child-bearing potential; NTD = neural tube defect; OI = opportunistic infection; WHO = World Health Organization (approach).
* Superscript letters indicate which strategy is favored by the outcome: D = DTG; E = EFV; W = WHO.
† Severe OIs are defined as WHO stage 3 or 4 opportunistic infections or cases of tuberculosis (pulmonary or extrapulmonary). Of the OIs reported with EFV, DTG, and WHO, 232 100, 208 700, and 223 800, respectively, were cases of tuberculosis.
‡ The number of deaths averted among women with DTG versus EFV (13 700) reflects a 0.44% absolute difference in mortality between strategies at 5 years (13 700 deaths averted ÷ 3 099 800 total cohort size = 0.44%).
§ Refers to pediatric deaths over 5 years from all causes, including NTDs.

person-years), with a 29% transmission reduction reflecting condom use (10, 16, 49, 61).

For each strategy, we projected the following clinical outcomes for women over a 5-year period: number with suppression while receiving ART, cumulative severe opportunistic infections (OIs), deaths, and first-order sexual transmissions. Then, we calculated the difference in these outcomes in 3 pairwise comparisons: DTG versus EFV, WHO approach versus EFV, and DTG versus WHO approach.

Projecting Live Births and NTDs

To project anticipated live births over 5 years for each strategy, we combined age-stratified fertility rates among women of child-bearing potential (2 to 139 live births per 1000 women per year) (23) with age-stratified cohort sizes based on HIV prevalence and then adjusted for CEPAC-derived maternal mortality (61). On the basis of the most recent Tsepamo estimates (from July 2018), we assumed that children born to women receiving dolutegravir had a 0.67% risk for NTDs, versus 0.05% with all other ART regimens (6, 8). With 95% mortality with NTDs in sub-Saharan Africa (9), we assumed 100% mortality in this population.

Infant Health Outcomes

We simulated peri- and postnatal HIV transmission with risks stratified by maternal ART use, CD4 count, and virologic suppression (**Table 1**) (11, 53, 56, 57, 60). We projected pediatric outcomes by using the CEPAC-Pediatric model, incorporating the effect of HIV exposure and infection on mortality, as well as disease progression, diagnosis, and treatment for HIV-infected children (19). Outcomes included HIV transmission and overall and HIV-free pediatric survival (further details are available at www.massgeneral.org/mpec/cepac/).

Sensitivity and Scenario Analysis

We evaluated whether the results were robust to changes in key parameters and assumptions and generalizable to alternative settings, focusing sensitivity analyses on the EFV and DTG strategies (for others, see the **Supplement**). In univariate analyses, we examined the effect of the following inputs on relevant outcomes: NNRTI PTDR, new ART starts annually, fertility rate, ART efficacy among new ART starts, sexual transmission rates, and peri- and postnatal transmission risks for women receiving ART. Given the substantial uncertainty around dolutegravir-associated NTD risks, we varied this parameter widely, intentionally beyond the Tsepamo study's 95% confidence limits (6, 8). In multivariate analyses, we simultaneously varied influential parameters on deaths among women with HIV and their children: NNRTI PTDR, dolutegravir-associated NTD risk, fertility rates, and new ART starts annually. Finally, we created a scenario analysis with associated univariate sensitivity analyses using data from the NAMSAL (New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries) trial (62), assuming equal 48-week ART efficacy for new ART starts with dolutegravir- and (low-dose) efavirenz-based ART (**Supplement Table A5** and **Supplement Figure A5**, available at Annals.org).

This study was approved by the Partners Human Research Committee, Boston, Massachusetts.

Role of the Funding Source

The funders had no role in study design, data collection, data interpretation, or writing of the manuscript.

RESULTS

Outcomes Among Women

At 5 years, the model projected that for women in the EFV strategy, 1 830 800 had achieved virologic suppression, 658 900 had experienced severe OIs, and 276 500 had died (Table 2). Compared with EFV, outcomes were better with DTG, which resulted in 70 400 more women with virologic suppression, 39 700 fewer severe OIs, and 13 700 fewer deaths among women with HIV (0.44% relative decrease in mortality). Compared with EFV, the WHO approach resulted in 24 900 more women with virologic suppression while averting 14 100 severe OIs and 4900 deaths among women. However, all outcomes among women were better with DTG than with the WHO approach.

Transmission Outcomes

Because of higher rates of durable virologic suppression, DTG resulted in 57 700 and 37 300 fewer projected sexual transmissions than EFV and the WHO approach, respectively, over 5 years. Likewise, DTG averted 7100 pediatric HIV infections versus EFV and 6700 versus the WHO approach.

Outcomes Among Children

Reflecting differences in survival among women, DTG resulted in 3000 more children being born than with EFV and 2800 more than with the WHO approach over 5 years (Table 2). The EFV strategy led to 90 300 pediatric deaths from non-NTD causes, 500 fatal NTDs, and 921 800 children alive and HIV-free at 5 years when pediatric transmissions were taken into account. Compared with EFV, DTG resulted in 2100 fewer non–NTD-related deaths and 6400 more projected NTDs; overall, 3000 more children were alive and HIV-free at 5 years. Pediatric outcomes with the WHO approach closely resembled those with EFV, because most conceptions with the WHO approach occurred among women receiving EFV.

Over 5 years, DTG led to 4400 more pediatric deaths than EFV and 4100 more than the WHO approach. Although EFV led to 4400 fewer pediatric deaths than DTG, DTG resulted in 3.1-fold fewer deaths (13 700 deaths) among women.

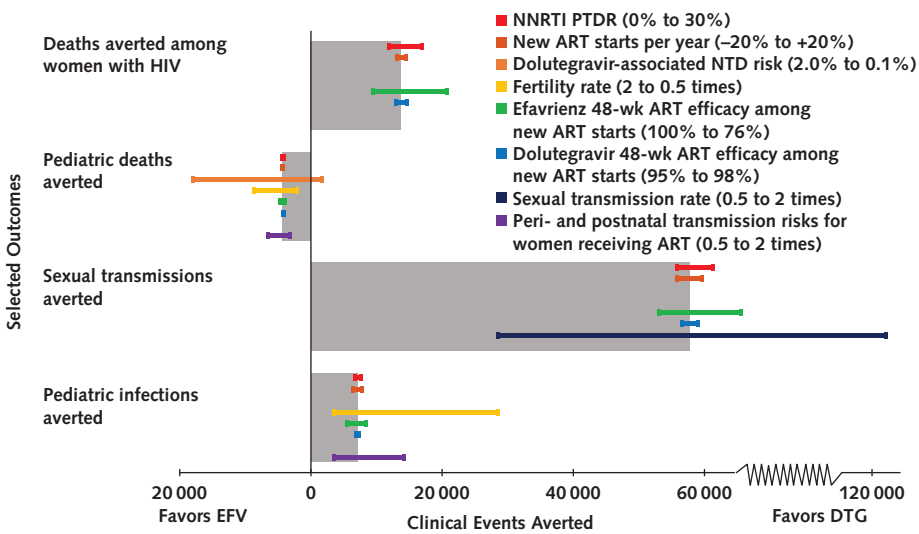
Sensitivity Analysis

Univariate

When the analysis considered the highest levels of efavirenz 48-week ART efficacy observed in clinical trials among new ART starts (100% efficacy) (63), DTG still resulted in 9500 fewer deaths among women with HIV and 53 100 fewer sexual transmissions compared with EFV (Figure 1, *green bars*). Conversely, with NNRTI PTDR increased to 30%, DTG averted more deaths among women (16 900 deaths) and sexual transmissions (61 200 transmissions) than in the base case (Figure 1, *red bars*).

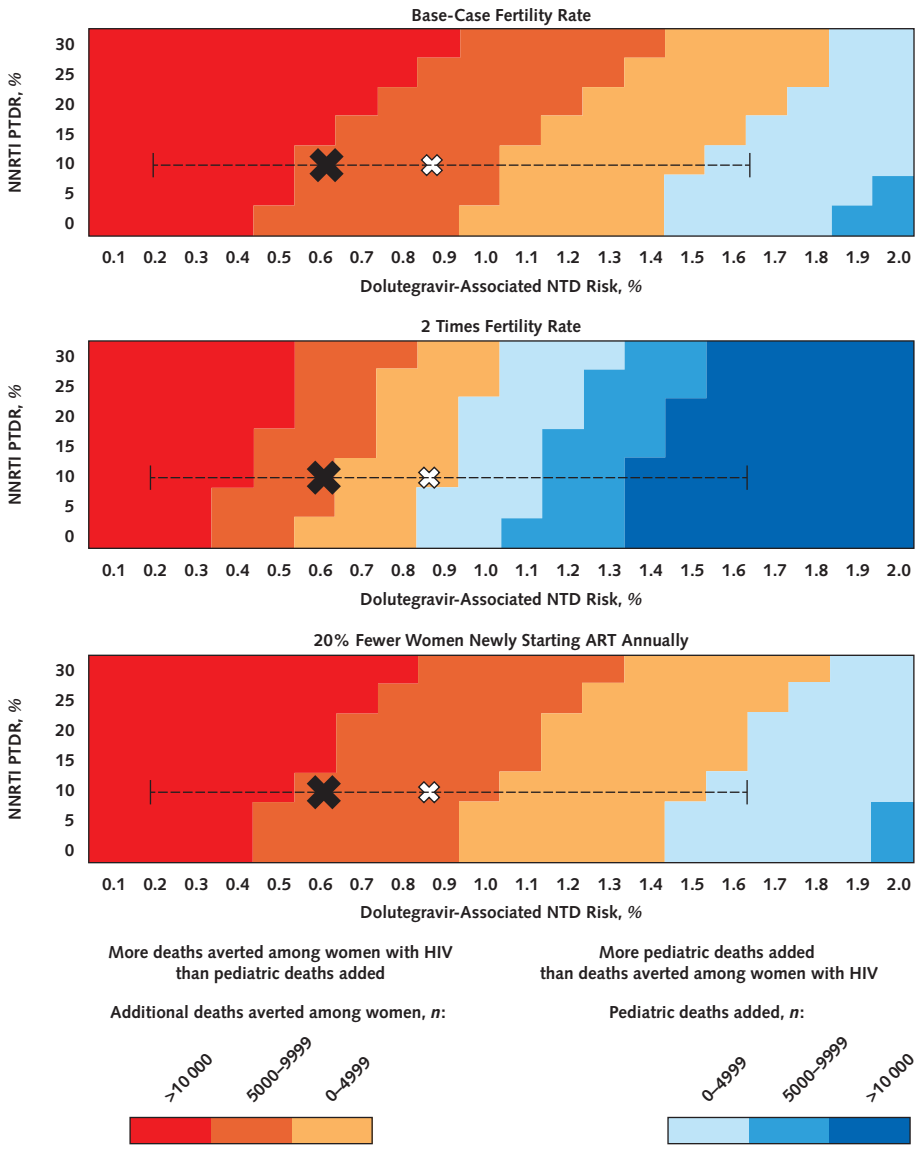
The dolutegravir-associated NTD risk (Figure 1, *orange bars*) and the fertility rate (*yellow bars*) influenced pediatric mortality the most. At a dolutegravir-

Figure 1. Tornado diagram of model-based outcomes for the comparison of EFV versus DTG.



The WHO approach outcomes represent a weighted average of EFV and DTG, and are depicted in Supplement Figures A3 and A4 (available at Annals.org). On the *y*-axis, each of the thick gray bars represents a different clinical outcome examined, where the length of the bar indicates the absolute number of clinical events averted in the base case, as indicated on the *x*-axis. Bars that extend to the left of the origin indicate situations in which there would be a preference, based on the outcome examined, for an efavirenz-based regimen among women of child-bearing potential. Bars that extend to the right of the origin indicate situations in which there would be a preference for a dolutegravir-based regimen. Thin colored bars demonstrate the changes in each of these outcomes averted when key parameters were varied in univariate sensitivity analyses. The color of the bar indicates which sensitivity analysis was conducted. The range examined in each sensitivity analysis is displayed in the key, with the value that most favors EFV on the left and the value that most favors DTG on the right. ART = antiretroviral therapy; DTG = dolutegravir for all women of child-bearing potential; EFV = efavirenz for all women of child-bearing potential; NNRTI = nonnucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PTDR = pretreatment drug resistance; WHO = World Health Organization.

Figure 2. Multivariate sensitivity analysis of the effect of NNRTI PTDR (*y*-axis) and dolutegravir-associated NTD risk (*x*-axis) on the number of deaths among women with HIV receiving ART, as well as the number of deaths among their children, over 5 years in South Africa.



The base-case estimate, with 10.7% NNRTI PTDR and the dolutegravir-associated NTD risk of 0.67% from the Tsepamo study, is indicated by the black × on each panel; the white × indicates the point estimates first reported from the Tsepamo study. Dashed lines and error bars indicate the current 95% CI around the dolutegravir-associated NTD risk from the Tsepamo study. Areas shaded in tan to red indicate where deaths averted among women with HIV exceed pediatric deaths added (including both NTD- and pediatric HIV-related deaths) with DTG relative to EFV; darkening of shades indicates an increasing number of excess deaths averted among women with HIV. Blue areas indicate where pediatric deaths added exceed deaths averted among women with HIV with DTG; darkening of shades indicates an increasing number of added pediatric deaths. **Top.** Results for the base case. **Middle.** Results for a fertility rate twice that of the base case. **Bottom.** Results for 20% fewer women newly starting ART annually. ART = antiretroviral therapy; DTG = dolutegravir for all women of child-bearing potential; EFV = efavirenz for all women of child-bearing potential; NNRTI = nonnucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PTDR = pretreatment drug resistance.

associated NTD risk of less than 0.24%, fewer overall pediatric deaths occurred with DTG than EFV because of fewer pediatric HIV transmissions and associated HIV-related pediatric mortality (*orange bar*). At the highest dolutegravir-associated NTD risk examined (2.0%), EFV averted 18 100 pediatric deaths compared with DTG (*orange bar*).

Multivariate

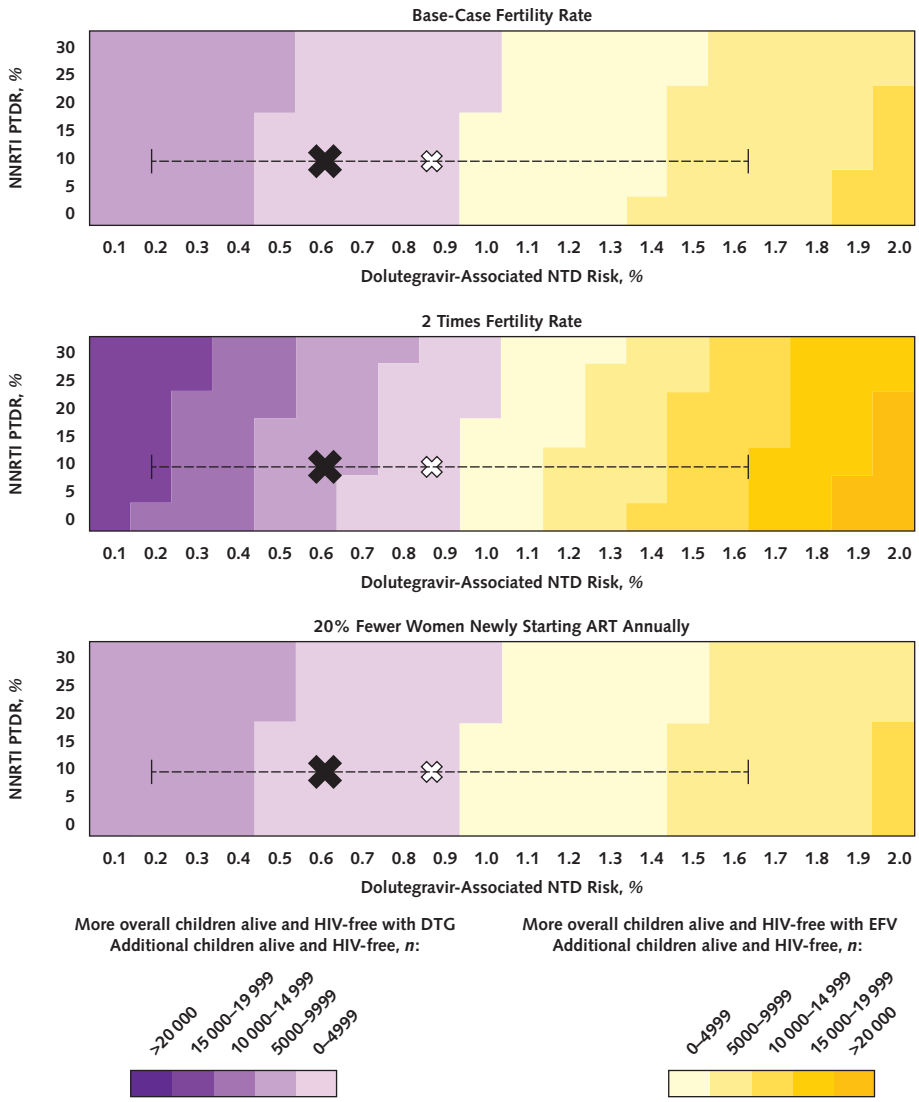
When the tradeoff between women's and pediatric mortality is considered, at base-case values deaths averted among women with HIV exceeded pediatric deaths added with DTG versus EFV, regardless of NNRTI PTDR, as long as the dolutegravir-associated NTD risk was 1.5% or lower (**Figure 2**, *top*). At fertility

rates twice the rate in South Africa—as in Tanzania or Uganda (64)—the impact of NTD risk increased (Figure 2, *middle*), with deaths averted among women with HIV exceeding additional pediatric deaths with DTG versus EFV at all values of NNRTI PTDR only if dolutegravir-associated NTD risks were 0.8% or lower. If 20% fewer women newly started ART (175 400 annually), the relative impact of NNRTI PTDR decreased (Figure 2, *bottom*). When only pediatric outcomes were considered, with base-case NNRTI PTDR, more children were alive and HIV-free with DTG than EFV, unless the dolutegravir-associated NTD risk was 1.0% or greater, regardless of fertility rates or the number of women newly starting ART each year (Figure 3).

The NAMSAL Scenario

Using equal dolutegravir and efavirenz efficacy estimates from the NAMSAL trial, DTG still averted 6500 deaths among women and 42 600 sexual transmissions compared with EFV, but fewer than in the base case (Supplement Table A5). However, DTG still averted 1.3-

Figure 3. Multivariate sensitivity analysis of the effect of NNRTI PTDR (*y*-axis) and dolutegravir-associated NTD risk (*x*-axis) on HIV-free survival among HIV-exposed children born to women receiving ART over 5 years in South Africa.



The base-case estimate is indicated by the black × on each panel; the white × indicates point estimates as first reported from the Tsepamo study. Dashed lines and error bars indicate the current 95% CI around the dolutegravir-associated NTD risk from the Tsepamo study. Purple areas indicate where there are more children alive and HIV-free with DTG than EFV; darkening of shades indicates an increasing excess of children alive and HIV-free with DTG. Yellow areas indicate where there are more children alive and HIV-free with EFV than DTG; darkening of shades indicates an increasing excess of children alive and HIV-free with EFV. **Top.** Results for the base case. **Middle.** Results for a fertility rate twice that of the base case. **Bottom.** Results for 20% fewer women newly starting ART annually. ART = antiretroviral therapy; DTG = dolutegravir for all women of child-bearing potential; EFV = efavirenz for all women of child-bearing potential; NNRTI = nonnucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PTDR = pretreatment drug resistance.

fold more deaths among women (n = 6500) than pediatric deaths added (n = 4900) compared with EFV. The WHO approach resulted in similar numbers of NTDs but fewer deaths among women versus the base case, leading to 400 and 2100 fewer cumulative deaths among women and children versus DTG and EFV, respectively.

DISCUSSION

Recent reports of an increased risk for NTDs in children born to women receiving dolutegravir-based ART at conception raised questions about the best choice of ART for women of child-bearing potential. This model-based analysis suggests that a policy that provides efavirenz rather than dolutegravir to women of child-bearing potential in South Africa will result in an additional 13 700 deaths among women with HIV, more than 39 700 more OIs, and more than 60 000 additional HIV transmissions (including 7100 pediatric HIV infections) over the next 5 years, while averting approximately 6400 NTDs. We projected that more than 3 times the number of deaths would be added among women than pediatric deaths averted with adoption of an efavirenz-for-all versus a dolutegravir-for-all policy. In assessing the relative number of deaths among women with HIV and deaths among children, NTD risks on dolutegravir would have to exceed 1.4% for pediatric deaths added to surpass deaths averted among women with HIV.

We also examined the WHO approach, which offers either efavirenz or dolutegravir on the basis of a woman's reliable access to contraception. We found that although the current WHO guidance would reduce deaths among children by 4100—primarily as the result of NTD prevention—it would lead to more than 8000 more deaths among women compared with a dolutegravir-for-all policy. However, our analysis did not account for the logistic challenges of the WHO approach, in which 2 ART "alternatives" would have to be stocked and accessible (5). "Harmonization" of HIV regimens—using the same drugs for nearly everyone—has markedly improved access to ART worldwide, ensured a more stable drug supply, simplified treatment so that ART can be provided by various cadres of health care workers, and facilitated equal access to treatment among men and women (5).

The most critical unknown parameter is the risk for NTDs in children born to women receiving dolutegravir at conception. The preliminary point estimates from the Tsepamo study reflect either the first description of a major problem or a chance statistical fluctuation that will not be confirmed later. Distinguishing these possibilities empirically will take time; in the interim, model-based analyses reflect the best opportunity to understand the implications of this information at a population level. More than 500 additional women who conceived while receiving dolutegravir will deliver in the next year; even if no NTDs are observed, the cumulative NTD risk would still exceed the 0.05% to 0.1% risk observed among those receiving other ART regimens or not living with HIV (6, 8, 9). Expanding pharmacovigilance and birth surveillance programs is a vital research priority to inform this uncertainty (65).

Another key uncertainty is the effectiveness of dolutegravir-based ART in resource-limited settings. With NNRTI PTDR rates escalating to more than 10% in sub-Saharan Africa and more than 18% in some areas of South Africa, widespread use of dolutegravir through a public health approach is likely to offer improved virologic suppression compared with efavirenz (27, 66). However, the NAMSAL study recently reported no statistically significant difference in 48-week virologic suppression (HIV RNA <50 copies/mL) between dolutegravir-based and low-dose efavirenz-based ART in Cameroon (62). We found that even with equal 48-week ART efficacy for new ART starts, dolutegravir resulted in fewer projected deaths among women and sexual transmissions over 5 years versus efavirenz. This benefit was observed primarily among those who currently are receiving first-line efavirenz-based ART but are not virologically suppressed. Data from ongoing trials comparing the efficacy of dolutegravir and efavirenz in resource-limited settings will further clarify the health tradeoffs between these regimens (67–69).

We present a quantitative analysis of outcomes for women of child-bearing potential with HIV, their sexual partners, and their children. We intentionally provide separate results for women and for children, rather than providing a measure of combined life-years, to allow for broad and nuanced interpretation of how these results might be weighed. Balancing of values attributed to women and their children is the topic of much discussion and requires considerations that are highly individualized, context specific, and not easily quantified (70). Data regarding prioritization of the health of a pregnant woman compared with that of her own child have charged many policy debates, including in the area of HIV (65, 71, 72). Because of the visible and catastrophic nature of NTDs, individuals, clinicians, and policymakers all seek to prevent these birth defects. Meanwhile, fear of adverse birth outcomes should be balanced against other important outcomes associated with providing less effective medications to women who may become pregnant. We project absolute differences among the ART policy approaches with regard to deaths among women; small relative differences in individual mortality are magnified by the large number of women at risk. For each woman with HIV making an informed decision about her choice of ART, the balance of risks and benefits of dolutegravir will depend on her individual preferences and circumstances.

Fertility rates are lower in South Africa than in many other African nations, in part because various effective contraception options are provided through the public sector and 58% of sexually active women use at least 1 such option (23, 64). Nonetheless, approximately half of pregnancies among women with HIV in South Africa are unplanned, a figure that can be as high as 65% in other areas of sub-Saharan Africa with more limited access to effective contraception (13, 23). The WHO proposes that women of child-bearing potential with "consistent and reliable contraception" use dolutegravir (1). We

found that the relative benefits of implementing dolutegravir versus efavirenz for women of child-bearing potential are likely to be attenuated in settings with higher fertility rates and poorer access to reproductive health services, where more total births might result in more NTDs.

As with all model-based analyses, uncertainty is inherent in long-term projections. We assume that trends in HIV prevalence, ART uptake, and fertility will remain relatively consistent over the 5-year horizon; policy conclusions, however, are robust to sensitivity analyses varying these parameters. This analysis considers the current, conservative prevalence of NNRTI PTDR; if transmitted drug resistance increases as anticipated (27), we would expect greater relative benefits for women and fewer relative pediatric HIV infections with dolutegravir- than efavirenz-based ART. We did not model engagement in care separately for younger versus older women; behavioral characteristics and contraceptive use in these unique subpopulations are unlikely to differ substantially by ART regimen. Our projections account for deaths among women over a 5-year horizon but not for subsequent deaths among any sexual partners who become HIV infected; inclusion of deaths related to sexual transmission of HIV over a lifetime would further favor dolutegravir. We also did not assess the drug interactions between efavirenz and hormonal contraception (73). Finally, and most critically, it is too early to know whether the signal of an increased risk for NTDs associated with dolutegravir will be borne out over time. We evaluated the effect of this key uncertainty as the crux of our analysis.

With the recent report of NTDs associated with dolutegravir at the time of conception, decisions must be made about expanding the use of dolutegravir-based regimens worldwide. Further data are forthcoming on the effect of dolutegravir use during conception on infant outcomes. In the meantime, as ART policies continue to be reevaluated, our analysis shows that compared with efavirenz (or the WHO approach), using dolutegravir for all women of child-bearing potential would avert more than 3 times the number of deaths among women with HIV than pediatric deaths added in South Africa, despite the possible NTD risk with dolutegravir. These results argue against a blanket policy of favoring efavirenz over dolutegravir in women of child-bearing potential. Rather, this study supports an open, context-specific discussion about the tradeoffs between the risks for harm and the benefits of these treatment options.

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