Projecting the clinical benefits and risks of using efavirenz-containing ART regimens in women of childbearing age in Sub-Saharan Africa

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Abstract

Objectives—Our aim was to project the outcomes of using either efavirenz or nevirapine as part of initial antiretroviral therapy (ART) in women of childbearing age in Côte d'Ivoire.

Methods—We used an HIV computer simulation model to project both the mother's survival and the birth defects at 10 years for a cohort of women who started ART with either efavirenz or nevirapine. The primary outcome was the ratio at 10 years of the difference in the number of women alive to the difference in the cumulative number of birth defects in women who started ART with efavirenz compared to nevirapine. In the base case analysis, the birth defect rate was 2.9% on efavirenz and 2.7% on nevirapine. In sensitivity analyses we varied all inputs across confidence intervals reported in the literature.

Results—In the base case analysis, for a cohort of 100,000 women, the additional number of women alive initiating ART with efavirenz at 10 years was 15 times the additional number of birth defects (women alive: nevirapine 67,969, efavirenz 68,880, difference = 911; birth defects: nevirapine 1,128, efavirenz 1,187, difference = 59). In sensitivity analysis, the teratogenicity rate with efavirenz had to be 6.3%, or 2.3 times higher than the rate with nevirapine, for the excess number of birth defects to outweigh the additional number of women alive at 10 years.

Conclusions—In Côte d'Ivoire, initiating ART with efavirenz instead of nevirapine is likely to substantially increase the number of women alive at 10 years with a smaller potential number of birth defects.

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INTRODUCTION

World Health Organization (WHO) guidelines for antiretroviral treatment (ART) in resource- limited countries recommend that first-line ART regimens should consist of one non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTIs) (1). The rationale for using NNRTIs in first-line ART while sparing protease inhibitors for second line is due to consideration of cost, ease of use, and resistance (2–3).

Two NNRTIs are available for first-line therapy: efavirenz and nevirapine. Efavirenz has two advantages over nevirapine. First, although efavirenz and nevirapine have similar risks of mucocutaneous and liver toxicities, these side-effects are much less frequent and of lower severity with efavirenz than with nevirapine (4). The most frequent side-effects from efavirenz are transient central nervous system symptoms, which rarely lead to drug discontinuation (5–6). Second, efavirenz can be safely routinely prescribed with rifampicine, the first-line treatment for tuberculosis, while the interaction between nevirapine and rifampicine is still unclear (7). Subsequently, since HIV-associated tuberculosis is extremely common in sub-Saharan Africa, nevirapine often needs to be discontinued (8).

However, reports of teratogenicity gave efavirenz one major disadvantage over nevirapine. Based on animal studies and human case reports (9–11), the United States Food and Drug Administration classifies efavirenz as a category D drug, thereby strictly recommending against efavirenz use during pregnancy (12). The 2010 revised WHO guidelines for ART allows efavirenz to be prescribed during the second and third trimesters of pregnancy, but not during the first trimester (13). As a consequence, efavirenz should not be prescribed in women of child-bearing age who are not using effective contraception. Due to limited access and ineffective use of contraception in sub-Saharan Africa (14–16), many physicians prescribe nevirapine rather than efavirenz in women of child-bearing age (1).

The consequences of these recommendations are unclear. Neither the additional risk of teratogenicity from efavirenz compared to nevirapine nor the potential harmful long-term consequences for women of starting ART with nevirapine rather than with efavirenz have been accurately assessed. Because efavirenz is strictly not recommended in women of child-bearing age without effective contraception, clinical studies comparing the maternal survival and pregnancy outcomes with both drugs would not be ethical.

We therefore used a simulation model to assess the trade-off between potential excess birth defects and potential long-term clinical benefits for women starting ART with efavirenz, rather than with nevirapine.

METHODS

Analytic Overview

Using a previously-validated computer-based simulation model of HIV disease in resource-limited settings (17–19), we projected the clinical benefits for women and the risk of birth defects for their infants in two cohorts of women of child-bearing age in Côte d'Ivoire: one started ART with an efavirenz-based regimen (EFV), and the other started ART with a nevirapine-based regimen (NVP). Inputs were derived from cohort studies and clinical trials

in sub-Saharan Africa. We used a mean pre-ART CD4 count of 154/µl, allowing the prescription of NVP. In the base case analysis, we assumed EFV and NVP had similar efficacy (20), but that NVP had a higher rate of toxicity-related drug discontinuation, as well as a higher rate of fatal toxicity than EFV (8). In sensitivity analysis, we varied major inputs widely. The main outputs were the number of women alive at 10 years and the cumulative number of birth defects at 10 years for a cohort of women starting EFV compared to one starting NVP. The cumulative number of birth defects was calculated in a separated decisions tree model using time of exposure to ART, the rate of pregnancy, the rate of live birth and the rate of birth defect. Using the main outputs, we calculated the ratio of the difference between both cohorts in the absolute number of women alive at 10 years to the difference in the cumulative absolute number of birth defects. Finally, we estimated the excess in birth defect rate with efavirenz compared to nevirapine that would equalize the additional number of women alive at 10 years and the additional number of birth defects with efavirenz compared to nevirapine.

Model description

The Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International model is a state-transition, first-order Monte Carlo simulation model of HIV infection incorporating natural history, disease progression, and treatment (18–19, 21). The model divides HIV infection into "health states," which include an acute state, a chronic state, and death. Simulated patients are randomly selected from an initial distribution of age, CD4 count, and HIV RNA level, and transition monthly to different health states. The probability of transition from one state to another depends on the CD4 stratum and the associated risk of opportunistic infections (OIs) or death (22) as well as ART. HIV RNA levels determine the rate of CD4 count decline in the absence of ART (23). Successful ART decreases HIV RNA and increases CD4 count. The model also takes into account ART toxicity, ART switching criteria, resistance, and number of ART lines available. Using the model, we simulated outcomes for two cohorts of 100,000 women, one starting ART with efavirenz and one with nevirapine.

Base case inputs

Baseline cohort characteristics, morbidity, and mortality data were derived from four studies in Côte d'Ivoire (24–26) (Table 1 All women started ART upon entry into the model. Two lines of ART were available; the first consisted of two NRTIs (tenofovir and emtricitabine) and either efavirenz or nevirapine, and the second-line consisted of two NRTIs (didanosine and abacavir) and lopinavir/ritonavir (1). Patients had a CD4 count assessed every six months. HIV RNA testing was not routinely available. Switching from first-line to second-line was dictated by immunological criteria, as recommended by the WHO in the absence of HIV RNA monitoring (1).

In the base case analysis, we used three assumptions, all of which were tested in sensitivity analyses. First, we assumed that EFV and NVP had similar virologic and immunologic efficacy (20, 26), and NVP had a higher rate of toxicity leading to drug discontinuation than EFV (8, 27–28). Second, we assumed that the rate of pregnancy was constant over time and disease stage, and did not vary from age 25 to 45 or according to ART regimen (9, 29). Finally, we assumed that the rate of birth defect was 0.2% higher with EFV than NVP, based on data from the US Antiretroviral Pregnancy Registry that had reported a birth defect rate of 2.7% for women on NVP and 2.9% for women on EFV (30). We used the same birth defect rate as NVP for the other ART regimens.

Model Outputs

The main model output was the number of women alive. Secondary outputs included time of exposure to each first-line and second-line ART regimen. We then incorporated the latter time of exposure into a decision tree, which included rates of pregnancy, live births, birth defects, abortions, miscarriages, and stillborns, to calculate the cumulative number of babies born with birth defects at 10 years using the following formula:

$$10-year\ number\ of\ birth\ defects = \sum_i [Time\_expo_i * Pregnancy\ rate * Live\ birth\ rate] * Rate\_Bdef_i$$

Where:

$Time\_expo_i$ = total time of exposure to ART regimen i at 10 years;

$Rate\_Bdef_i$ = the birth defect rate due to ART regimen i

i =1, 2, 3…n = the different lines of ART regimen

Study main outcomes

This study had two outcomes. The primary outcome was the difference in number of women alive per additional birth defect (" NWA per additional birth defect"), defined as the ratio of the difference in the absolute number of women alive at 10 years to the difference between both populations in the cumulative absolute number of birth defects at 10 years. This outcome was calculated using the following formula:

$$\Delta NWA\ per\ additional\ birth\ defect = (NWA\_EFV - NWA\_NVP)/(NBD\_EFV - NBD\_NVP);$$

Where:

NWA = number of women alive at 10 years

NBD = number of birth defects over 10 years

The secondary outcome was the "equivalence birth defect rate difference," defined as the difference in birth defect rate per 100 live births that would be necessary to equalize the additional number of women alive at 10 years and the additional number of birth defects with EFV.

Sensitivity Analysis

Sensitivity analyses were done in three steps.

First, in one-way sensitivity analysis, we varied all major parameters in the model. These included patient and regimen characteristics (age, pre-ART CD4 count, virological efficacy of EFV and NVP-based regimens, pregnancy rate (31–32), birth defect rate, drug discontinuation and fatal toxicity rates of EFV and NVP-based regimens), as well as program characteristics (interval between clinic visits, interval between CD4 counts, third-line ART availability for patients failing second-line ART, rate of lost-to-follow-up, and availability of contraception). The latter included a mixed-scenario in which the women on effective contraception received EFV while the others received NVP. One-way sensitivity analyses were either confidence interval or extreme case range analyses, according to the confidence intervals or extreme values found in the literature.

Second, we classified the parameters into three groups according their impact on the outcomes. If the sensitivity analysis on a variable produced a variation in number of

women alive greater than ±10 per additional birth defect or a variation in equivalence birth defect rate difference greater than ±3%, that variable was classified as 'highly-sensitive'. If the variation in   number of women alive per additional birth defect was between ±5 and ±10 or the variation in equivalence birth defect rate difference was between ±1.5% and ±3%, the variable was classified as 'moderately sensitive'. Finally, if the variation was less than ±5 for the   number of women alive per additional birth defect and less than ±1.5% for the equivalence birth defect rate difference, the variable was classified as 'minimally-sensitive'.

Third, we included all highly-sensitive variables in a multi-way sensitive analysis.

RESULTS

Base case analysis

During the first 10 years of ART, 92 of the 100,000 women who started ART with EFV experienced severe acute toxicity (of whom none died and all 92 switched to LPV/r), compared to 6,000 of the 100,000 women who started ART with NVP (of whom 62 died and 5937 switched to LPV/r). In women who started ART with EFV, the mean time per woman spent on EFV and on LPV/r was 7.03 years and 8.61 years. In women who started with NVP, the mean time spent on NVP and on LPV/r was 6.61 and 8.63 years. As shown in Table 2, 68,880 of the 100,000 women who started ART with EFV were alive at 10 years, compared to 67,969 women who started ART with NVP. The cumulative number of birth defects that occurred over the 10 years was 1,187 in women who started with EFV and 1,128 in women who started with NVP. Thus, the difference in absolute number of women alive at 10 years was 911, and the difference in absolute number of birth defects on EFV compared to NVP was 59. The "difference in number of women alive per additional birth defect," was 15, and the "equivalence birth defect rate difference" was 3.4 per 100 live births. As the birth defect rate with EFV was 2.9 per 100, this means that the absolute birth defect rate with EFV had to be greater than 6.3 per 100 live births, and the birth defect rate with EFV had to be more than 2.3 times as higher as the birth defect rate with NVP for the additional number of birth defects to exceed the additional number of women alive at 10 years in women starting ART with EFV (Table 2).

Sensitivity analysis

In one-way confidence interval and extreme case sensitivity analysis, both the   NWA per additional birth defect and/or the equivalence birth defect rate difference were highly sensitive to the pregnancy rate, the difference in virologic efficacy between EFV and NVP and EFV toxicity-induced drug discontinuation (Table 3).

Decreasing the pregnancy rate increased the ratio of the benefits for women to the risks for children on EFV. When the pregnancy rate decreased from 15 per 100 woman-years (32) to 5 per 100 woman-years (31), the "   NWA per additional birth defect" increased from 9 to 26 and the "equivalence birth defect rate difference" increased from 1.8 per 100 live births (i.e. absolute birth defect rate with EFV was 4.7 per 100 live births, 1.7 times as high as the birth defect rate with NVP) to 5.3 per 100 live births (i.e. absolute birth defect rate with EFV was 8.2 per 100 live births, 3 times as high as the birth defect rate with NVP) (Table 3). To make the "   NWA per additional birth defect" lower than 1.0, the pregnancy rate had to be over 50 per 100 woman-years.

When assuming that EFV efficacy at 6 months was 2% higher than that of NVP, the "   NWA per additional birth defect" increased to 23, and the "equivalence birth defect rate difference" increased to 5.4 per 100 live births (i.e. absolute birth defect rate with EFV was 8.3 per 100 live births, 3 times as high as the birth defect rate with NVP). To make the "

NWA per additional birth defect" lower than 1.0, the efficacy of EFV at 6 months had to be 3% lower than the efficacy of NVP.

When assuming that EFV had the same rate of severe toxicity leading to drug discontinuation as NVP, the " NWA per additional birth defect" was 4.0 and the "equivalence birth defect rate difference" was 0.9 per 100 live births (i.e. absolute birth defect rate with EFV was 3.8 per 100 live births, or 1.4 times as high as the birth defect rate with NVP) (Table 3). To make the " NWA per additional birth defect" lower than 1.0, the absolute rate of EFV severe toxicity leading to drug discontinuation had to be 7.0%, i.e. 0.7% higher than NVP's base case rate of severe toxicity.

If a third-line ART regimen was available in the country, the " NWA per additional birth defect" ranged from 5 to 12, and the "equivalence birth defect rate difference" ranged from 1.2 to 2.5 per 100 live births, depending on third-line efficacy (Table 4). When assuming a scenario under which EFV is given only to women who take contraception while other women receive NVP, both the " NWA per additional birth defect" and the "equivalence birth defect rate difference" were at least as high as in the base case analysis, and tended to be even higher with decreasing rates of pregnancy in women receiving contraception. If loss-to-follow-up rates were considered, the women in both strategies did worse in terms of survival, and there were fewer birth defects (Table 4). As a result, there was no substantial change in the main results

Finally, we varied EFV efficacy compared to NVP and EFV toxicity-induced drug discontinuation in different scenarios of pregnancy rates, to estimate the impact of three-way variations on the "equivalence birth defect rate difference" (Figure 1). In settings with medium rates of pregnancy (Figure 1a), an equivalence birth defect rate difference lower than 1% was found in two situations : First, when the rate of EFV toxicity-inducing drug discontinuation was higher than 1% and the EFV 6-month virological suppression was 2% lower than the NVP 6-month virological suppression; second, when the rate of EFV toxicity-inducing drug discontinuation was higher than 2% and the EFV 6-month virological suppression was 1% lower than the NVP 6-month virological suppression.

DISCUSSION

While EFV is better tolerated than NVP, many women start ART with NVP in sub-Saharan Africa. This is mainly due to the fear of efavirenz teratogenicity, which may be higher than that of nevirapine. This is a particular concern in countries where pregnancy rates are high and where contraception is not widely available.

Many physicians, however, are concerned with guidelines that recommend the more toxic NVP for women on the basis of a suspected, but not clearly known, higher rate of teratogenicity with EFV. Starting ART with a more toxic drug may lead to a switch in ART regimen earlier, thus shortening the time on effective ART for women in countries where the number of available ART lines is limited. This, in turn, may decrease long-term survival. Because EFV is strictly contraindicated in women without effective contraception, randomized trials could not be conducted to measure the rate of teratogenicity in women starting ART with EFV, and compare it to women starting ART with NVP. Furthermore, even if such trials were feasible, they would be unable to estimate outcomes over a 10-year period.

Models can explore long-term clinical outcomes in situations where trials are not feasible or ethical. In this study we used a simulation model of HIV infection to compare survival in women and pregnancy outcomes at 10 years in cohorts of women starting ART with EFV or with NVP in Côte d'Ivoire. Using a conservative approach, we first assumed that the two

drugs had similar virological efficacy, and that the only differences between drugs were a higher rate of acute toxicity in women with NVP and a higher rate of birth defects in infants with EFV. We used published data for the difference in toxicity, for which there is extensive evidence (6, 8, 33). For birth defect rates, we first assumed that the difference between drugs was reasonably small (29–30, 34). We then did extensive sensitivity analyses on all of these parameters.

We found that starting ART with the drug that leads to the lowest rate of switching due to acute toxicity provides a benefit in survival at 10 years, even when assuming that both drugs have the same efficacy. In a cohort of 100,000 women, there were 911 more women alive at 10 years with EFV compared to NVP, approximately a 0.9% benefit. Albeit small, the additional number of women alive was higher than the additional number of birth defects occurring with EFV compared to NVP over 10 years (59 birth defects). Consequently, the ratio of additional number of women alive per additional number of birth defect was very high (15 NWA per addition birth defects). To make the additional number of women alive equivalent to the additional number of birth defects, the rate of birth defects with EFV needed to be at least 2.3 times the rate with NVP, a very unlikely figure. These outcomes were found under conservative assumptions regarding differences in toxicity and efficacy between EFV and NVP. When assuming that EFV may have a slightly higher rate of virologic efficacy than NVP (33, 35–39), or that NVP may have a higher rate of fatal toxicity than that we used in the base case (28, 33), we found results even more favourable to EFV.

There are several limitations to this study. First, we used birth defect rates from the Antiretroviral Pregnancy Report (APR), which pools data from different sources (30). Other studies reported different birth defect rates (9, 29, 34). Furthermore, other model inputs were also from different African countries. However, we varied birth defect rates and other inputs widely in sensitivity analysis, and found that the outcomes were robust. Second, our primary outcome is an atypical one, as it posed survival in women against birth defects in children. One may argue that birth defects and women's deaths are altogether different. Birth defects lead to a higher risk of death in children (40–41), but also to consequences in terms of quality of life (42–43) that we did not take into account in this study. Finally, both birth defects and women's death may also affect other family members both in terms of mortality and of quality of life (44–45) that we also did not take into account. For a direct comparison of outcomes in women and in infants related to the use of NVP or EFV, or for a cost-effectiveness analysis, QALYs and DALYs would be more appropriate outcomes than the ones we used. However, our aim was not to compare adult deaths to birth defect, but to evaluate in parallel the severe clinical outcomes related to the use of NVP or EFV in both he infants and their mothers. For the infants, the most severe outcome associated with EFV is birth defect. For the mothers, the most severe outcome associated with starting ART either with EFV or with NVP is death. The first outcome can be measured early. The second one requires a long-term analysis, because it's most important determinant is not virological efficacy but the rate of toxicity-induced drug discontinuation. Showing these two outcomes in parallel could allow people to take the long-term survival of mothers into consideration when debating the merits of EFV versus NVP. Currently birth defects are considered the most important part of this debate, and survival in mothers is rarely taken into consideration.

Our aim was not to suggest that birth defects are preferable to women's deaths. Our aim was to estimate the extent to which recommending NVP over EFV might affect women's long-term survival. Our analysis suggests that women's survival could be substantially improved if EFV was recommended first in all women of childbearing age, and that the additional number of birth defects would be likely to be lower than the additional number of women

alive over a 10-year period. This trade off should be carefully considered when recommending first-line ART regimens in resource-limited countries.

Acknowledgments

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Author's contribution

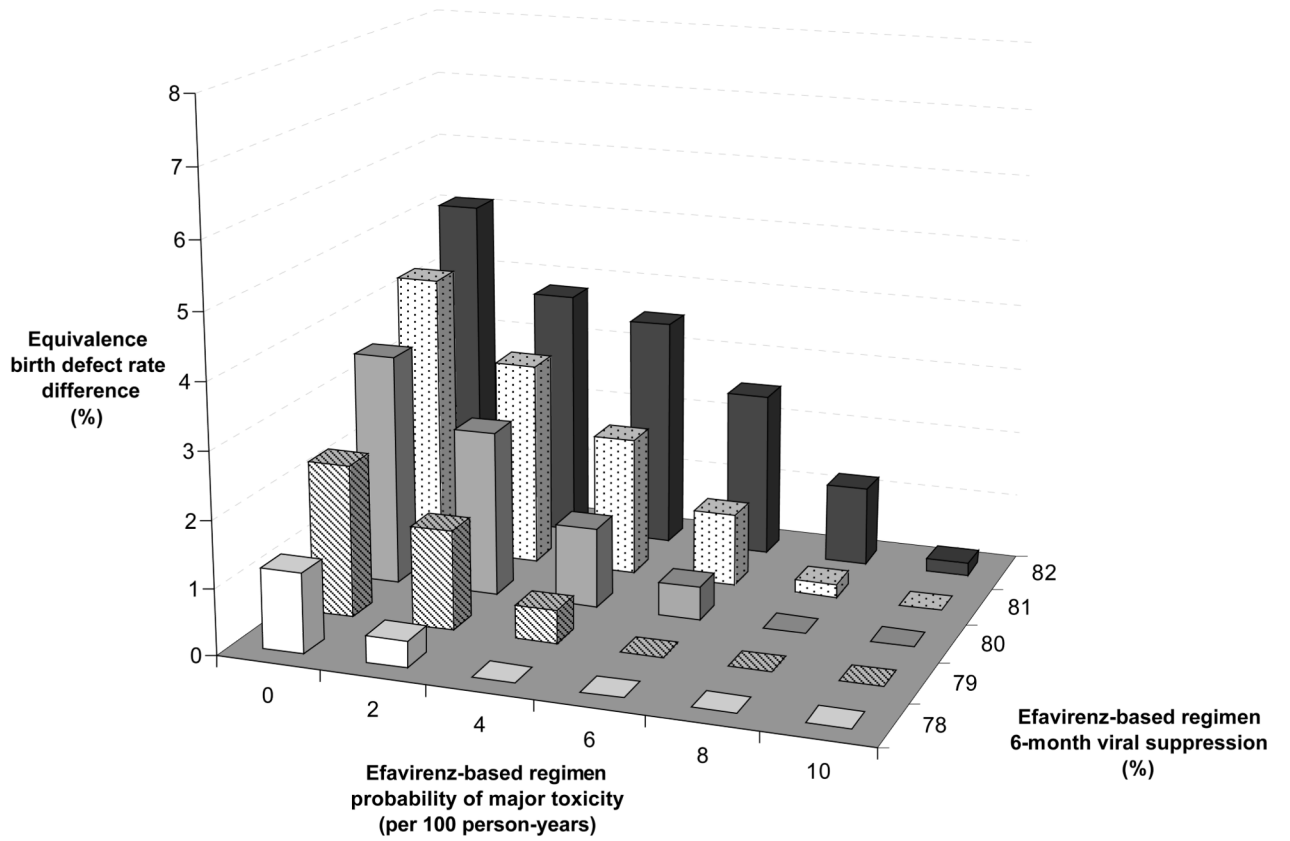|	
Eric N. Ouattara, MD, MPH	Conception and design
	Doing runs and calculations
	Drafting and writing of the manuscript
	Tables and figures
Xavier Anglaret, MD, PhD	Conception and design
	Clinical expertise

	Modeling expertise	
	Critical revision of the manuscript	
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Heather E. Hsu, MPH	Modeling expertise	
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Figure 1a:
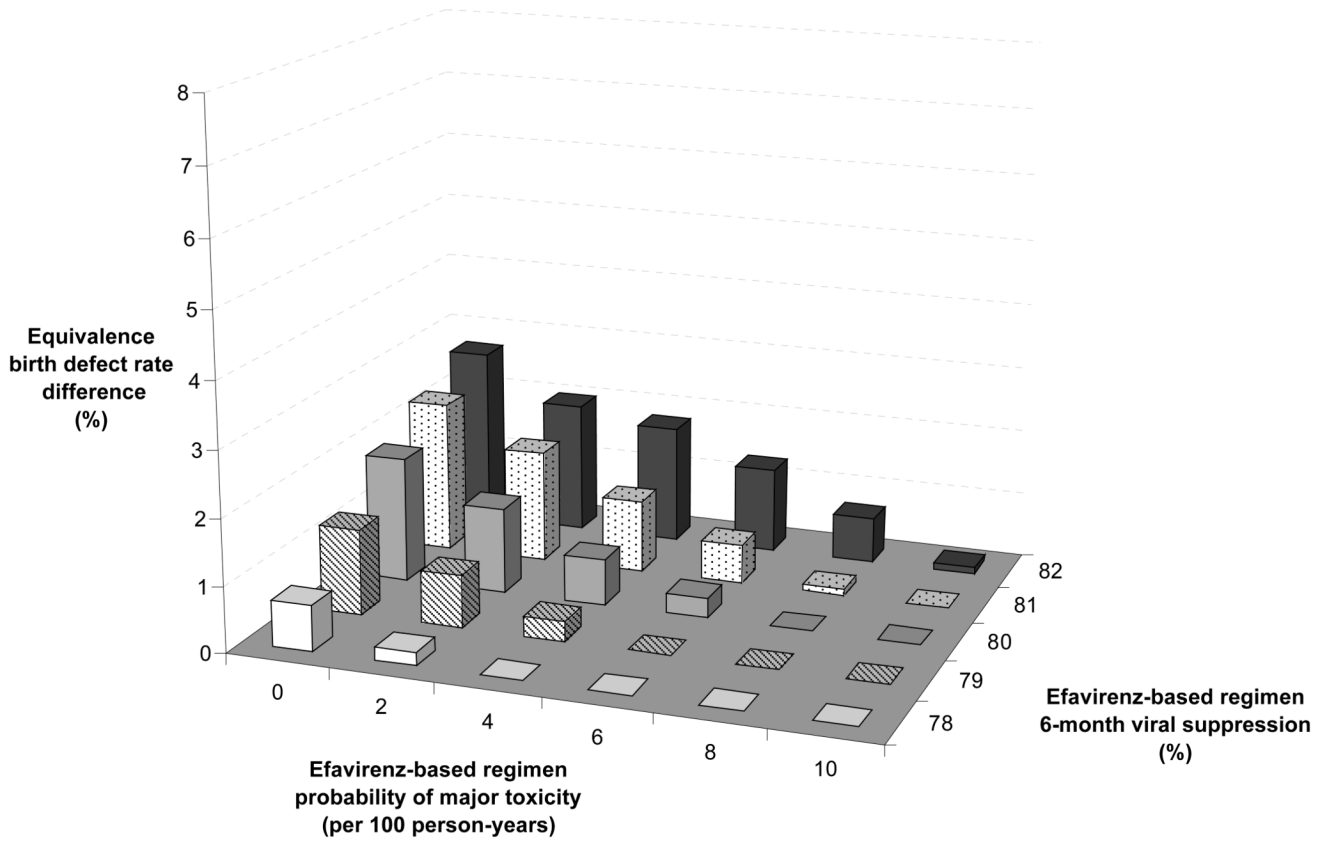
Figure 1b:

Figure 1c:

Figure 1. Multi-way sensitivity analysis
These figures show the variation of the equivalence birth defect rate difference in different scenarios of pregnancy rate, according to different rates of drug discontinuation in women on EFV (X-axis) and to different rates of 6-month HIV-1 RNA suppression on EFV (Z-axis).
Figure 1a: Base case scenario: pregnancy rate = 7.9 per 100 person-years
Figure 1b: Low pregnancy rate scenario: pregnancy rate = 5.0 per 100 person-years
Figure 1c: High pregnancy rate scenario: pregnancy rate = 15.0 per 100 person-years

Table 1

Main model input parameters

	Base case value	Sensitivity analyses [4]		References
		Range	Type	
Baseline characteristics				
Mean age, years (SD)	33.6 (7.7)	[26 – 41]	CI	(24)
Mean CD4, cells/μl (SD)	154 (102)	[52 – 256]	CI	(20)
Sex, female, %	100			
Plasma HIV-1 RNA, copies/ml, %				
>100,000	52.6			(24)
30,001–10,0000	21.8			(24)
10,001–30,000	13.1			(24)
3,001–10,000	5.5			(24)
501–3,000	3.1			(24)
500	3.9			(24)
Monitoring				
Interval between clinic visits, months	3	1; 6 months	Extr. values	ASMPT
Interval between CD4 tests, months	6	3; 12 months	Extr. values	ASMPT
First-line ART efficacy and toxicity				
HIV-1 RNA suppression at 24 weeks, % [1]	80.2	[65 – 85]	Extr. Values	(2, 20)
CD4 cell/μl increase at 24 weeks [1]	152			(20)*
Toxicity, %				
EFV:				
Drug discontinuation	0.1	[0 – 6.3]	Extr. values	(8)
Fatal toxicity [2]	0.1	[0 – 1.0]	Extr. values	(27)
NVP:				
Drug discontinuation	6.3	[4.3 – 8.3]	CI	(8)
Fatal toxicity [2]	1.0	[0 – 3.0]	Extr. values	(28)
Pregnancy				
Pregnancy rate, per 100 woman-years [3]	7.9	[5.0 – 15.0]	Extr. values	(9)
Outcomes, %				
Abortion	11.7			(29)
Miscarriage	5.2			(29)
Stillborn	6.7			(29)
Live births [3]	76.4	[60.0 – 85.0]	Extr. values	(29) (9, 34)
Birth defects, %				
EFV	2.9			(30)
NVP	2.7			(30)

EFV: ART regimen including efavirenz and 2 nucleoside reverse transcriptase inhibitors (tenofovir + emtricitabine); NVP: ART regimen including nevirapine and 2 nucleoside reverse transcriptase inhibitors (tenofovir + emtricitabine);

[1] In the base case analysis we assumed that EFV and NVP had the same immunological and virological efficacy;

(2)In the base case analysis we assumed that 0.1% of the 0.1% patients who had major toxicity on EFV died ($0.001 \times 0.001 = 0.00001$), and 1% of the 6.3% patients who had major toxicity on NVP died ($0.063 \times 0.01 = 0.00063$);

(3)In the base case analysis we assumed that women on EFV or NVP had the same rate of pregnancy and live birth;

(4)In one-way sensitivity analysis, we varied each parameter within the range of confidence interval (CI) or of highest or lowest values (Extreme values - Extr.values) as found in the literature. The column 'references' refers to the papers where CI and extreme values were found (ASMPT: assumption).

Table 2

10-year outcomes for a cohort of 100,000 women of child-bearing age starting on EFV or NVP-based ART regimens in Côte d'Ivoire: base case analysis

	EFV	NVP	(EFV-NVP)
Women			
At 10 years, number of women:			
Alive	68,880	67,969	911
Still on first-line regimen	24,585	23,121	1,464
With undetectable plasma HIV-1 RNA	65,144	64,613	531
Overall time on ART during child-bearing years, person-years	694,341	692,413	1,928
Including time on first-line ART (EFV or NVP)	456,153	430,748	25,405
Pregnancies and newborns			
Pregnancies at 10 years, number	54,853	54,701	152
Abortions, miscarriages and stillbirths	12,945	12,909	36
Live births	41,908	41,791	117
Birth defects	1,187	1,128	59
Combined outcomes			
NWA per additional birth defect [1]			**15**
Equivalence birth defect rate difference [2]			**3.4%**

EFV: ART regimen including efavirenz and 2 nucleoside reverse transcriptase inhibitors (tenofovir + emtricitabine); NVP: ART regimen including nevirapine and 2 nucleoside reverse transcriptase inhibitors (tenofovir + emtricitabine);

[1] NWA per additional birth defect = The ratio of number of women alive at ten years on EFV compared to NVP to the additional number of birth defects on EFV compared to NVP

$$= (NWA\_EFV - NWA\_NVP)/(NBD\_EFV - NBD\_NVP)$$

Where:

NWA = number of women alive at 10 years

NBD = number of birth defects over 10 years

[2] Equivalence birth defect rate difference: difference in birth defect rate per 100 live births between EFV and NVP that would be necessary to make the NWA at 10 years equivalent to the number of birth defects

Table 3

10-year outcomes for a cohort of 100,000 women on EFV or NVP-based ART regimens in Côte d'Ivoire: One-way sensitivity analysis (patients and treatment characteristics)

	Women alive, at 10 years [1]	Birth defects, at 10 years [1]	NWA per additional birth defect [2]	Equivalence birth defect rate difference [3]
Base case	911	59	**15**	**3.4%**
Mean Age, years				
26	913	68	**13**	**3.0%**
41	836	38	**22**	**4.8%**
Mean CD4, cells/μl				
52	795	49	**16**	**3.7%**
256	949	66	**14**	**3.2%**
HIV-1 RNA suppression at 6 months, %				
Varying both regimens, with EFV=NVP				
EFV : 65 ; NVP : 65	922	53	**17**	**4.0%**
EFV: 85 ; NVP: 85	1023	61	**17**	**3.7%**
Varying EFV only				
EFV : 78 ; NVP : 80.2	323	53	**6**	**1.3%**
EFV: 82 ; NVP: 80.2	1474	63	**23**	**5.4%**
EFV-based regimen toxicity, %				
Drug discontinuation				
0 (EFV < NVP: −6.3%)	961	58	**17**	**3.6%**
6.3 (EFV = NVP)	190	54	**4**	**0.9%**
Fatal toxicity [2]				
0 (EFV < NVP: −1%)	1040	59	**18**	**3.9%**
1.0 (EFV = NVP)	915	59	**16**	**3.5%**
NVP-based regimen toxicity, %				
Drug discontinuation				
4.3 (NVP > EFV: +4.2)	937	59	**16**	**3.5%**
8.3 (NVP > EFV: +8.2)	930	60	**16**	**3.5%**
Fatal toxicity				
0.1 (NVP = EFV)	973	58	**17**	**3.7%**
3.0 (NVP > EFV: +2.9)	979	59	**17**	**3.7%**
Pregnancy rate/100 person-years				
5.0	911	35	**26**	**5.3%**
15.0	911	105	**9**	**1.8%**
Live births, %				
60.0	911	43	**21**	**4.3%**
85.0	911	61	**15**	**3.0%**

EFV: ART regimen including efavirenz and 2 nucleoside reverse transcriptase inhibitors (tenofovir + emtricitabine); NVP: ART regimen including nevirapine and 2 nucleoside reverse transcriptase inhibitors (tenofovir + emtricitabine);

[1] : Difference between EFV and NVP

[2] NWA per additional birth defect = The ratio of number of women alive at ten years on EFV compared to NVP to the additional number of birth defects on EFV compared to NVP

$$=(NWA\_EFV - NWA\_NVP)/(NBD\_EFV - NBD\_NVP)$$

Where:

NWA = number of women alive at 10 years

NBD = number of birth defects over 10 years

[3] Equivalence birth defect rate difference: difference in birth defect rate per 100 live births between EFV and NVP that would be necessary to make the number of women alive at 10 years equivalent to the number of birth defects

Table 4

10-year outcomes for a cohort of 100,000 women on EFV or NVP-based ART regimens in Côte d'Ivoire: One-way sensitivity analysis (program characteristics)

	Women alive, at 10 years *(1)*	Birth defects, at 10 years *(1)*	NWA per additional birth defect *(2)*	Equivalence birth defect rate difference *(3)*
Interval between scheduled visits				
Every months	1031	59	**17**	**3.9%**
Every 6 months	994	59	**17**	**3.8%**
Routine CD4 tests				
Every 3 months	1025	58	**18**	**4.0%**
Every 12 months	863	62	**14**	**3.1%**
EFV only for women on contraception *(4)*				
Pregnancy rate = 90% × base case	546	31	**17**	**3.8%**
Pregnancy rate = 50% × base case	546	17	**31**	**6.8%**
Pregnancy rate = 30% × base case	546	10	**52**	**>10.0%**
Third-line ART available				
6-month HIV-1 RNA suppression: 30 %	304	58	**5**	**1.2%**
6-month HIV-1 RNA suppression: 50 %	401	57	**7**	**1.6%**
6-month HIV-1 RNA suppression: 80 %	658	56	**12**	**2.5%**
Lost to follow-up (LTFU) on ART				
12-month LTFU percentage: 8 %	696	43	**16**	**3.5%**
12-month LTFU percentage: 16%	482	41	**12**	**2.6%**

EFV: ART regimen including efavirenz and 2 nucleoside reverse transcriptase inhibitors (tenofovir + emtricitabine); NVP: ART regimen including nevirapine and 2 nucleoside reverse transcriptase inhibitors (tenofovir + emtricitabine);

(1) : Difference between EFV and NVP

(2) NWA per additional birth defect = The ratio of number of women alive at ten years on EFV compared to NVP to the additional number of birth defects on EFV compared to NVP

$$=(NWA\_EFV - NWA\_NVP)/(NBD\_EFV - NBD\_NVP)$$

Where:

NWA = number of women alive at 10 years

NBD = number of birth defects over 10 years

(3) Equivalence birth defect rate difference: difference in birth defect rate per 100 live births between EFV and NVP that would be necessary to make the number of women alive at 10 years equivalent to the number of birth defects

(4) In this analysis, we assumed that 60% of HIV-infected women actually take effective contraception, and we compared two strategies: (i) all women start ART with NVP, irrespective of whether they are on contraception or not; (ii) women on contraception start ART with EFV, and other women start ART with NVP.