Treatment switches during pregnancy among HIV-positive women on antiretroviral therapy at conception.

Short title:

ART treatment switches during pregnancy

Authors:

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Abstract

Objectives:

To describe antiretroviral therapy (ART) use and clinical status, at start of and during pregnancy, for HIV-positive women receiving ART at conception, including the proportion conceiving on drugs (efavirenz and didanosine) not recommended for use in early pregnancy.

Methods:

Women with a pregnancy resulting in a live birth after 1995 (n=1,537) were identified in an observational cohort of patients receiving HIV care at 12 clinics in the UK by matching records with national pregnancy data. Treatment and clinical data were analysed for 375 women conceiving on ART, including logistic regression to identify factors associated with changing regimen during pregnancy.

Results:

Of the 375 women on ART, 39 (10%) conceived on dual therapy, 306 (82%) on triple therapy and 30 (8%) on >3 drugs. In total, 116 (31%) women conceived on a regimen containing efavirenz or didanosine (69 efavirenz, 54 didanosine, 7 both). Overall, 38% (143) changed regimen during pregnancy, of whom 44% (n=51) had a detectable viral load around that time. Detectable viral load was associated with increased risk of regimen change (adjusted odds ratio 2.97, 95% confidence interval [1.70, 5.19]), while women on efavirenz at conception were three times more likely to switch than women on other drugs (3.40, [1.84, 6.25]). Regimen switching was also associated with year at conception (0.89, [0.83-0.96]).

Conclusions:

These findings reinforce the need for careful consideration of ART use among women planning or likely to have a pregnancy in order to reduce viral load before pregnancy and avoid drugs not recommended for early antenatal use.

Keywords: HIV; pregnancy; antiretroviral agents; antiretroviral therapy; United Kingdom.

Introduction

With the advent of reliable therapy to delay disease progression and prevent mother-to-child transmission (MTCT), an increasing number of women known to be HIV-positive are having children; currently >1200 deliveries are reported annually in this group in the UK [1]. Around 70% of these are among women diagnosed prior to pregnancy, half of whom are on combination antiretroviral therapy (ART) when they conceive [2].

Unique considerations apply to ART use during pregnancy reflecting the dual goals of preventing transmission and delaying maternal disease progression, while considering the needs of the developing fetus. All HIV-positive pregnant women in the UK are recommended ART to prevent MTCT as well as for their own health if required [3]. Women conceiving on therapy are recommended to stay on the same regimen throughout pregnancy unless it is failing and those not yet on therapy are recommended to initiate ART after the first trimester, the period of greatest concern for teratogenicity [3].

Efavirenz together with a nucleoside backbone is the recommended first-line combination ART regimen in the UK [4] but current guidelines recommend that women who are likely to conceive avoid its use due to safety concerns [3]. Limited animal study data and case reports of neural tube defects in infants exposed to efavirenz in the first trimester form the basis for these concerns [5,6,7]. Birth defects, including neural tube defects, were observed in 2.8% live births with first trimester exposure to efavirenz, as reported to the Antiretroviral Pregnancy Registry [8]. However, observational cohorts indicate that the prevalence of all congenital abnormalities is not significantly higher among infants exposed to efavirenz *in utero* than to those exposed to other antiretroviral drugs [9,10,11]. There are insufficient data to exclude a small increase in the risk of specific malformations and it is recommended that women wishing to

become pregnant in the UK are treated with nevirapine-based regimens (if their CD4 count is <250 cells/mm^3) or boosted protease inhibitor-based regimens (PI) [4].

Didanosine, no longer widely used, may be associated with a higher incidence of birth defects in exposed infants compared with commonly used antiretroviral drugs; birth defects occurred in 4.7% live-births with first trimester exposure, although no pattern of defects was seen [8]. While UK treatment guidelines recommend that women who may conceive avoid using efavirenz or didanosine [3], they also recommend that if women conceive on these drugs they should continue this regimen, unless it is failing [3]. The rationale for this recommendation is that if a woman conceives on efavirenz and then switches treatment, the fetus is unlikely to avoid exposure during the period of initial neural development because the drug has a long half-life and there is normally some delay before presenting for antenatal care [3].

Through data linkage of two observational HIV studies in the UK, we identified women who were receiving ART at conception of their first reported pregnancy. Our objectives were to describe the virological, immunological and treatment characteristics of these women, including the proportion using efavirenz or didanosine at conception, and to investigate the frequency of and risk factors associated with antenatal ART switching.

Methods

Data collection

The UK Collaborative HIV Cohort (UK CHIC) is an observational study collating HIV-related clinical data from many of the largest HIV clinical centres in the UK (see Appendix). UK CHIC includes demographic data, dates and results of all CD4 count/viral load assessments, and dates of starting and stopping ART drugs; data on pregnancy status is not reported. UK CHIC includes approximately one-third of HIV-

positive individuals receiving care in the UK over this period and is described in detail elsewhere [12].

Through the National Study of HIV in Pregnancy and Childhood (NSHPC), data on HIV-positive women diagnosed prior to or during antenatal care are collected from every maternity unit in the UK/Ireland through confidential quarterly active reporting. Data collected includes demographic details, timing of maternal diagnosis, expected date of delivery (EDD), date of delivery, pregnancy outcome, dates and results of CD4 count/viral load taken during pregnancy and ART use at conception and during pregnancy. Further details are available at www.nshpc.ucl.ac.uk, and elsewhere [2].

Identifying women with a pregnancy in the UK CHIC dataset

Women in the UK CHIC dataset who had a pregnancy were identified by matching records to the NSHPC dataset. Both UK CHIC and NSHPC datasets are pseudonymised. Initially, records in the NSHPC dataset were linked to records in UK CHIC using maternal date of birth (DOB) (Fig. 1a). Other data fields were then used to confirm matches between records linked using maternal date of birth. Records with an exact CD4 date match were confirmed as a match if they also had either CD4 count (±10 cells/mm^3) match on that date, had attended the same hospital or had identical HIV diagnosis dates (b). The same criteria were then used to identify matches between records which had matching CD4 date ±30 days (c). Records which did not have matching CD4 dates ±30 days but had matching drug start and/or stop dates were then confirmed as a match (d). Further matches were manually identified from the remaining linked records using drug start and stop dates, date of HIV diagnosis, country of birth, and viral load dates (e). Mortimer Market Centre, which provides HIV services, is closely located to University College Hospital, which provides maternity care; during the matching process these were classed as the same site.

Figure 1. Diagram showing the matching process between records in the NSHPC and UK CHIC datasets.

Footnote: Brackets indicate the number of records linked.

Study population

A total of 1710 records for women seen for HIV care between 1996 and mid-2009 were matched to a record in the NSHPC dataset. Matched records were representative of all records in the NSHPC dataset, with respect to factors including ethnicity, mode of HIV acquisition and clinical status. Further records (n=144) were linked using maternal DOB and hospital but could not be confirmed as a match due to missing/discrepant site, diagnosis date or CD4 data. Pregnancies resulting in termination (n=61), miscarriage (n=92) or stillbirth (n=17) and ectopic pregnancies (n=2) were excluded as well as one case where the woman left the UK before delivery. Of the 1,537 women with a pregnancy resulting in a live birth, 720 (47%) were in HIV-related care before the start of their first pregnancy reported to the NSHPC (typically their first pregnancy since HIV diagnosis and/or arrival in the UK); 375 (24%) women were on ART at time of conception of their first reported pregnancy, representing 52% of those receiving clinical care. This group of 375 women forms the study population for the current analyses.

Variables and definitions

Duration of pregnancy varied and actual date of delivery was up to 98 days before EDD, therefore estimated date of conception was calculated as 266 days before EDD (normally calculated using ultrasound scan) or before actual date of delivery if EDD was not reported. Data from UK CHIC were used in the analysis; where demographic data or date of diagnosis was missing from this dataset, data from the NSHPC dataset

were used. Viral load was defined as undetectable if it was below the detection threshold of the viral load assay used at the time, typically <50 copies/ml.

Data analysis

A regimen switch was defined as a discontinuation or introduction of at least one ART drug during pregnancy. The Kaplan-Meier method was used to estimate median time to first regimen switch. Fisher's exact test was used to assess changes in drug use over time. Univariate and multivariable logistic regression were used to identify factors associated with any regimen switch; factors considered included type of ART at conception, viral load at conception and calendar year at conception. Data analysis was undertaken using SAS 9 (SAS Institute Inc. Cary, NC, USA).

Results

Characterising women on ART at conception

Almost three-quarters of the 375 women on ART at conception were black-African and the vast majority were infected heterosexually (Table 1). At conception, median time since HIV diagnosis was nearly 4 years; half were severely immunosuppressed (CD4 <200 cells/mm^3) around the time of HIV diagnosis (within 90 days of diagnosis in the UK and before starting ART) (Table 1). The median time since starting ART was 2.4 years and one-fifth (n=81, 22%) had initiated ART in the 12 months prior to conception. Ninety-three percent of women had a CD4 count <350 cells/mm^3 at time of initiating ART (Table 1).

By the time of conception, median CD4 count had substantially increased and 74% of women had achieved undetectable viral load (Table 2). Median viral load among the 27% of women with detectable levels at conception was 900 copies/ml (interquartile

range (IQR) 134-5914 copies/ml). The majority of women with CD4 <200 cells/mm^3 at conception (n=44) had also been severely immunosuppressed at diagnosis (81%, 21/26, where data was available), which occurred a median of 16 months before conception in this group.

ART use

The majority of women were receiving a combination of three ART drugs (n=306, 82%) and NNRTI-based regimens predominated (Table 2). Of the 39 women on fewer than three drugs, 38% (n=15) conceived after 2005. One-third of women (132/375, 35%) were using a regimen containing nevirapine; 18% (n=69) were using efavirenz and 14% (n=54) didanosine, including 7 women (2%) using efavirenz and didanosine. Of those using efavirenz, 43% (n=30) were on their first regimen, 25% (n=7) had efavirenz in their first regimen but had changed another component of the regimen and 32% (n=22) had switched to using efavirenz. Of women conceiving on didanosine, 19% (n=10) were on their first regimen. Overall, at conception women had been on their current regimen for a median of just under one year. Around half of those conceiving on efavirenz or didanosine had started the regimen within the previous year (37/69 [54%] and 27/54 [50%] respectively).

The proportion of women using either didanosine or efavirenz at time of conception was 14% (6/42) in 1996-1999, 37% (50/134) in 2000-2004 and 30% (60/199) in 2005-2009. The proportion of women using didanosine at conception fell from 30% (7/23) in 2001 to 0 in 2009 (5% (2/40) in 2008) (p=0.07). Use of efavirenz fell from 30% (7/23) in 2001 to 13% (2/15) in 2009 (p=0.7). Four women were on darunavir (two in 2008 and two in 2009), two of whom were also on etravirine - none of these women switched treatment during pregnancy. Twenty-one women conceived on atazanavir, of whom 6 (29%) discontinued its use during pregnancy (3 with undetectable viral load and 3 with

detectable viral load around the time of switch); among these six women, four switched to zidovudine, one to boosted saquinavir (a protease inhibitor (PI)) and one remained on a boosted PI. No women conceived on tipranavir.

ART switching during pregnancy

More than one-third (n=143, 38%) of women switched regimen during pregnancy, including 22 women who interrupted treatment. Regimen switches occurred during the first, second and third trimesters (62% (n=98), 29% (n=41) and 9% (n=13), respectively). The median time to switch was 2.1 months (IQR 1.1-4.3 months) from time of conception. The median CD4 count in the 90 days before regimen change was 290 cells/mm^3 (IQR 186-460 cells/mm^3). The median viral load around the time of changing was 50 copies/ml (IQR 50-6047 copies/ml) and 56% (65/116) had an undetectable viral load at this time.

Fifty-nine percent (41/69) of those who conceived on efavirenz changed regimen during pregnancy compared to 50% (27/54) of women on didanosine and 24% (32/132) of those on nevirapine. Most regimen changes among women on efavirenz were discontinuations of this drug (85%, 35/41), higher than for didanosine (66%, 18/27 discontinued this drug) or nevirapine (53%, 17/32). Among women discontinuing efavirenz, 17 (49%) stopped during the first six weeks, 9 (26%) between 6 and 12 weeks after conception and 9 (26%) after 12 weeks, the latest at 21 weeks. In contrast, among women discontinuing didanosine, 4 (22%), 5 (28%) and 9 (50%) stopped in these three periods respectively. There were also differences with respect to virological status in early pregnancy, with 25% (8/32) of women switching from efavirenz having detectable viral load around the time of conception, compared with 56% (10/18) of those switching from didanosine.

Among women discontinuing efavirenz, four switched to nevirapine; 13 started a PI (ritonavir (n=10), saquinavir (n=1) or nelfinavir (n=1)); two started tenofovir and 11 started zidovudine (5 monotherapy). The majority remained on at least one NRTI (22/35, 63%), two remained on just NRTIs and two started additional NRTIs. Among those discontinuing didanosine, the most common regimen change was to switch to an alternative NRTI (zidovudine (n=10), abacavir (n=1), emtricitabine (n=1) or stavudine (n=1)); one woman started efavirenz and two restarted didanosine in their second trimester. One woman who conceived on didanosine and efavirenz interrupted ART at 11 weeks, restarting after the pregnancy.

Conception on an efavirenz-containing regimen was the strongest risk factor for treatment switch identified in multivariable logistic regression. Adjusting for viral load around time of conception and calendar year at conception, women who conceived on efavirenz were more likely to change regimen during pregnancy compared with women on other drugs (adjusted odds ratio 3.40 [95% confidence interval 1.84, 6.25] p<0.001). Women were less likely to switch treatment in later years even after adjusting for ART use and viral load at conception (0.89 [0.83, 0.96] p=0.002), (Table 3). Repeating this logistic regression using drug discontinuation as the outcome produced similar results (data not shown).

Viral load

Among the 27% (n=84) women with a detectable viral load at start of pregnancy, 51% (36/70) achieved undetectable levels by their third trimester (52% [23/44] of those who switched regimen and 50% [13/26] of those who did not). Nearly two-thirds of those with detectable viral load at the start of pregnancy had been on ART for $\geq$1 year (63%, n=53) with 27% (n=23) on ART for <6 months. With respect to the current ART regimen, 43% (n=36) of women with detectable viral load around conception had

started this in the previous 6 months. Thirty-four women had detectable viral load at both conception and delivery, of whom 13 (38%) did not switch treatment during pregnancy (3.5% (13/375) of the overall group).

Overall, 82% (252/306) women had viral load below the limit of detection in their third trimester; among the 54 women with detectable viral load, the median was 289 copies/ml (IQR 113-942 copies/ml).

Transmission

HIV infection status was available for 340 infants. One child (0.3%, 95% CI 0.0-0.9%), born in 2007, was infected. In this case the mother conceived whilst using lamivudine and abacavir, additional drugs were included in her regimen during the second trimester but viral load was not suppressed by delivery.

Discussion

In our study, HIV-positive women conceiving on ART had been diagnosed for a median of 3.7 years and treated on average for nearly 2.5 years. At conception median CD4 count was 390 cells/mm^3 indicating that most women were in good health, despite many having a CD4 count <200 cells/mm^3 at diagnosis. However, 14% started pregnancy with CD4 <200 cells/mm^3, similar to results from other European studies [13]. The transmission rate was low as would be expected among women conceiving on combination therapy [14].

Most women (78%) had received ART for over a year at conception. NNRTI-based regimens predominated, with efavirenz taken in one-third of these. Despite treatment guidelines recommending that women planning a pregnancy avoid efavirenz or didanosine, as they may increase risk of congenital abnormalities, almost one-third

conceived whilst receiving one of these drugs. This is higher than the proportion reported from an Italian study which reported that 17% of women conceiving on ART from 2002-2008 were receiving these drugs [15].

Treatment changes during pregnancy may be required due to a failing regimen or toxicities, or may be prompted by safety concerns. Overall, 38% of pregnant women here switched regimens, the amount of switching decreasing over time. UK guidelines recommend that women conceiving on efavirenz should continue this regimen, unless it is failing. Half the women conceiving on efavirenz here changed regimens, three-quarters in the first trimester, suggesting that these treatment changes were prompted by safety concerns. This is supported by our finding that the probability of switching was 3.26 times greater in women on efavirenz compared with women on other drugs at conception. In Italy, women conceiving on efavirenz were also more likely to change treatment during pregnancy than women conceiving on other ART drugs [16]. However, this reflects use of US guidelines which differ from UK guidelines in stating that women conceiving on efavirenz should change to a suitable alternative if they present during the first trimester [5].

In our study more than half the women switching from efavirenz did so after the first six weeks of pregnancy, therefore not avoiding fetal exposure to the drug during the weeks when neural fusion occurs [11]. Of note, around 80% of women conceiving on efavirenz-based regimens had undetectable viral loads. Treatment interruptions and unnecessary switching of regimens that are effectively suppressing viral load should be avoided, particularly for women already on second-line therapy [4].

Around half the women conceiving on efavirenz had started this within the year prior to pregnancy, indicating that either they were not planning a pregnancy, did not discuss a

planned pregnancy with their clinician or were planning a pregnancy but decided to use efavirenz despite possible risks. Efavirenz is an effective treatment, with health benefits over non-efavirenz regimens [17] particularly in settings with high levels of HIV/TB co-infection as it can be used in combination with rifampicin-based TB therapy. In Ivory Coast, where efavirenz use is common among women, a study comparing pregnancy outcomes between women conceiving on efavirenz (n=213) and nevirapine (n=131) observed no visible congenital malformations in either group [11]. Further risk-benefit analysis is needed regarding the use of efavirenz among women of child bearing age. Pregnancies which did not result in a live birth were excluded from the analysis, however it would be of interest, in future analyses, to look at pregnancy outcome in relation to ART use at conception and treatment switches during pregnancy.

Guidelines recommend that women planning a pregnancy are offered counselling prior to conception [3] and that HIV physicians should discuss pregnancy plans with women when making treatment decisions [4]. Our results reinforce this need, both to identify where increased adherence support or regimen change is required or to discuss switching to an alternative regimen among women on efavirenz who do not wish to conceive on this drug. Any changes to treatment should be made swiftly to avoid switching during or close to the start of pregnancy. Given the probable high number of unplanned pregnancies in this population [16,18,19], it is important that clinicians prescribing ART consider that women of childbearing age may become pregnant and that all HIV-positive women should have access to appropriate contraception and advice.

Etravirine, a second generation NNRTI, and darunavir, a second generation PI, are among a handful of drugs approved for use in the past five years. In our study a small number of women conceived on these drugs in recent years and a larger number

conceived on atazanavir, a PI approved for use in 2003. It is likely that the number of women who conceive on these drugs will increase, although little is known about their safety profiles, and close monitoring of their pregnancy outcomes is thus crucial [8].

Viral load, the most important factor associated with vertical transmission, [14,20,21] was generally low around the time of conception. However, more than a quarter of women had non-suppressed viral load at this time (although with low median viral load), similar to other reports [22]; this group included those who recently initiated ART (28% within the last six months) but 64% had been on ART for at least one year. This may be due to delays in treatment switching, previously reported as a concern in the UK [23]. More than half of those who did not switch regimen, despite having an unsuppressed viral load at the start of pregnancy, attained viral suppression. Similarly, in a European study of women conceiving with unsuppressed viral load, 40% of the women not changing treatment attained viral suppression by delivery [22]. This may be due to improved adherence during pregnancy, as has been reported elsewhere [24,25], probably because women receive increased adherence support and/or because they have increased motivation to adhere. Women on a failing regimen should have resistance testing [4] and although changing regimen is not always necessary, half the women who had detectable viral load at the start of pregnancy and did not switch treatment did not achieve undetectable viral load by the end of pregnancy. This group might have benefitted from switching treatment.

Median viral load among women with detectable levels in their third trimester was 289 copies/ml compared with 900 copies/ml among those with a detectable viral load at conception. Given more time some of these women may have achieved undetectable levels. Although this group represent a small proportion of the overall group, they are at increased risk of MTCT, particularly as transmission is more likely to occur in the later

stages of pregnancy [14,20,21]. During pregnancy swift action is required to improve adherence or change a failing regimen among treated women with a detectable viral load, to attain viral suppression as quickly as possible.

Linkage between the NSHPC and UK CHIC datasets has allowed us to examine clinical data prior to as well as during pregnancy. However, several limitations of these datasets must be acknowledged. Firstly, as with most large observational databases, both databases may contain missing or incorrect data, resulting in under-linkage of pregnant women. Secondly, whilst participants in UK CHIC are broadly representative of the UK HIV population, clinical practice in participating centres may differ from those at non-participating clinics. Thirdly, UK CHIC does not collect information on the reasons why women did (or did not) switch treatments, on adherence or ART use prior to treatment at a centre participating in the study. Finally, the NSHPC does not collect information on the date when each woman found out that she was pregnant; a date which is arguably of most relevance for any subsequent changes to her care.

In summary, women planning a pregnancy should be encouraged to discuss their plans with their physician to facilitate optimal management, including avoidance of antiretroviral drugs for which there may be specific safety concerns. For women on treatment, the opportunity to achieve an undetectable viral load before pregnancy and to maintain this throughout pregnancy should not be missed, given that MTCT can occur before, as well as during, the last trimester. Clinicians prescribing ART to all women of childbearing age must consider that these patients might conceive. All treated HIV-positive women who become pregnant require a high level of clinical support, in particular those with unsuppressed viral load, who either require a change in regimen or support with their existing regimen. As the number of pregnancies among HIV-positive women on ART is increasing [1,22,26] and more women conceive on new

ART drugs, continued surveillance and monitoring of pregnancy outcomes is vital.

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Table 1. Characteristics and ART history of women receiving ART at conception (n=375).

		n	%
Ethnicity	White	55	(15)
	Black-African	277	(74)
	Other	43	(11)
Probable route of infection	Heterosexual sex	328	(87)
	Injecting drug use	9	(2)
	Other route	35	(9)
	Not reported	3	(1)
Age	Median (IQR) (years)	33 (29 - 35)	
	Range	16 - 45	
Time since HIV diagnosis in the UK	Median (IQR) (years)	3.7 (1.9 - 6.2)	
	1 year or less	39	(10)
	>1 - 3 years	112	(30)
	>3 - 5 years	85	(23)
	>5 years	135	(36)
	Not reported	4	(1)
CD4 count (cells/mm^3) at time of diagnosis in the UK (n=244) [1]	Median (IQR)	238 (130-357)	
	<200	104	(43)
	200-350	182	(32)
	>350	244	(25)
Time since initiating (any) ART	Median (IQR) (years)	2.4 (1.2 - 4.6)	
	<6 months	42	(11)
	6-12 months	39	(10)
	>12m – 2 yrs	76	(20)
	>2 yrs – 3 yrs	69	(18)
	>3 yrs	149	(40)
CD4 count (cells/mm^3) at time of initiating ART (n=292) [1]	Median (IQR)	170 (97- 250)	
	<200	179	(61)
	200-350	90	(31)
	>350	23	(8)
Viral load (copies/ml) at time of initiating ART (n=263) [1]	Median (IQR)	52,228 (10,093-157,402)	

[1] Within 90 days.

Table 2. ART use, immune and virological status at time of conception (n=375).

		N	(%)
Number of ART drugs received [1]	<3	39	(10)
	3	306	(82)
	>3	30	(8)
ART regimen	Non-nucleoside reverse transcriptase inhibitor	203	(54)
	Unboosted protease inhibitor (PI)	30	(8)
	Ritonavir-boosted PI	95	(25)
	Nucleoside reverse transcriptase inhibitors only	37	(10)
	Other	10	(3)
Regimen includes efavirenz		69	(18)
Regimen includes didanosine		54	(14)
Time since starting current ART regimen	Median (IQR) (months)	11.2	(4.6 - 23.5)
	<6 months	113	(30)
	6-12 months	84	(22)
	>12 months – 2 years	88	(23)
	>2 years – 3 years	45	(12)
	>3 years	45	(12)
CD4 count (cells/mm^3)[2] (n=320)	Median (IQR)	390	(259 - 544)
	<200	44	(14)
	200-350	88	(28)
	>350	188	(59)
Viral load (copies/ml)[2] (n=317)	Median (IQR)	50	(50 - 74)
	Undetectable	233	(74)
	Detectable	84	(27)

[1] A PI boosted with ritonavir was counted as one drug.
[2] Within 90 days of conception.

Table 3. Results from unadjusted and adjusted logistic regression analysis of factors associated with switching ART regimens during pregnancy

		Unadjusted			Adjusted		
		OR	CI	p	AOR	CI	p
ART at conception	Not nevirapine	1			1		
	Nevirapine	0.47	0.30-0.74	0.07	0.69	0.41-1.16	0.16
	Not efavirenz	1			1		
	Efavirenz	2.93	1.71-5.01	<0.001	3.40	1.84-6.25	<0.001
	Not didanosine	1			1		
	Didanosine	2.11	1.18-3.77	0.01	1.77	0.94-3.33	0.08
Viral load at conception	Undetectable	1			1		
	Detectable	3.32	1.98-5.57	<0.001	2.97	1.70-5.19	<0.001
	No VL reported	0.97	0.52-1.80	0.92	1.04	0.53-2.02	0.92
Year of conception (per later year)		0.88	0.82-0.94	<0.001	0.89	0.83-0.96	0.002