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PATTERNS OF EFAVIRENZ USE AMONG HIV-POSITIVE WOMEN IN URBAN HIV AND HIGH-RISK OBSTETRICS CLINICS

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PATTERNS OF EFAVIRENZ USE AMONG HIV-POSITIVE WOMEN IN URBAN HIV AND HIGH-RISK OBSTETRICS CLINICS. Matthew P. Kronman, B. Joyce Simpson, Warren A. Andiman, and Krystn R. Wagner. Sections of Infectious Diseases, Departments of Internal Medicine and Pediatrics, Yale University School of Medicine and Pediatric AIDS Care Program, Yale-New Haven Children's Hospital, New Haven, CT.

We investigated patterns of efavirenz use among physicians caring for HIV-positive women in the primary HIV and high-risk obstetrics clinics (HROC) of an academic teaching hospital. Efavirenz, a non-nucleoside reverse transcriptase inhibitor approved for HIV treatment, is a potential teratogen. The FDA recommends that women prescribed efavirenz use two forms of birth control and avoid becoming pregnant. We conducted a retrospective analysis of medical records of reproductive-age HIV-positive women seen between September 1998 and December 2002, recording information documented at initial prescription of efavirenz, pregnancies occurring on efavirenz, other antiretroviral medications taken during pregnancy, and fetal malformations noted at birth. We administered a quiz regarding efavirenz's side effects to the HIV clinic providers.

Four hundred fifty-six reproductive-age HIV-positive women were treated in the adult (N=442) and pediatric (N=14) clinics. Ninety-nine adult (22.4%) and 3 pediatric (21.4%) reproductive-age women were prescribed efavirenz. At efavirenz's initial prescription, 21.3% and 33.3% of medical records mentioned efavirenz's side effects, 3.8% and 0.0% documented birth control method, and 0.0% and 0.0% documented mention of teratogenicity or pregnancy test, respectively. Four percent of adult efavirenz-takers became pregnant while on efavirenz.

Fifty-seven pregnancies were managed at the HROC; 98.2% resulted in live births and 1.8% resulted in intrauterine fetal demise. 7.3% of these women took efavirenz during pregnancy, one of which resulted in intrauterine fetal demise, one in pre-term delivery, and two in uncomplicated births. Another pregnant efavirenz-taker suffered intrauterine fetal demise before her first visit to the HROC.

Eighty-seven percent of the adult HIV clinic providers participated in the quiz; of these, 50% knew efavirenz was potentially teratogenic, 100% noted communicating medication side effects at initial prescription, and 45% noted documenting this discussion in the medical record.

We found strong evidence that HIV-positive women are at risk of exposing their fetuses to efavirenz's potentially teratogenic effects.

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Introduction

The global HIV pandemic has had a tremendous impact on international health and medical practice. Despite twenty years of prevention efforts, there are an estimated 14,000 HIV new infections daily with an estimated 36 million people infected worldwide. Approximately 70 percent of these people live in Sub-Saharan Africa (1). The Centers for Disease Control estimate that approximately 1 million HIV-infected people live in the United States, with an estimated 40,000 new infections per year (2).

Since the first antiretroviral drug, zidovudine, was introduced in 1987, there has been rapid development and FDA approval of new drugs for the treatment of HIV (1). In the early years of HIV treatment, there were few medications to offer patients to stay the inevitable course toward advanced immunodeficiency and, ultimately, death. In August 1995, the first protease inhibitor was approved and within 18 months three additional protease inhibitors had been approved (1). Within the next two years physicians began to administer a complex "drug-cocktail" – a combination of protease and reverse transcriptase inhibitors – that dramatically reconstituted the immune systems of their HIV patients. However, these powerful new medications were not without their side effects, and patients were sometimes unable to tolerate the number of pills they were being asked to take.

Efavirenz (*Sustiva*, made by Bristol-Myers Squibb), a non-nucleoside analogue reverse transcriptase inhibitor (NNRTI), was FDA-approved in September 1998, and with it new "protease-sparing" regimens were introduced (3). Efavirenz is one of the most potent and commonly prescribed HIV-specific NNRTIs. Its appeals include once-a-day dosing, low pill volume, and the patient's ability to take it with or without food. Given

the long-term toxicities and pill burden associated with the protease inhibitors, efavirenz is an obvious therapeutic choice for many patients.

Efavirenz in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) is among the "strongly recommended" regimens for initial treatment of asymptomatic HIV infection (4). This recommendation is based in part on a number of studies that have proved the efficacy and tolerability of efavirenz in combination with NRTIs, or in combination with protease inhibitors, both for antiretroviral-experienced HIV patients (5,6) and for antiretroviral treatment-naïve HIV patients (7-10). Small recent studies have also shown that efavirenz is effective when included in therapy for patients with high viral loads (>100,000 copies/ml) or low CD4 counts (<100 cells/µl) (11,12). However, because cross resistance among members of its class develops easily, efavirenz has only had modest efficacy when included in a salvage regimen for patients failing prior antiretroviral therapies (13,14).

Despite the proven efficacy of efavirenz, less is known about its safety in pregnancy. In general, there is a paucity of data regarding the safety of all antiretrovirals during pregnancy. For this reason, the Antiretroviral Pregnancy Registry was created, a database to which physicians may voluntarily report exposures and adverse reactions to antiretrovirals during pregnancy (15). Most antiretrovirals are classified as either pregnancy category B (no evidence of risk in humans, though chance of fetal harm remains a possibility) or category C (risk cannot be ruled out because human studies are lacking and animal studies have shown a risk to the fetus or are lacking). There are only five medications in Category B: didanosine, nelfinavir, ritonavir, saquinavir, and tenofovir (16). Table 1 lists the Category C HIV medications (16).

TABLE 1. SAFETY STUDIES OF THE CATEGORY C ANTIRETROVIRAL MEDICATIONS.

Drug	Type of safety study	Toxicity	Dose Level[A]
Abacavir	Rats	Fetal malformations	High
Amprenavir	Rats, rabbits	Fetal malformations	Low
Delavirdine	Rats	Fetal malformations	High
Efavirenz	Monkeys	Fetal malformations	Equivalent
Indinavir	Rats	Developmental toxicity	Equivalent
Lamivudine	Rabbits	Early embyolethality	Equivalent
Lopinavir+Ritonavir	Rats	Fetal malformations	High
Nevirapine	Rats	Decreased fetal weights	Equivalent
Stavudine	Rats	Developmental toxicity	High
Zalcitabine	Rats	Fetal malformations	High
Zidovudine	Rats	Fetal malformations	High

[A]Dose Level – Refers to relation of animal plasma level from dose given to therapeutic human plasma levels.

With the exception of zidovudine and nevirapine, which are approved for use in the reduction of maternal-fetal transmission of HIV, there have been few clinical trials conducted to determine human safety of antiretrovirals during pregnancy. Small Phase I safety trials of didanosine and lamivudine in pregnancy have been completed; indinavir, nelfinavir, ritonavir, saquinavir, and stavudine are currently undergoing Phase I/II safety studies in pregnancy (15). It is clear, therefore, that much of what we are to learn about the safety of antiretrovirals in pregnancy will come from post-approval data collection.

Efavirenz is listed as a pregnancy category C drug based on toxicity studies in primates. The early animal studies of efavirenz noted significant central nervous system fetal malformations in progeny of 3 out of 20 cynomolgus monkeys given efavirenz during pregnancy at plasma concentrations similar to human therapeutic levels, but in none of the 20 controls (17). One monkey was born with anencephaly and unilateral anophthalmia, one with microophthalmia, and a third with cleft palate. Efavirenz impaired neither the fertility of male and female rats nor the reproductive performance of

offspring born to female rats to whom it was given (15). However, an increase in fetal resorptions was noted in rats whose peak plasma concentration and AUC values were equivalent to or lower than that achieved in humans given the standard 600mg daily dose (15). Pregnant rabbits given doses of efavirenz producing peak plasma concentrations similar to, and AUC values approximately half of, human therapeutic levels displayed no reproductive toxicities (15). Due to the teratogenicity potential of efavirenz, Bristol-Myers Squibb has not conducted human safety studies in pregnancy.

Multiple sources note that efavirenz is contraindicated during pregnancy, including the Bristol-Myers Squibb packet insert and the recent European consensus on management of pregnancy and HIV infection (17,18). The packaging information also recommends that physicians document a negative pregnancy test before administering efavirenz for the first time, and that women of childbearing age be on two forms of birth control, including a barrier method, because it is unknown whether efavirenz interacts with oral contraceptives or injectable hormone preparations (17).

Women may nevertheless accidentally become pregnant while taking efavirenz, and there have been two recent reports of a neural tube defect in a child exposed in utero to efavirenz (19,20). The Antiretroviral Pregnancy Registry noted 71 exposures to efavirenz during the first trimester, four of which resulted in birth defects, though the relationship with efavirenz may or may not be causal (15). Those defects include polydactyly, hepatosplenomegaly, hydronephrosis, and cerebral atrophy in a premature infant with a family history of seizures (though in this case the mother's reported use of efavirenz during the first trimester could not be confirmed in the medical record). None of the Antiretroviral Pregnancy Registry's ten reported maternal exposures to efavirenz

during the second and third trimesters resulted in fetal malformations (15). Although the Registry does not publish the details on each of its approximately 2,600 prospective cases, these exposures to efavirenz likely occurred in women who were simultaneously exposed to other antiretrovirals.

Statement of purpose and hypothesis

We proposed to investigate the knowledge and practices of physicians regarding the use of efavirenz. The physicians provide care to HIV-positive women in a primary, urban HIV clinic (The Nathan Smith Clinic) and a high-risk obstetrics clinic at Yale-New Haven Hospital. We hypothesized that physicians commonly prescribe efavirenz to women of reproductive age. In addition, we hypothesized that physicians routinely fail to document that they have informed women of the teratogenicity risks or counseled them regarding appropriate birth control. Given the small numbers of pregnancies occurring in our HIV clinic, we believed we would not be able to determine a statistically significant association between use of efavirenz and any congenital malformations that might occur; nevertheless, we reviewed all pregnancies and outcomes of HIV-positive women treated at the High Risk Obstetrics Clinic (HROC) to assess possible associations between efavirenz use and adverse pregnancy outcomes.

Methods

We performed a retrospective review of medical records of patients followed at the Yale-New Haven Hospital HIV clinic. The clinic actively follows 900 patients, of which approximately 30% are women. In addition, we analyzed the medical records of

HIV-positive women followed in a high-risk obstetrics clinic in the same hospital. Our study sample included all women of reproductive age, i.e., ages 12 to 50 years, based on national averages of menarche and menopause (21, 22). Our study therefore included women from the Nathan Smith Clinic (NSC), as well as the pediatric AIDS Clinic.

A list of all women seen in the clinic since 1995 was computer-generated. Using the charts and/or computerized medical records, we reviewed the antiretroviral history of each of the women seen since initiation of efavirenz's clinical trials and FDA approval of efavirenz in September 1998 and before January 1, 2003. For all women who had been prescribed efavirenz, we looked for documentation of discussion of potential teratogenic risk associated with use of efavirenz, documentation of birth control method, and pregnancy test at the time when efavirenz was first prescribed. Reasons for discontinuation of efavirenz as well as any pregnancies that occurred while on efavirenz were recorded. We also noted whether hysterectomy, bilateral tubal ligation, or other causes of infertility were documented in the problem list at the front of the patient's chart.

We also reviewed the charts of the HIV-positive pregnant women seen in the HROC. These patients' charts were previously abstracted as part of an NIH study. The chart abstractions as well as the associated relevant parts of the original chart that had been reproduced were reviewed. The following information was extracted: the woman's age, the fetal age at the time of the first visit to the HROC, the antiretroviral medications taken during the entire pregnancy, the baby's fetal age at delivery, whether any spontaneous abortions occurred, and whether any malformations were noted in the baby at birth. The study group included pregnant women who delivered after the FDA approval of efavirenz in September 1998 and prior to January 1, 2003.

To test the HIV clinicians' knowledge of the potential teratogenicity of efavirenz, we administered a brief quiz to the providers at the adult HIV clinic. The quiz listed five antiretroviral medications, including efavirenz, along with set of potential side effects (Appendix I). The providers were asked to note which of the side effects are most commonly associated with each of five antiretrovirals. After taking the quiz, the providers were informed of the purpose of the study and the teratogenicity risks associated with efavirenz. Because the majority of these quizzes were administered in late December 2002, the study enrollment ended January 1, 2003.

The $?^2$ test for statistical significance was used in comparing the number of malformations seen at the HROC with those noted through the Antiretroviral Pregnancy Registry.

With the exception of the primary chart abstraction of the women seen through the HROC, I performed all medical record review and abstraction. I designed all of the abstraction materials, performed the data analysis, and designed the physician questionnaire with the oversight of my advisors.

Results

Nathan Smith Clinic – General Characteristics

A total of 478 women have received care at the NSC since September 1998, when efavirenz was FDA approved. Use of efavirenz among female patients in the NSC has been significant: 123 (25.7%) of the 478 women treated since September 1998 were prescribed efavirenz for some period of time. Table 2 describes the characteristics of the women who were prescribed efavirenz. Ninety-nine (80.5%) of the 123 women given

efavirenz were classified as being of reproductive age. These 99 women constitute 22.4% of the 442 women of reproductive age seen in the NSC since September 1998. The other 24 women prescribed efavirenz were not classified as of reproductive age based on age criteria (9, 7.3%), post-surgical sterility noted at initial prescription (5, 4.1%), or post-surgical sterility noted in the problem list at the front of the patient's chart (10, 8.1%).

TABLE 2. CHARACTERISTICS OF EFAVIRENZ USE AMONG THE WOMEN SEEN AT THE NSC.

Total number of women seen in the Nathan Smith Clinic	478 (100.0)
Number of women of reproductive age (%)	442 (92.5)
Total number of women ever on efavirenz	123 (100.0)
Number of women on efavirenz of reproductive age (%)	99 (80.5)
Number of women on efavirenz not of reproductive age (%)	24 (19.5)
Based on age criteria (%)	9 (7.3)
Based on post-surgical sterility noted at initial prescription (%)	5 (4.1)
Based on post-surgical sterility noted in problem list (%)	10 (8.1)
Total number of women currently on efavirenz (%)	39 (100.0)
Number of reproductive age (%)	27 (69.2)
Number not of reproductive age (%)	12 (30.8)

Nathan Smith Clinic – Chart availability and documentation

Table 3 describes further characteristics of the women prescribed efavirenz. Eighty (80.8%) of the ninety-nine women of reproductive age have medical records that contain the note written at the time of the initial prescription of efavirenz. Eleven (11.1%) were prescribed efavirenz at an outside institution, 2 (2.0%) had no documentation of the initial prescription, and 6 (6.1%) women whose charts are unavailable are assumed to have been of reproductive age based on age criteria alone.

TABLE 3. CHARACTERISTICS OF EFAVIRENZ USE AMONG THE WOMEN SEEN AT THE NSC (CONT).

Total number of women on efavirenz of reproductive age (%)	99 (100.0)
Number of women of reproductive age on EFV[A] with initial prescription note available (%)	80 (80.8)
Number of women of reproductive age on EFV without initial prescription note (%)	19 (19.2)
Number prescribed EFV at an outside institution (%)	11 (11.1)
Number with no documentation of initial prescription (%)	2 (2.0)
Number with no chart available (%)	6 (6.1)
Number of women of reproductive age on EFV with initial prescription note available (%)	80 (100.0)
Number of reproductive-age women with documentation of side effects at initial prescription (%)	18 (22.5)
Number of women with documentation of birth control method (%)	3 (3.8)
Number of women with documentation of discussion of potential teratogenicity (%)	0 (0.0)
Number of women with documentation of pregnancy test (%)	0 (0.0)
Number of ninety-nine total women who became pregnant while on EFV (%)	4 (4.0)

[A]EFV— efavirenz

Eighteen (22.5%) of these medical record notes contained some mention of a discussion of potential side effects of efavirenz or of any other antiretroviral therapy initiated at that time. These written comments range in quality from "risk discussed" in one chart to "spent 45 min. today discussing NIH rx guidelines, rx options, adv. rxn. & toxicity" in another. None of the notes available for the 80 women of reproductive age prescribed efavirenz contained documentation of the physician's discussion with the patient of efavirenz's potential teratogenicity.

Documentation of pregnancy tests and birth control methods were similarly lacking. Three (3.8%) of the chart notes contained documentation of birth control method: two of the women were described as using condoms for birth control, and the other woman was described as using Depo-Provera as her birth control method. None of the notes documented performance of a pregnancy test.

Of the 11 women who were prescribed efavirenz at an outside institution, there was no documentation that any had a pregnancy test, birth control method, or a

discussion of efavirenz's potential teratogenicity at the time of their first visit to the NSC while still taking efavirenz.

Nathan Smith Clinic – Pregnancies, Ages, Discontinuation

Four (4.0%) of the 99 women of reproductive age prescribed efavirenz became pregnant while taking efavirenz; the outcomes of these pregnancies are described below along with those who received care at the HROC.

Age at initial prescription was available for 99 (100.0%) of the 99 women of reproductive age given efavirenz. Their ages ranged from 18 to 49; the percent of women prescribed efavirenz increased as a function of age, so that women between 35 and 50 accounted for 69.7% of those prescribed efavirenz (Fig. 1).

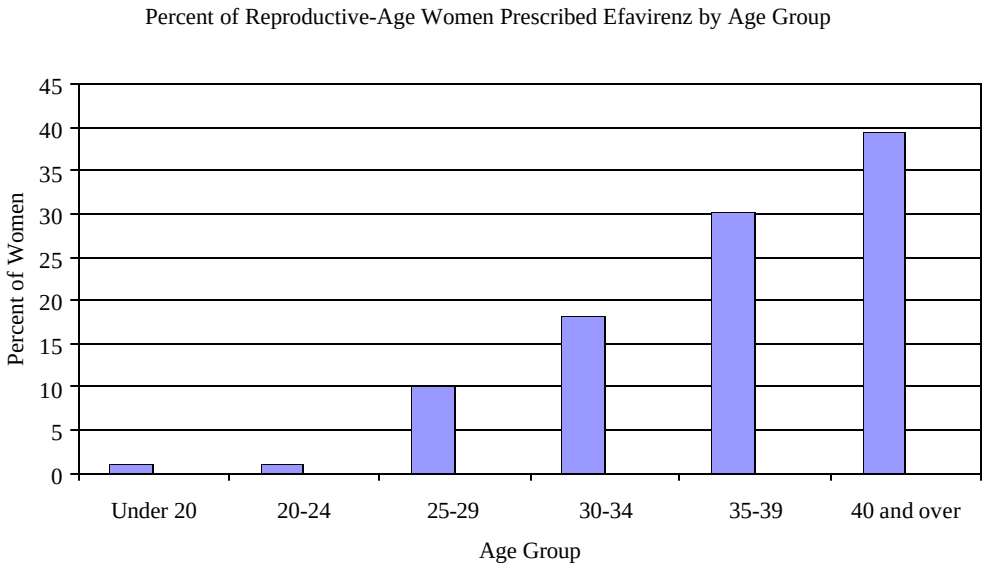

Figure 1. Percent of Reproductive-Age Women Prescribed Efavirenz by Age Group. Age at initial prescription was available for 99 (100.0%) of the 99 women of reproductive age, and ranged from 18 to 49. Values are shown as percent of total. Women between 35 and 50 years of age accounted for 69.7% of those prescribed efavirenz.

Eighty-four (68.3%) of the 123 women prescribed efavirenz have discontinued its use. Reasons for discontinuation were given in 57 (67.9%) of the 84 cases (Fig. 2). Of

these 57 reasons for discontinuation, self-discontinuation was the most common reason given, accounting for 21 (36.8%) of the women. Providers listed treatment failure as the reason in 10 (17.5%) of the women, while another 6 (10.5%) were taken off efavirenz after drug resistance was demonstrated based on an HIV genotype. Central nervous system side effects associated with use of efavirenz resulted in discontinuation for 5 (8.8%) of the women. All 4 (7.0%) women who became pregnant while taking efavirenz were told to discontinue the medication because of their pregnancy. The remaining 11 (19.3%) discontinued efavirenz for a variety of reasons, including GI distress, desire for medication holiday, "housing problems," and difficulty swallowing.

Reasons for discontinuation of efavirenz were unavailable for 27 (32.1%) women: 16 (19.0%) women's charts did not contain a documented reason for the discontinuation of efavirenz, 6 (7.1%) women's charts were unavailable, and 5 (6.0%) women's charts did not include notes at the time of discontinuation.

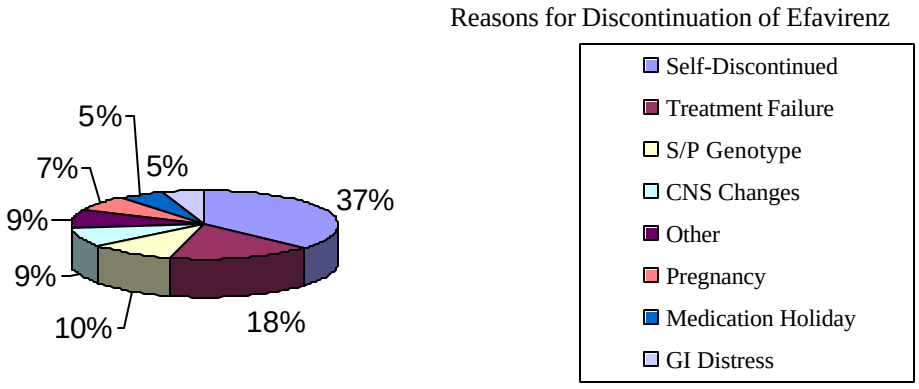

Figure 2. Reasons for Discontinuation of Efavirenz. Of the 57 women whose reason for discontinuing efavirenz were documented, 37% self-discontinued it, 18% discontinued it because of treatment failure, 10% after resistance was documented on an HIV genotype, 9% for central nervous system changes, 7% because of pregnancy, 5% for medication holiday, 5% for gastrointestinal distress, and 9% for assorted other reasons.

At the end of the study interval, 39 women in the NSC were taking efavirenz; this comprises 31.7% of the 123 women ever prescribed efavirenz. Twenty-seven (69.2%) of

the current users are of reproductive age. Again, of these 27 reproductive-age women currently taking efavirenz, only 2 (7.4%) had documentation of birth control method and none (0.0%) had written documentation of potential teratogenicity at the time of initial prescription.

Pediatric AIDS Clinic

There were 14 young women who received their care at the Pediatric AIDS Clinic; they ranged in age from 12 to 20 years (Table 4). Three (21.4%) of these young women were prescribed efavirenz at some time during the study period. This proportion is similar to the proportion of reproductive-age women who received efavirenz (p=0.93). None of the charts document a pregnancy test, birth control method, or discussion of teratogenicity at the time of initial prescription of efavirenz. In the chart of the patient who had been placed on efavirenz most recently, there was documentation of a discussion of side effects, and two weeks after the original prescription there is a documented discussion of teratogenicity and use of condoms as birth control method. One of the women currently takes efavirenz; the other two discontinued its use after resistance was documented in an HIV genotype analysis. Two (14.3%) of these 14 young women became pregnant during the study period, but neither of them was taking efavirenz at the time.

TABLE 4. CHARACTERISTICS OF THE YOUNG WOMEN SEEN IN THE PEDIATRIC AIDS CLINIC

Total number of women of reproductive age seen in the Pediatric AIDS Clinic	14 (100.0)
Number who have ever been prescribed efavirenz (%)	3 (21.4)
Number with documentation of any discussion of side effects (%)	1 (33.3)
Number with documented discussion of teratogenicity at time of initial prescription (%)	0 (0.0)
Number with documentation of pregnancy test at time of initial prescription (%)	0 (0.0)
Number with documentation of birth control method at time of initial prescription (%)	0 (0.0)
Number of the 14 women who have become pregnant since 1998 (%)	2 (14.3)
Number of current users of efavirenz (%)	1 (7.1)
Number who have discontinued efavirenz (%)	2 (14.3)
Number who discontinued after resistance shown on genotype analysis (%)	2 (14.3)

High-Risk Obstetrics Clinic – General Characteristics

The High-Risk Obstetrics Clinic (HROC) has provided care to 53 HIV-positive women since the FDA approval of efavirenz. Of these 53 women, 30 (56.4%) were NSC patients prior to becoming pregnant, and the remainder obtained care for their HIV infection elsewhere or else had their HIV infection diagnosed during pregnancy. One woman treated at the NSC became pregnant twice during the study period, and one woman treated elsewhere became pregnant twice during the study period. Two women gave birth to twins, and so altogether there were 57 total fetuses available for study. The medical records were available for 55 (96.5%) of these fetuses; records were unavailable for one of the women from the NSC who gave birth to twins. The 30 pregnant women from the NSC constitute 6.8% of the 442 women of reproductive age seen in the clinic since 1998.

Table 5 describes the characteristics of the HIV-positive women who received their prenatal care in the HROC. Of the 55 available fetuses, 47 (85.5%) resulted in live term births, 7 (12.7%) resulted in live pre-term births, and 1 (1.8%) resulted in intrauterine fetal demise.

High-Risk Obstetrics Clinic – Women exposed to efavirenz

Notably, 4 (7.3%) of the women seen at the HROC were taking efavirenz at the beginning of their pregnancy, and their efavirenz was discontinued either prior to their first HROC visit or at their first HROC visit. Three of these women received their routine HIV care at the NSC; the fourth was incarcerated at the time and was receiving care elsewhere.

One woman exposed to efavirenz during pregnancy was noted early in pregnancy to have a positive screen for Trisomy 18 but refused amniocentesis. She had an intrauterine fetal demise at 23 weeks gestational age and at delivery of the fetus she was noted to have purulent amniotic fluid. At delivery the pediatricians documented overlapping sutures and hydrops in the fetus. The mother had remained on efavirenz until her pregnancy was diagnosed at 4 weeks, 6 days gestational age.

One of the women exposed to efavirenz during pregnancy delivered at 33 weeks without other risk factors for pre-term delivery. The baby had no recorded malformations. She had been exposed to efavirenz until pregnancy was diagnosed at 4 weeks, 2 days gestational age.

Two of the women delivered their babies without complication. One woman had been exposed to efavirenz until approximately 19 weeks gestational age, and the other until 6 weeks, 5 days gestational age when the pregnancy was diagnosed.

Finally, a NSC patient who became pregnant while on efavirenz was referred to the HROC, but at approximately 8 weeks gestational age was already noted to have had an intrauterine fetal demise. There are therefore in total 5 women who became pregnant

while on efavirenz and were referred to the HROC during the study period. The four NSC women who became pregnant while on efavirenz represent 13.3% of the 30 female NSC patients who became pregnant during the study period.

High-Risk Obstetrics Clinic – Fetal events, Deliveries, Ages

Unexpected fetal events occurred in 8 (14.5%) of the 55 total pregnancies at the HROC. Two (3.6%) of these events were cardiac malformations, and there was one (1.8%) of each of the following: tracheoesophageal fistula, encephalocele, bilateral polydactyly, flat nose bridge, intrauterine growth retardation, and intrauterine fetal demise. This group of 55 pregnancies had significantly more unexpected fetal events than those among the women who have been reported to the Antiretroviral Pregnancy Registry. We noted 8 events among the 55 pregnancies. In contrast, for women exposed to any antiretroviral therapy during the first trimester, the Antiretroviral Pregnancy Registry notes 24 events out of 952 exposures ($p<0.000005$).

TABLE 5. CHARACTERISTICS OF THE WOMEN CARED FOR AT THE HIGH-RISK OB CLINIC

Total number of HIV-positive pregnant women who have received care at HROC[A]	53
Number of women seen at HROC who are NSC[B] patients (%)	30 (56.6)
Total number of fetuses delivered (%)	57 (100.0)
Total number of these fetuses with records available (%)	55 (96.5)
Number of live-births (%)	54 (98.2)
Number of intrauterine fetal demises (%)	1 (1.8)
Total number of fetuses with records available (%)	55 (100.0)
Number of women taking efavirenz during pregnancy (%)	4 (7.3)
Number of women taking efavirenz during pregnancy from NSC (%)	3 (5.5)
Number of adverse fetal events among women taking EFV[C] during pregnancy (%)	1 (1.8)
Intrauterine fetal demise (%)	1 (1.8)
Number of unexpected fetal events (%)	8 (14.5)
Cardiac malformations (%)	2 (3.6)
Tracheoesophageal fistula (%)	1 (1.8)
Encephalocele (%)	1 (1.8)
Bilateral polydactyly (%)	1 (1.8)
Flat nose bridge (%)	1 (1.8)
Intrauterine growth retardation (%)	1 (1.8)
Intrauterine fetal demise (%)	1 (1.8)

[A]HROC – High Risk OB Clinic
[B]NSC – Nathan Smith Clinic
[C]EFV – efavirenz

The number of women delivering each year has increased only slightly from 1999-2002, with 9 women delivering in 1999, and then 15 women delivering in each of 2000, 2001, and 2002 (Fig. 3). Data from 1998 are not included because information on the women treated through the HROC was only collected for the part of that year after September.

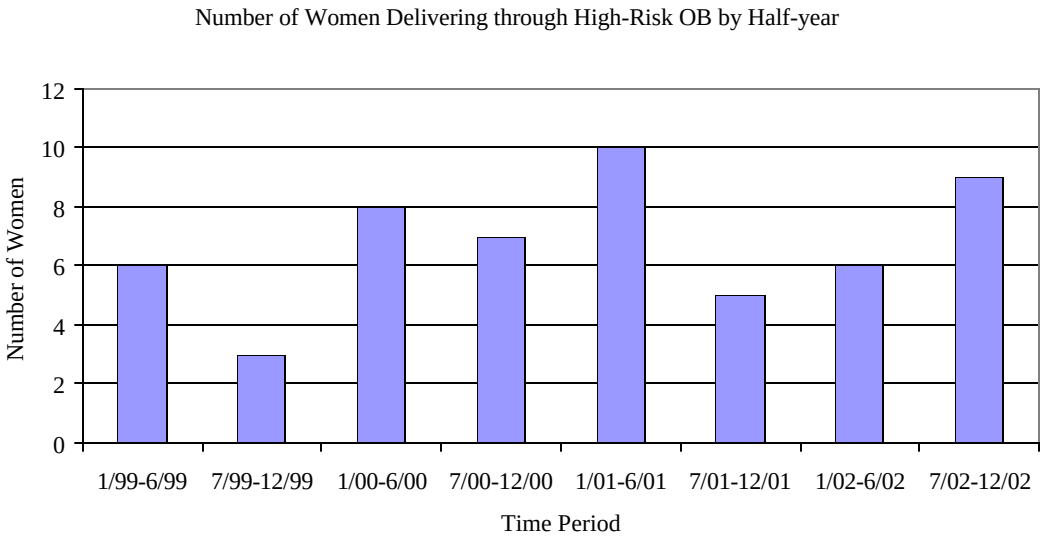

Figure 3. Number of Women Delivering through the High-Risk Obstetrics Clinic by Half-year. The number of women has increased only slightly since the beginning of the study, from 9 deliveries in 1999, to 15 deliveries in each subsequent year through 2002.

Age at delivery was available for all 55 women who received care at the HROC. The ages ranged from 18 to 42, with the majority (44, 80.0%) of the women ranging in age from 25 to 39. Thirty-nine (70.9%) of the women were under age 35 years at delivery (Fig. 4).

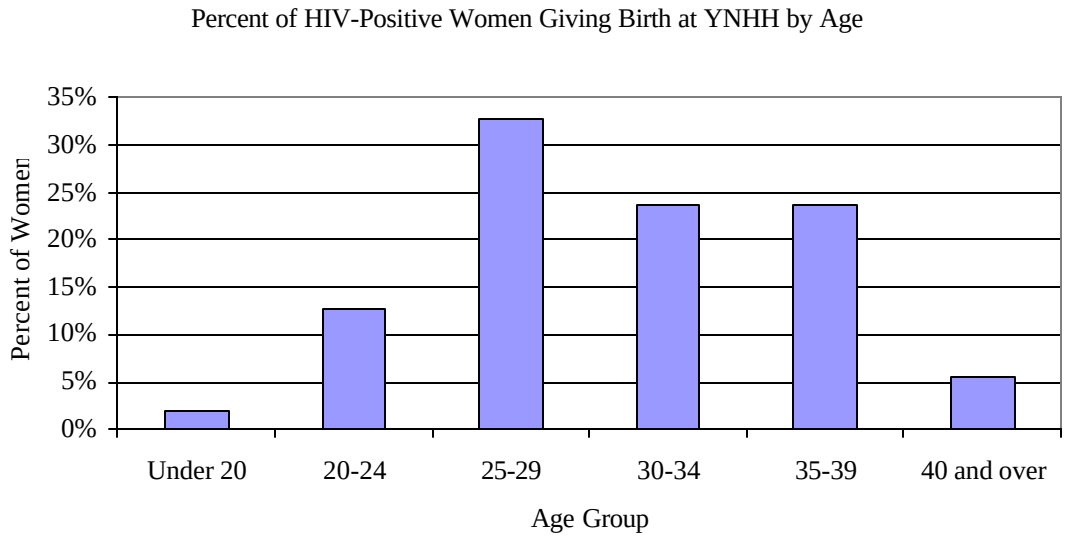

Figure 4. Percent of HIV-Positive Women Receiving Care at the High-Risk Obstetrics Clinic by Age. The women's ages ranged from 18 to 42. Of the 55 total women, 39 (70.9%) were under the age of 35, and 44 (80.0%) were between the ages 25 and 39.

Nathan Smith Clinic Providers

The NSC has 23 providers. These include two physician assistants, one nurse practitioner, one board-certified pediatrician, and 19 physicians board-certified in internal medicine with or without board-certification in infectious diseases. Twenty (87.0%) of the 23 NSC providers completed the quiz that tested their knowledge and documentation of the side effects most commonly associated with each of five antiretrovirals (Appendix I). Two of the physicians did not take the quiz due to their involvement in the study design; a third physician was on leave at the time of the study. Table 6 describes the results of the quiz. Ten (50.0%) of the providers knew that efavirenz is potentially teratogenic. All 20 (100.0%) of the providers indicated that they routinely communicated potential serious adverse effects/reactions to the listed medications (including efavirenz) when they first prescribed them. Nine (45.0%) answered that they routinely documented their teaching to patients in the chart at the time of initial prescription.

TABLE 6. RESULTS OF THE MEDICATION-KNOWLEDGE QUIZ

Number of Nathan Smith Clinic providers to take the medication quiz (%)	20 (87.0)
Number who answered that efavirenz is potentially teratogenic (%)	10 (50.0)
Number who report communicating potential adverse reactions at initial prescription (%)	20 (100.0)
Number who report documenting their teaching at initial prescription (%)	9 (45.0)

Discussion

This study provides clear evidence that women of reproductive age are commonly prescribed efavirenz and are at risk of becoming pregnant and exposing their fetuses to a potentially teratogenic drug. Efavirenz has been used extensively among reproductive-age women in the Nathan Smith Clinic since its approval by the FDA in 1998, creating a large pool of potential exposures. Our survey of the NSC providers shows that half of

them were unaware of efavirenz's potential teratogenicity prior to our study and none of them documented a discussion of this serious adverse event with their patients.

Although 45% of the providers believed they routinely documented in the medical record their discussions of potential adverse effects with patients, only 21% of the women of reproductive age prescribed efavirenz had documentation of any discussion of its side effects at the time of initial prescription. Despite the FDA's recommendations that providers employ two forms of birth control including a barrier method and document a negative pregnancy test when prescribing efavirenz to women of childbearing age, the providers rarely documented birth control method and never documented a negative pregnancy test at the time of initial prescription of efavirenz. Most significantly, 3 of the 5 women referred to the HROC who became pregnant while taking efavirenz had either fetal demise or premature delivery.

A similar proportion of the young women treated at the Pediatric AIDS Clinic have also been prescribed efavirenz. Given that two young women treated at the PAC became pregnant during the study period, there is also the risk that these young women would expose their fetuses to efavirenz should the drug be prescribed for them without benefit of knowing their pregnancy status or the extent of their use of birth control.

Our assessment of women in the High Risk Obstetrics Clinic also demonstrates the potential for fetal exposure to efavirenz; four women seen in the clinic were taking efavirenz when they became pregnant. We did not document any serious central nervous system malformations among the fetuses exposed to efavirenz in utero; we did, however, document two instances of intrauterine fetal demise. The association of these events with the use of efavirenz cannot be evaluated.

As more women live longer and healthier lives in the era of HAART therapy, the desire to become pregnant may become increasingly common among HIV-positive women. Should more HIV-positive women choose to become pregnant, the results of our study would be all the more relevant to their future care. Our study does not, however, support this trend since the number of HIV-positive deliveries per year through the High-Risk Obstetrics Clinic has remained constant over the last three years.

The combination of efavirenz's extensive use, the incomplete knowledge of its potential teratogenicity on the part of the physicians prescribing it, the imperfect documentation of its potential teratogenicity and the need for proper birth control raises great concern for the children born to these women. Our study suggests a few interesting questions. How should physicians continue to learn about important side effects of new medications, a challenge particularly relevant to HIV care in which the number and interactions of the many antiretrovirals grows yearly? Does part of the burden of learning about new medications and new information about medications fall upon the companies that produce those medications or the FDA? Is there a legal obligation to document discussion of potential serious side effects upon prescribing a medication? Is documenting this discussion of potential serious side effects in the medical record of any benefit to the patient?

Expecting physicians to document a negative pregnancy test, birth control method, and their discussion of the potential teratogenicity upon prescribing efavirenz to a woman of reproductive age may seem excessive, particularly when the physicians in our study noted that they unfailingly explain potential side effects at the time when they prescribe new antiretrovirals. However, the medical community has decided that

documentation is absolutely necessary in cases of known teratogens. For example, the entry for thalidomide in the Physicians' Desk Reference (PDR) begins with an extensive warning of its teratogenic effects, and the drug is listed as contraindicated in women unless they receive both oral and written warnings of its teratogenicity, have a negative pregnancy test within 24 hours prior to beginning therapy, and can acknowledge in writing their understanding of the physician's warnings (23). A final question, then, is how much potential evidence of teratogenicity in humans due to a medication (such as the case report of the child exposed in utero to efavirenz born with myelomeningocele or the two intrauterine fetal demises encountered in our study) is needed before physicians should be obligated to document negative pregnancy tests, birth control methods, and understanding on the part of the patient of the potential teratogenicity of that medication (19)? The PDR does not currently contain warnings on efavirenz as obvious or powerful as those listed for thalidomide (23).

One potential solution to the problem of staying current with medications and their side effects is that as hospitals and clinics move to entirely computerized systems of record keeping, these systems could be used to teach physicians about the side effects of new medications. For instance, before a physician prescribes efavirenz through a computerized system, it could require her to work through a checklist in order to ensure that the patient is not at risk of serious side effects. Such a system might be cumbersome, but would guarantee that the physician was aware of potential adverse reactions. This system would also allow documentation of having discussed the potential side effects with the patient.

Our results suggest that the potential of exposing fetuses to efavirenz may be less than one might initially have presumed. Nearly 70% of the women who were prescribed efavirenz were 35 years of age or older, while 70% of the women who became pregnant and were treated in the High Risk Obstetrics Clinic were less than 35 years of age. The overlap of these two groups is small; the number of women who were likely to become pregnant while on efavirenz was therefore smaller than if efavirenz had been prescribed predominantly to younger women.

There have been studies suggesting that HIV-positive women suffer from menstrual abnormalities and undergo menopause earlier than their HIV-negative counterparts (24-28). Our study sample may have included women under 50 years of age who were peri- or post-menopausal. Thus, by using 50 years of age as our upper limit of childbearing potential, we might have overestimated the risk of efavirenz teratogenicity in our cohort.

Our retrospective assessment of the women treated in the High Risk Obstetrics Clinic is also limited. The two intrauterine fetal demises on efavirenz are of concern, but we cannot rule out other confounding factors nor can we reliably attribute these demises to efavirenz. While the early safety studies of efavirenz demonstrated central nervous system defects in subhuman primates, the prospective data from the Antiretroviral Pregnancy Registry demonstrate one case each of polydactyly, hepatosplenomegaly, hydronephrosis, and cerebral atrophy among children exposed in utero to efavirenz (14). We cannot be sure whether efavirenz could also cause chromosomal abnormalities such as Trisomy 18, as seen in one of the fetuses that was exposed to efavirenz and died. Additionally, our study is too small to detect a significant difference between the rate of

malformations seen in fetuses exposed to efavirenz and the rate recorded in the Antiretroviral Pregnancy Registry.

Our study was able, however, to detect a significant increase in the number of fetal events compared with that seen in data collected by the Antiretroviral Pregnancy Registry among women exposed in the first trimester to any antiretroviral therapy. This may represent a true difference in the rate of malformations seen in the groups, or it may reflect underreporting to the Antiretroviral Pregnancy Registry.

All of the NSC providers noted that they routinely communicated potential serious adverse effects of new medications to their patients. Luck *et al.* demonstrated that chart abstraction may underestimate the quality of care given to outpatients based on comparison with standardized patients (29). Therefore, our chart abstraction might have underestimated how many of the ten NSC providers who knew of efavirenz's teratogenicity communicated this potential adverse effect to their patients.

Further studies are needed to investigate the extensive use of efavirenz among HIV-positive women in the United States, and could also investigate the extent of knowledge of efavirenz's potential adverse effects among other physicians. Prospectively collected birth information, such as that accumulated by the Antiretroviral Pregnancy Registry, is invaluable in tracking the effects on fetuses of exposure to efavirenz in utero, and, within the context of its known limitations, may have much greater power in determining the human teratogenicity risk.

In summary, we found that efavirenz is prescribed widely among the HIV-positive women treated in an urban HIV clinic at an academic teaching hospital; that only half of the HIV-providers at the clinic were aware of efavirenz's potential teratogenicity;

and that potential adverse effects, the importance of birth control method, and a negative pregnancy test were seldom documented in the medical record at the time of initial prescription by the physicians. As HIV-positive women are increasingly supported in their desire to have children, clinicians need to understand, communicate, and document the potential teratogenic risks associated with efavirenz in particular and other antiretrovirals in general. The results of this study therefore suggest the need to develop both strategies that better inform physicians of the serious risks associated with some of the medicines they prescribe and better methods to remind them of these adverse reactions at the time they prescribe these medicines.

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Appendix I

Nathan Smith Provider Quiz

Please circle all that apply.

1. Which of the following are potential significant risks of the use of Abacavir?

- Thrombocytopenia	- GI Side Effects	- CNS Effects
- Peripheral Neuropathy	- Lactic Acidosis	- Stevens-Johnson
- Teratogenicity	- Pancreatitis	- Lipid abnormalities
- Hypersensitivity Reactions	- New Onset DM	

2. Which of the following are potential significant risks of the use of Efavirenz?

- Thrombocytopenia	- GI Side Effects	- CNS Effects
- Peripheral Neuropathy	- Lactic Acidosis	- Stevens-Johnson
- Teratogenicity	- Pancreatitis	- Lipid abnormalities
- Hypersensitivity Reactions	- New Onset DM	

3. Which of the following are potential significant risks of the use of Kaletra?

- Thrombocytopenia	- GI Side Effects	- CNS Effects
- Peripheral Neuropathy	- Lactic Acidosis	- Stevens-Johnson
- Teratogenicity	- Pancreatitis	- Lipid abnormalities
- Hypersensitivity Reactions	- New Onset DM	

4. Which of the following are potential significant risks of the use of Tenofovir?

- Thrombocytopenia	- GI Side Effects	- CNS Effects
- Peripheral Neuropathy	- Lactic Acidosis	- Stevens-Johnson
- Teratogenicity	- Pancreatitis	- Lipid abnormalities
- Hypersensitivity Reactions	- New Onset DM	

5. Which of the following are potential significant risks of the use of Nelfinavir?

- Thrombocytopenia	- GI Side Effects	- CNS Effects
- Peripheral Neuropathy	- Lactic Acidosis	- Stevens-Johnson
- Teratogenicity	- Pancreatitis	- Lipid abnormalities
- Hypersensitivity Reactions	- New Onset DM	

6. Do you routinely communicate potential serious adverse effects/reactions to these drugs when you first prescribe them to a patient? Yes _____ No_____

7. Do you routinely document your teaching of these adverse effects/reactions in the patient's chart? Yes_____ No_____