922

Pregnancy, efavirenz, and birth outcomes In Johannesburg, South Africa

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Abstract

Background: Efavirenz is a mainstay of first-line highly active antiretroviral therapy (HAART) in South Africa and elsewhere. Due to concerns about efavirenz teratogenicity, the drug is contraindicated in women with intentions to become pregnant; these women are typically initiated on nevirapine. Despite this, women who initiate HAART with efavirenz become pregnant during follow-up.

Methods: We analyzed prospectively collected data from the Themba Lethu Clinic, an urban HAART clinic in Johannesburg. We used Cox proportional hazards regression to examine risk factors for pregnancy after HAART initiation. We clinically investigated a subset of pregnancies in women receiving efavirenz for birth outcomes.

Results: Between 1 April 2004 and 31 March 2007, 5011 women initiated HAART in the Clinic; of those, 351 (7%) became pregnant, a rate of 4.1 pregnancies per 100 woman-years (95% confidence limits [CL] 3.7, 4.5). Rate of incident pregnancy during follow-up was lower among those aged >35 years, with a lower CD4 count, or employed. As expected, women who initiated HAART with efavirenz were less likely than nevirapine initiators to become pregnant (HR=0.6, 95% CL 0.4, 0.8). However the majority of pregnancies (68%, n=238) occurred in efavirenz initiators. Of these 238 pregnancies, 136 were investigated for pregnancy outcomes. There were 3 maternal deaths, 39 women were lost to follow-up or could not be contacted, 1 woman refused interview, and 12 women were still pregnant at time of interview. Of the remaining 81 pregnancies, 8 elected voluntary termination of the pregnancy, 13 experienced a miscarriage. There were 60 lives births of which 41 were examined using the Denver Developmental Screening Test. The Denver scale classified 30 infants as “within normal limits”, and 11 as “suspect” for neurodevelopment delay. No congenital abnormalities were found.

Conclusions: Pregnancy after initiation of efavirenz-based HAART is relatively common in our cohort. We found no evidence of congenital defects, but we found that over 25% of examined infants were suspect for neurodevelopmental delay. In addition, we found a relatively high risk of miscarriage. While further study including a formal comparison group is required to ascertain whether neurodevelopmental delays or miscarriages are attributable to efavirenz use rather than to HIV disease or to HAART generally, these results suggest that the risk of efavirenz in pregnancy may be less catastrophic than feared.

Background

- **Women of reproductive age comprise a plurality of patients receiving highly active antiretroviral therapy (HAART) in sub-Saharan Africa, and South Africa in particular**
- **Efavirenz is a mainstay of first-line HAART, but is thought to be teratogenic**
- **Women who intend to become pregnant are not prescribed efavirenz, but typically receive nevirapine**
- **However, many pregnancies among HIV+ women are unplanned, and early months of pregnancy may overlap with exposure to efavirenz**
- **The impact of efavirenz on births in this setting is unknown**
- **This research was conducted at the Themba Lethu Clinic, a large urban public-sector ART clinic in Johannesburg, South Africa, which provides HIV care to over 17,000 infected persons**

Methods

- **We analyzed prospectively collected data from the Themba Lethu Clinic, an urban HAART clinic in Johannesburg, South Africa.**
- **We examined women who initiated HAART between 1 April 2004 and 31 March 2007**
- **We used discrete time hazards models to examine risk factors for pregnancy after HAART initiation, using hazard ratios (HR) and 95% confidence limits (CL).**
- **We clinically investigated a subset of pregnancies in women receiving efavirenz for birth outcomes.**

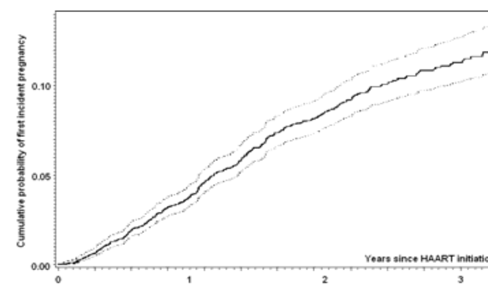
Results

Incident pregnancies:

5,011 women initiated HAART in study period

- There were 351 incident pregnancies, a rate of 4.1 (95% CL, 3.7, 4.5) /100 woman-years; see Figure (right) for incidence curve
- Risk factors for incident pregnancy are described in the Table below

Risk factors for pregnancy	Hazard ratio (95% CL)
Age > 35 years	0.17 (0.12, 0.24)
Employed	0.78 (0.61, 0.99)
Current CD4 count < 100 *vs. >200 cells/mm³*	0.63 (0.41, 0.97)
Current CD4 count 100-199 *vs. >200 cells/mm³*	0.90 (0.68, 1.20)
Use of efavirenz (EFV)	0.74 (0.56, 0.97)
Current low hemoglobin	0.94 (0.72, 1.23)
Pregnant at HAART initiation	0.68 (0.47, 0.99)
Free treatment	1.44 (0.88, 2.34)



Efavirenz-exposed pregnancies:

- Women receiving efavirenz were less likely than nevirapine initiators to become pregnant (Table 1)
- However the majority of pregnancies (68%, n=238) occurred in efavirenz initiators
- Of these, 136 investigated for pregnancy outcomes; 41 infants were analyzed for developmental delay
  - Denver Developmental Screening Test used
  - 30 infants “within normal limits”
  - 11 infants “suspect” for neurodevelopment delay
  - No congenital abnormalities were found among these 41 infants

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Discussion

- Pregnancy after initiation of efavirenz (EFV)-based HAART is relatively common in our cohort.
  - Many pregnancies in women receiving HAART may be unplanned.
- Over 25% of examined infants (n = 41) were suspect for neurodevelopmental delay. We found no evidence of congenital defects after EFV-exposed pregnancy; however, selection bias may be a factor here.
- A formal comparison group is required to ascertain whether neurodevelopmental delays or miscarriages are attributable to EFV rather than to HIV disease or to HAART generally.
- We found a relatively high risk of miscarriage (Abstract). In addition, if use of EFV were associated with an increased rate of early miscarriage, we would have failed to observe additional miscarriage events.
- Risk of EFV in pregnancy may be less catastrophic than feared.

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