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TDF-containing Antiretroviral Regimens in Pregnancy: Findings from the Antiretroviral Pregnancy Registry

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Introduction

- Tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor (NtRTI), is licensed for the treatment of HIV-1 infection and chronic hepatitis B infection in adults
- TDF is available in the following products:
  - TDF (Viread™)
  - FTC (emtricitabine)/TDF (Truvada™)
  - EFV (efavirenz)/FTC/TDF (Atripla™)
- TDF is classified as an FDA Pregnancy Category B drug
  - No evidence of risk to fetus in animal studies
  - No adequate and well-controlled studies in humans

Background

- TDF is recommended as a preferred component of initial regimens for chronic HIV infection by many treatment guidelines
- A zidovudine (ZDV)-based regimen, however, is still the recommended regimen for the treatment of HIV during pregnancy or for the prevention of mother to child transmission by many guidelines
- Although TDF-containing regimens have been shown to be well tolerated in pregnancy and reduce mother-to-child transmission of HIV-1 in animal models and in humans[1-4], additional data on the use of TDF-containing regimens during pregnancy are needed

Antiretroviral Pregnancy Registry (APR)

- APR is an international prospective exposure-registration cohort study established in January 1989 to monitor major teratogenic effects of any HIV and HBV drug in the Registry following exposure during pregnancy
- Reporting is voluntary; data are not verified
- An independent advisory committee of members from CDC, FDA, and NIH provides oversight of APR scientific conduct and analysis
- Interim primary analysis reports are issued semi-annually
  - Pregnancy must be prospectively registered with the APR
  - Pregnancy outcome must be known and reported to the APR
- Majority of cases are reported from the US
  - Approximately 1300 new cases from the US and 200 new cases from other countries are added annually
- APR interim report issued December 2008 collected 11,950 prospective cases (includes data from January 1,1989 through July 31, 2008)[5]
- APR began collecting data on exposure to TDF in 2001

Objectives

- To compare baseline demographics between pregnant women exposed to TDF-based regimens and those exposed to all drugs registered in APR
- To identify birth defect rates for infants with *in utero* exposure to APR-registered drugs, by class and by individual drugs, using the APR data
- To compare birth defect rates with exposure to TDF-based regimens to that with exposure to other APR registered drugs

Methods

- Use cumulative APR data that meet primary analysis inclusion criteria up to 31 July 2008
- Compare baseline demographics between pregnant women exposed to TDF-based regimens and those exposed to all drugs registered in the APR
- Compare overall APR birth defect rate to CDC's population-based birth defect rate
- Compare birth defect rate of:
  - 1st trimester NtRTI exposure to that of other drug classes in the APR in live births
  - 1st trimester NtRTI exposure to that of all APR-registered drugs in non-live births
  - TDF-based regimens exposure to that of all APR-registered drugs in 1st or 2nd/3rd trimester

Methods (cont'd)

APR Sample Size and Statistical Considerations

- Compared to CDC's expected prevalence, with 80% power and a Type 1 error rate of 5%
  - A cohort of 200 newborns exposed to antiretroviral (ARV) drugs in the 1st trimester is sufficient to detect a 2.2-fold increased risk of overall birth defects
  - A cohort of 1000 newborns exposed to ARV drugs in the 1st trimester is sufficient to detect a 1.5-fold increased risk of overall birth defects

Results

Table 1. Population for Analysis - Prospective Registry Cases
(Enrolled January 1, 1989 Through 31 July 2008)

	All Drugs in APR	TDF-based Regimen in APR
Pregnancy Enrolled	11950	1146
Pending Cases	494 (4.1%)	3 (0.3%)
Cases Lost to Follow-up	985 (8.2%)	87 (7.6%)
Cases Used in Analysis	10471 (87.6%)	1056 (92.1%)

Table 2. APR Primary Analysis Cases: Maternal Demographics at Registration

Pregnancies Enrolled		All Drugs N=10471	TDF-based N=1056
Median Age (interquartile range)		28.0 (9.0) yrs	30.0 (8.0) yrs
CD4+ T-Cell Count at Start of Pregnancy	≥ 500 cells/µL	3204 (30.6%)	247 (23.4%)
	200-499 cells/µL	4811 (45.9%)	517 (49.0%)
	<200 cells/µL	1902 (18.2%)	234 (22.2%)
HIV Infected	A. Asymptomatic, acute (primary) HIV or PGL[a]	7591 (72.5%)	588 (55.7%)
	B. Symptomatic, not (A) or (C)	963 (9.2%)	59 (5.6%)
	C. AIDS-indicator conditions	1341 (12.8%)	354 (33.5%)
HIV Uninfected	HIV post-exposure prophylaxis	28 (0.3%)	0
	Hepatitis B mono-infected[b]	71 (0.7%)	3 (0.3%)

a. Persistent generalized lymphadenopathy
b. APR started systematically collecting data on HBV in January 2003

Table 3. Demographics: TDF-based Regimens (Primary Analysis, N=1056)

Race	
Black	671 (63.5%)
Hispanic	175 (16.6%)
White	130 (12.3%)
Asian	18 (1.7%)
Other	24 (2.3%)
Missing	38 (3.6%)

Birth Defect Prevalence: APR Data vs CDC's MACDP Data

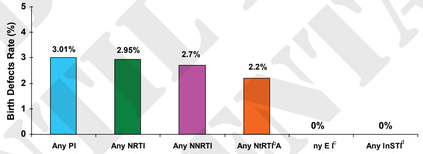
- Overall birth defect prevalence following exposure to any APR registered drugs during any trimester is 2.7% (272/9948)[5]
- CDC's population-based birth defects surveillance system, the Metropolitan Atlanta Congenital Defects Program (MACDP) reported total prevalence of birth defects of 2.72% of live births (1989-2003)

Results (cont'd)

Table 4. Birth Defect Prevalences for First Trimester Exposure to ARVs with ≥ 200 Reported Exposures[5]

ARVs	Defects/Live Births	Prevalence, % (95%CI)
Abacavir	18/578	3.1 (1.9, 4.9)
Atazanavir	5/246	2.0 (0.7, 4.7)
Didanosine	16/362	4.4 (2.5, 7.1)
Efavirenz	13/407	3.2 (1.7, 5.4)
Emtricitabine	8/252	3.2 (1.4, 6.2)
Indinavir	6/275	2.2 (0.8, 4.7)
Lamivudine	91/3089	2.9 (2.4, 3.6)
Lopinavir	8/420	1.9 (0.8, 3.7)
Nelfinavir	37/1066	3.5 (2.5, 4.8)
Nevirapine	18/785	2.3 (1.4, 3.6)
Ritonavir	18/783	2.3 (1.4, 3.6)
Stavudine	19/696	2.7 (1.7, 4.2)
Tenofovir DF	**14/606**	**2.3 (1.3, 3.9)**
Zidovudine	94/3068	3.1 (2.5, 3.7)

Figure 1. Birth Defect Rates for First-Trimester Exposure, By Antiretroviral Therapy Class Regimen[a]



a. As any individual ARV may have been used in combination with other ARVs, the count represents the number of outcomes with at least one exposure in that class; data collection January 1, 1989 through July 31, 2008; APR interim report issued December 2008
b. NtRTI includes TDF (n=606), ADV (n=30)
c. EI=entry inhibitor
d. InSTI=integrase strand transfer inhibitor

Table 5. Number of Birth Defects in Non-Live Births a with First Trimester Exposure to NtRTI Regimensand to All APR Drugs[5]

	TDF/ADV (Any NtRTI) (Total Outcomes[b] = 775)		All Drugs in the Registry (Total Outcomes = 4,958)	
	Birth Defects (N)	Non-Live Births (N)[c]	Birth Defects (N)	Non-Live Births (N)[d]
Spontaneous Losses	0	56	0	221
Stillbirths	0	21	3 (4.2%)[e]	72
Induced Abortions	0	69	4 (1.2%)[e]	336

a. Defined as a stillborn infant, or a spontaneous or induced abortion ≥ 20 weeks gestation
b. Total outcomes include live births and non-live births
c. Total number of non-live births = 146
d. Total number of non-live births = 629
e. Percentage of non-live births

Table 6. Birth Defect Rates By Trimester of Earliest Exposure to TDF Regimens and All Drugs in the Registry

Earliest Exposure to Drugs		All APR-registered Drugs	All TDF Regimens	TDF+FTC +3rd agent[a]	TDF+FTC +EFV[b]
1st Trimester	**Number of Defects/ Live Births**	126/4329	14/606	6/219	0/4
	Prevalence (95% CI)	2.9% (2.4 - 3.5)	2.3% (1.3 - 3.9)	2.7%	0
2nd/3rd Trimester	**Number of Defects/ Live Births**	145/5618	5/336	2/118	0/1
	Prevalence (95% CI)	2.6% (2.2 - 3.0)	1.5% (0.5 -3.4)	1.7%	0
Total	**Number of Defects/ Live Births**	271/9947	19/942	8/337	0/5
	Prevalence	2.72%	2.02%	2.37%	0%

a. An antiretroviral medication other than efavirenz
b. Efavirenz (EFV) is FDA pregnancy class D drug, pregnancy should be avoided in women receiving EFV

Table 7. Birth Defect Rates Among HIV Mono-infection Women Exposed to TDF-based Regimen During Pregnancy (Comparing to Overall APR Prevalence)

Earliest Exposure to Drugs		All APR-registered Drugs[a]	TDF+FTC +3rd agent[b]	TDF+FTC +EFV[c]	Any other TDF Regimens
Any Trimester[a]	**Number of Defects/ Live Births**	272/9948	7/321	0/5	8/556
	Prevalence (95% CI)	2.7% (2.4-3.1)	2.2% (0.9 – 4.5)	0	1.4% (0.6 – 2.8)

a. One additional case with birth defects not able to be accounted under a specific trimester due to unknown trimester of exposure data
b. An antiretroviral medication other than efavirenz
c. Efavirenz (EFV) is FDA pregnancy class D drug, pregnancy should be avoided in women receiving EFV

APR Advisory Committee Consensus
Primary Registry Analysis (Prospective Reports)[5]

- For the overall population exposed to antiretroviral drugs in this Registry, no increases in risk of overall birth defects or specific defects have been detected to date when compared with observed rates for "early diagnoses" in population-based birth defects surveillance systems or with rates among those with earliest exposure in the second or third trimester
- In analyzing individual drugs with sufficient data to warrant a separate analysis, no increases in risk have been detected, with the exception of didanosine during previous years. No pattern of birth defects has been detected with didanosine, and no new reports of defects with didanosine exposure have been received in recent reporting periods
- For abacavir, atazanavir, efavirenz, emtricitabine, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, and tenofovir DF, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date
- For lamivudine and zidovudine, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date, with the exception of hypospadias following first trimester exposure to zidovudine from the addition of the Women and Infants Transmission Study (WITS) data. With additional accrual of first trimester exposures, this finding has not persisted. The Registry has received a total of 407 live births with first trimester exposure to efavirenz. During this reporting period, the Registry received a first case of anophthalmia, a defect reported in a study in monkeys. However, this case also included severe oblique facial clefts and amniotic banding, a known association with anophthalmia
- While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients

Limitations of APR Data

- Underreporting (i.e., not every report of an exposure is obtained)
- Differential reporting (e.g., there may be reasons why one report would be provided to the Registry and another would not)
- Under ascertainment of birth defects (e.g., not every birth defect is identified, reporter may not see the defect at birth)
- Differential ascertainment of birth defects (e.g., variable use of diagnostic tests)
- Loss to follow up (e.g., no outcome information is obtained)
- Lack of power to detect the risk of relatively rare birth defects
- Small number of cases of HBV mono-infection or co-infection

Conclusions

- **Prevalence of birth defects among women with 1st-trimester exposure to APR-registered drugs (2.9%) is similar to prevalence of defects with the first exposure during the 2nd/3rd trimesters (2.6%)**
- **Overall Birth defect prevalence with exposure to TDF regimens (2.02%) is similar to birth defect rate (or prevalence) for all drugs in the APR (2.7%). In addition, this is comparable to the CDC population-based surveillance data (2.72%)**
  - **Earliest exposure in the 1st trimester was similar for all TDF-based regimens 2.3%, TDF/FTC-based regimens 2.7%, all regimens in the APR 2.9%**
  - **The majority of of individuals receiving TDF were African American 63.5% and Hispanic 16.6%**
- **No specific patterns of birth defects were observed**
- **No defects in non-live births were reported with 1st-trimester use of TDF-based regimens**
- **It is critical to monitor birth defects among infants born to women with exposure to ARVs and anti-HBV drugs during pregnancy to prospectively assess the safety of these agents**

APR Contact Information

Health care providers are encouraged to report pregnancy exposures to ARVs and anti-HBV drugs to the APR

APR website: www.APRegistry.com

Phone/Fax contacts:

US, Canada:	**(800) 258-4263 (Phone)** **(800) 800-1052 (Fax)**
International:	+1-910-256-0238 (Phone) +1-910-256-0637 (Fax)
UK, Germany, France:	(00800) 5913-1359 (Phone) (00800) 5812-1658 (Fax)
Europe:	+32-2-714-5028 (Phone) +32-2-714-5024 (Fax)
Brazil:	(888) 259-5618 (Fax)

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