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Tenofovir Disoproxil Fumarate-Containing Regimens in Pregnancy: Report 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 chronic HIV-1 infection and chronic hepatitis B infection in adults
- TDF is classified as a Food and Drug Administration (FDA) Pregnancy Category B drug
  - No evidence of risk to fetus in animal studies
  - No adequate and well-controlled studies in humans
- TDF-containing regimens are well tolerated in pregnancy and reduce mother-to-child transmission (MTCT) of HIV-1 in animal models and in humans[1-4]

1. European Collaborative Study. Clin Infect Dis. 2005; 40(3):458-65;
2. European Collaborative Study. J Acquir Immune Defic Syndr. 2003; 32(4):380-387;
3. Cooper ER, et al. JAIDS. 2002; 29:484-494;
4. Centers for Disease Control and Prevention. MMWR. June 2, 2006; 55(21):592-597.

Antiretroviral Pregnancy Registry (APR)

- APR is an international prospective exposure-registration cohort study established in January 1989 to monitor major teratogenic effects of antiretroviral (ARV) drugs and anti-HBV drugs following exposure during pregnancy
- Reporting is voluntary; data are not verified
- Majority of cases (87.5%) are reported from the US
  - Approximately 1,300 new cases from the US and 200 new cases from other countries are added annually
- Interim primary analysis reports are issued semiannually
  - Current APR interim report includes 12,451 prospective cases (includes data from January 1,1989 through January 31, 2009)
- Inclusion criteria (primary analysis)
  - Pregnancy must be prospectively registered with the APR
  - Pregnancy outcome must be known and reported to the APR
- An independent advisory committee of members from Centers for Disease Control and Prevention (CDC), FDA, and National Institute of Health (NIH) provides oversight of APR scientific conduct and analysis
- APR began collecting data on exposure to tenofovir disoproxil fumarate (TDF) in 2001

Study Objectives

- To identify birth defect rates for infants with in utero exposure to TDF regimens
- Compare birth defect rates:
  - 1st trimester NtRTI regimen (tenofovir DF, adefovir dipivoxil) exposure vs. other ARV classes
  - 1st, or 2nd or 3rd, trimester TDF regimen exposure vs. all ARV regimens
  - 1st vs. 2nd or 3rd trimester exposure to TDF regimen and all other ARV regimens
  - All TDF regimen exposure vs. population-based control

APR Sample Size and Statistical Considerations

- Compared to CDC's expected prevalence for a general US population, with 80% power and a Type I error rate of 5%
  - A cohort of 200 newborns exposed to ARV drugs in the 1st trimester is sufficient to detect a 2.2-fold increased risk of overall birth defects
  - A cohort of 1,000 newborns exposed to ARV drugs in the 1st trimester is sufficient to detect a 1.5-fold increased risk of overall birth defects

Primary Registry Analysis

Population for Analysis – Prospective Registry Cases (Enrolled January 1, 1989 Through January 31, 2009)	
Pregnancies Enrolled	12451
Pending Cases[a]	426 (3.4%)
Cases Lost to Follow-Up[b]	1082 (8.7%)
Reports Used in Analysis	10942 (87.9%)

a. Cases where the outcome of pregnancy is not yet known
b. Cases where the outcome of pregnancy has never been received, despite requests, or in which the reporter did not know whether there was a birth defect

Table 1. APR Primary Analysis Cases Maternal Demographics at Registration (Pregnancies Enrolled=10,942)

Median Age (interquartile range)		28.0 (8.0) yrs
CD4+ T-Cell Count at Start of Pregnancy	≥500 cells/μL	3337 (30.5%)
	200-499 cells/μL	5028 (46%)
	<200 cells/μL	1971 (18%)
HIV Infected[a]	A. Asymptomatic, acute (primary) HIV or PGL[b]	7890 (72.1%)
	B. Symptomatic, not (A) or (C)	981 (9%)
	C. AIDS-indicator conditions	1443 (13.2%)
HIV Uninfected[c]	HIV post-exposure prophylaxis	28 (0.3%)
	Hepatitis B mono-infected	89 (0.8%)

a. Includes 111 patients co-infected with HIV and hepatitis B
b. Persistent generalized lymphadenopathy
c. Where ARV drugs have been used for therapy
Note: APR started systematically collecting data on HBV in January 2003

Results

Table 2. TDF Regimens Maternal Demographics at Registration (Pregnancies Enrolled=1,186)

Median Age (interquartile range)		30.0 (8.0) yrs
Race	Black	749 (63.2%)
	Hispanic	193 (16.3%)
	White	140 (11.8%)
	Asian	26 (2.2%)
	Other	31 (2.6%)
CD4+ T-Cell Count at Start of Pregnancy	≥500 cells/μL	276 (23.3%)
	200-499 cells/μL	580 (48.9%)
	<200 cells/μL	254 (21.4%)
HIV Infected[a]	A. Asymptomatic, acute (primary) HIV or PGL[b]	672 (56.7%)
	B. Symptomatic, not (A) or (C)	68 (5.7%)
	C. AIDS-indicator conditions	372 (31.4%)
HIV Uninfected[c]	HIV post-exposure prophylaxis	0
	Hepatitis B mono-infected	8 (0.7%)

a. Includes 30 patients co-infected with HIV and hepatitis B
b. Persistent generalized lymphadenopathy
c. Where ARV drugs have been used for therapy
Note: APR started systematically collecting data on HBV in January 2003

Table 3. Birth Defect[a] Rates in APR and in Large Prospective Cohort Studies of HIV-Infected Pregnant Women with Exposure to ARV Medications

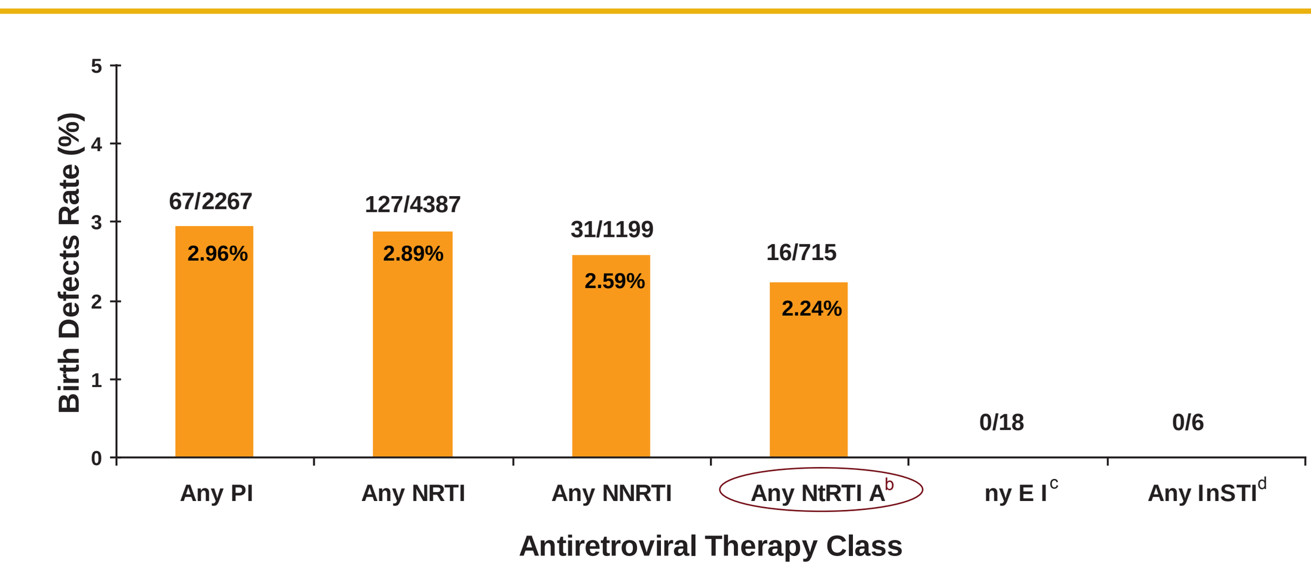
Earliest Exposure to ARVs		APR[b]	UK and Ireland Surveillance[c]	European Collaborative Study[c]
1st Trimester	Number of Defects/ Live Births	130/4530	45/1236	18/880
	Prevalence (95% CI)	2.9% (2.4 - 3.4)	3.6% (2.7 - 4.9)	2.0% (1.2 - 3.2)
2nd or 3rd Trimester	Number of Defects/ Live Births	147/5874	114/4162	21/1765
	Prevalence (95% CI)	2.5% (2.1 - 2.9)	2.7% (2.3 - 3.3)	1.2% (0.7 - 1.8)
Any Trimester	Number of Defects/ Live Births	278/10405	159/5398	39/2645
	Prevalence (95% CI)	2.7% (2.4 - 3.0)	2.9% (2.5 - 3.4)	1.5% (1.1 - 2.0)

a. Defects meeting the CDC criteria only. Excludes reported defects in pregnancy losses <20 weeks
b. Reporting period of January 1, 1989 – January 31, 2009
c. As reported in the APR interim report; data were collected December 1984 – March 2007

Comparison to a Population-Based Birth Defect Rate

- Comparison to CDC's population-based birth defects surveillance system, the Metropolitan Atlanta Congenital Defects Program (MACDP)
- MACDP actively searches for birth defects among all births in five counties of metropolitan Atlanta area (approximately 50,000 annual births)
- MACDP reported total prevalence of birth defects of 2.72% of live births (1989 – 2003)

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 – January 31, 2009; APR interim report issued June 2009
b. NtRTI includes TDF (n=678), ADV (n=37)
c. EI=entry inhibitor
d. InSTI=integrase strand transfer inhibitor

Table 4. Birth Defect Prevalences for First Trimester Exposure to Anti-HBV Drugs[a]

Regimen	Defects/Live Births	Prevalence, % (95%CI)
Lamivudine	93/3226	2.9 (2.3, 3.5)
Tenofovir DF	16/678	2.4 (1.4, 3.8)
Adefovir dipivoxil	0/37	0
Entecavir	0/8	0
Telbivudine	0/3	0

a. Data collected January 1, 1989 – January 31, 2009; APR interim report issued June 2009

Table 5. Birth Defect[a] Rates By Trimester of Earliest Exposure to TDF Regimens and All ARV Regimens in APR[b]

Earliest Exposure to ARVs		TDF Regimens	All ARV Regimens
1st Trimester	Number of Defects/ Live Births	16/678	130/4530
	Prevalence (95% CI)	2.4% (1.4 - 3.8)	2.9% (2.4 - 3.4)
2nd or 3rd Trimester	Number of Defects/ Live Births	6/385	147/5874
	Prevalence (95% CI)	1.6% (0.6 -3.4)	2.5% (2.1 - 2.9)

a. Defects meeting CDC criteria only. Excludes reported defects in abortions <20 weeks
b. Data collected January 1, 1989 – January 31, 2009; APR interim report issued June 2009

Table 6. TDF Regimens (Prospective Registry Cases in Any TDF Regimen[a])

	Pregnancies Enrolled	Pending Cases[b]	Cases Lost to Follow-Up[c]	Reports Used in Analysis
All Infections	1301	2	113	1186
HIV Monoinfection	1157 (88.9%)	0	74 (65.5%)	1083 (91.3%)
HIV/HBV Co-Infection	30 (2.3%)	0	1 (0.9%)	29 (2.4%)
HBV Monoinfection	9 (0.7%)	0	1 (0.9%)	8 (0.7%)

a. Enrolled through January 31, 2009
b. Cases where the outcome of pregnancy is not yet known
c. Cases where the outcome of pregnancy has never been received, despite requests, or in which the reporter did not know whether there was a birth defect

Table 7. Summary of Pregnancy Outcomes[a]: TDF Regimens

	With Birth Defects[b]:Without Birth Defects[c]				
	Live Births	Spontaneous Losses	Stillbirth	Induced Abortions	Overall
Number of Outcomes[d]	20:1045	0:61	0:27	2:61	1216
Earliest Exposure[e]					
1st Trimester	15:663	0:59	0:23	1:60	821
2nd or 3rd Trimester	5:380	0:1	0:4	1:1	392
1st Trimester: All Infections	15:663	0:59	0:23	1:60	821
HIV Monoinfection	10:612	0:49	0:23	1:46	741
HIV/HBV Co-infection	2:17	0:0	0:0	0:1	20
HBV Monoinfection	1:2	0:0	0:0	0:0	3

a. Outcome defined as a live or stillborn infant, or spontaneous or induced abortion ≥20 weeks gestation
b. Defects meeting CDC criteria only. Excludes reported defects in abortions <20 weeks
c. Includes cases where the occurrence of a birth defect was not reported
d. Includes 30 multiple births
e. Data is not included for birth defect cases with an unknown trimester of exposure

Table 8. Number of Birth Defects[a] by Earliest Exposure: TDF Regimens

	Earliest Trimester of Exposure					
	1st Trimester		2nd or 3rd Trimester		Overall	
	Defects/ Live Births	Prevalence (95% CI)[b]	Defects/ Live Births	Prevalence (95% CI)[b]	Defects/ Live Births	Prevalence (95% CI)[b]
Proportion of Defects Reported with Exposure to any TDF Regimen[c,d]	16/678	2.4% (1.4%, 3.8%)	6/385	1.6% (0.6%, 3.4%)	22/1065	2.1% (1.3%, 3.1%)
All Infections	16/678	2.4% (1.4%, 3.8%)	6/385	1.6% (0.6%, 3.4%)	22/1065	2.1% (1.3%, 3.1%)
HIV Monoinfection	11/622	1.8% (0.9%, 3.2%)	6/364	1.6% (0.6%, 3.6%)	17/986	1.7% (1.0%, 2.8%)
HIV/HBV Co-infection	2/19	*	0/10	*	2/29	*
HBV Monoinfection	1/3	*	0/5	*	1/8	*

a. Defects meeting CDC criteria only. Excludes reported defects in abortions <20 weeks
b. Prevalence and 95% confidence intervals are reported for 1st trimester exposures to drugs that have a denominator of ≥200
c. Includes cases where the occurrence of a birth defect was not reported
d. Includes 30 multiple births
* Prevalence and 95% confidence intervals are not reported because no regimen has 1st trimester exposure with a denominator of ≥200
Note: For each category of infection status and category of TDF regimen within infection status, counts are mutually exclusive

EMBARGOED UNTIL AFTER PRESENTATION

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

- In analyzing individual drugs with sufficient data to warrant a separate analysis, no increases in risk have been detected.
- For abacavir, atazanavir, efavirenz, emtricitabine, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, stavudine, and tenofovir, 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.

a. Data collected January 1, 1989 – January 31, 2009; APR interim report issued June 2009

Limitations of APR Data

- Limitations of the APR include, but are not limited to:
  - 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)

Conclusions

- **Antiretroviral Pregnancy Registry overall birth defect prevalence is the same as the Centers for Disease Control and Prevention population-based surveillance data (2.7%). No specific patterns of birth defects were observed in all antiretroviral regimens**
- **Birth defect prevalence with 1st-trimester exposure to nucleotide reverse transcriptase class is similar to other antiretroviral classes**
- **Birth defect prevalence is similar between 1st trimester vs. 2nd or 3rd trimester for tenofovir disoproxil fumarate-containing regimens, and between tenofovir disoproxil fumarate-containing regimens vs. all antiretroviral regimens within 1st, or 2nd or 3rd, trimester**
  - **Earliest exposure in the 1st trimester (tenofovir disoproxil fumarate-containing regimens 2.4%, all antiretroviral regimens 2.9%)**
  - **Earliest exposure in the 2nd or 3rd trimester (tenofovir disoproxil fumarate-containing regimens 1.6%, all antiretroviral regimens 2.5%)**
- **Monitoring of birth defects among infants born to women with exposure to antiretrovirals and anti-hepatitis B virus drugs during pregnancy is important**
- **In this largest-known registry to date, there are limited data for the use of anti-hepatitis B virus drugs in hepatitis B virus mono-infected pregnant patients**
- **It is recommended that physicians report pregnancy exposures to antiretrovirals and anti-hepatitis B virus drugs to the Antiretroviral Pregnancy Registry**

APR Advisory Consensus Statement[a]

"In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral drugs exposure, the Registry finds that the defects reported show no apparent increases in frequency and no pattern to suggest a common cause. 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. However, potential limitations of registries such as this one should be recognized. The Registry is ongoing. Health care providers are encouraged to report eligible patients to the Registry at www.APRegistry.com."

a. Data collected January 1, 1989 – January 31, 2009; APR interim report issued June 2009

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)
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Brazil:	(888) 259-5618 (Fax)