

Introduction

- Tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor (NtRTI), has been widely used in combination with other antiretroviral drugs for the treatment of chronic HIV-1 infection in adults
- TDF is available in the following products:
 - TDF (Viread)
 - FTC (emtricitabine)/TDF (Truvada)
 - EFV (efavirenz)/FTC/TDF (Atripla)
- TDF was recently approved for the treatment of chronic hepatitis B infection (HBV) in the EU region in April 2008 and in the U.S. in August 2008
- TDF is classified as an FDA Pregnancy Category B drug (i.e. no evidence of risk in animal studies; no adequate and well-controlled studies in humans)

Background

- Antiretrovirals (ARVs) were first demonstrated to reduce mother-to-child transmission of HIV in ACTG Study 076, a study of zidovudine (ZDV) monotherapy compared to placebo, which was published in 1994¹
- The CDC currently recommends ZDV and lamivudine (3TC) as the preferred dual NRTI backbone for use in combination antiretroviral regimens in pregnancy, while ZDV/3TC is no longer recommended as a preferred component of initial therapy for non-pregnant women^{2,3}
- Use of TDF-containing regimens in pregnancy and inclusion of TDF in treatment strategies for the Prevention of Maternal To Child Transmission (PMTCT) have been demonstrated to be well tolerated while reducing MTCT both in animal models and in humans^{4,5,6,7}
- Birth defect rates in infants exposed *in utero* to ARVs are studied and reported in a number of settings, including the Antiretroviral Pregnancy Registry

Antiretroviral Pregnancy Registry (APR) Background

- An international prospective exposure-registration cohort study established in January 1989 to monitor major teratogenic effects of ARV drugs following exposure during pregnancy
- Interim Primary Analysis reports are issued biannually
- Inclusion criteria (for the Primary Analysis)
 - The pregnancy must be prospectively registered with the APR
 - Pregnancy outcome must be known and reported to the APR
- An independent advisory committee consisting of members from CDC, FDA, and NIH provides oversight of the APR for scientific conduct and analysis
- The current APR interim report has collected 11209 prospective cases and includes data from January 1989 through January 31, 2008
- APR began collecting data from exposure to TDF in 2001

Study Objectives

- To identify birth defect rates for infants with maternal exposure to ARVs by class, and by individual drugs using the Antiretroviral Pregnancy Registry
- To compare birth defect rates with TDF exposure to that of other ARV exposure

Methods

Based upon data from the primary analysis in the January 2008 interim APR report:

- Identify overall birth defect rate for exposure to ARVs registered in the APR
- Compare birth defect rate of:
 - 1st trimester NtRTI exposure to that of other ARV class exposure
 - 1st trimester NtRTI exposure to that of all ARVs in non-live births
 - Earliest TDF exposure to that of all ARVs in 1st or 2nd/3rd trimester

APR Statistical Sample Size 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 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. APR Primary Analysis Cases Maternal Demographics at Registration

Pregnancies Enrolled	9889 ^a	
Median Age (interquartile range)	28.0 (9.0) years	
CD4+ T-Cell at start of pregnancy	≥ 500 cells/μL	3014 (30.5%)
	200-499 cells/μL	4531 (45.8%)
	<200 cells/μL	1830 (18.5%)
HIV Infected^b	A. Asymptomatic, acute HIV or Persistent Generalized Lymphadenopathy	7219 (73%)
	B. Symptomatic, not (A) or (C)	922 (9.3%)
	C. AIDS- indicator	1208 (12.2%)
HIV Uninfected^c	HIV post-exposure prophylaxis	26 (0.3%)
	Hepatitis B mono-infected	61 (0.6%)

a. 11209 registered, 889 lost to follow-up, 431 outcome pending
b. Among cases prospectively registered in APR, 98 patients co-infected with HIV and HBV
c. APR started systematically collecting data on HBV in Jan. 2003

Table 2. Birth Defect Rates in APR and in Large Prospective Cohort Studies of HIV-Infected Pregnant Women with Exposure to ARV Medications

Earliest Exposure to ARVs		APR	UK and Ireland Surveillance ^a	European Collaborative Study ^a
1 st trimester	Number of defects/live births	117/3951	45/1236	18/880
	Prevalence (95% CI)	3.0% (2.5 - 3.5)	3.6% (2.7 - 4.9)	2.0% (1.2 - 3.2)
2 nd /3 rd trimester	Number of defects/live births	143/5446	114/4162	21/1765
	Prevalence (95% CI)	2.6% (2.2 - 3.1)	2.7% (2.3 - 3.3)	1.2% (0.7 - 1.8)
Any Trimester	Number of defects/live births	260/9397	159/5398	39/2645
	Prevalence (95% CI)	2.8% (2.5 - 3.1)	2.9% (2.5 - 3.4)	1.5% (1.1 - 2.0)

a. As reported in the APR interim report; data was collected December 1984-March 2007

Results (cont'd)

Comparison to a Population-based Birth Defect Rate

- 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)
 - MACDP actively searches for birth defects among all births in five counties of metropolitan Atlanta area with approximately 50,000 annual births

APR Advisory Consensus Statement

- 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 diagnosis" in population-based birth defects surveillance systems or with rates among those with earliest exposure in the second or third trimester

Figure 1. Birth Defect Rates for First Trimester Exposure by Antiretroviral Therapy Class^a

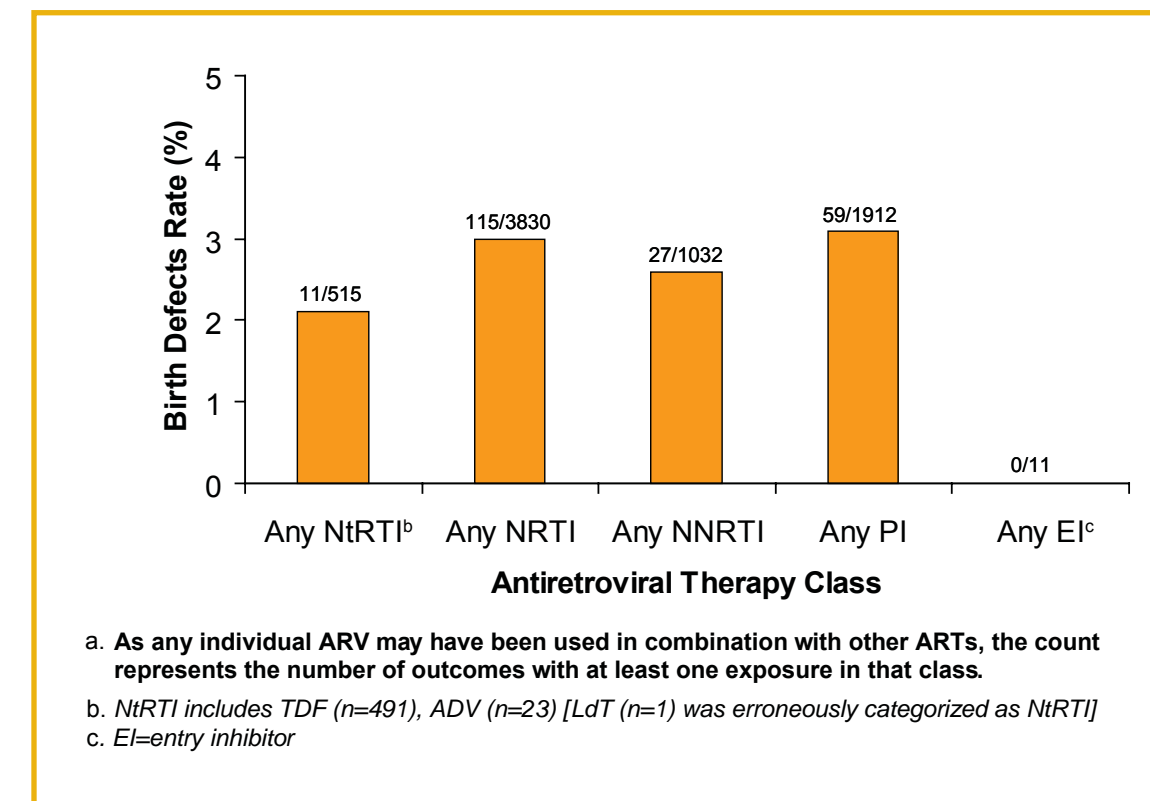


Table 3. Number of Birth Defects in Non-Live Births^a with 1st Trimester Exposure to NtRTI and to All ARVs

	NtRTI (Total outcomes ^b = 641)		All ARVs (Total Outcomes = 4,538)	
	Birth defects (N)	Non-live Births (N)	Birth defects (N)	Non-live Births (N)
Spontaneous Losses	0	44	0	199
Still Birth	0	20	3	69
Induced Abortions	0	62	4	319

a. Defined as a stillborn infant, or a spontaneous or induced abortion ≥ 20 weeks gestation
b. Total outcomes includes live births and non-live births

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

Regimen	Defects/Live Births	Prevalence % (95%CI)
Zidovudine	87/2808	3.1 (2.5, 3.8)
Lamivudine	85/2784	3.1 (2.4, 3.8)
Nelfinavir	33/972	3.4 (2.3, 4.7)
Nevirapine	18/737	2.4 (1.5, 3.8)
Stavudine	19/651	2.9 (1.8, 4.5)
Ritonavir	16/628	2.5 (1.5, 4.1)
Abacavir	17/512	3.3 (1.9, 5.3)
Tenofovir	11/491	2.2 (1.1, 4.0)
Efavirenz	10/364	2.7 (1.3, 5.0)
Didanosine	16/353	4.5 (2.6, 7.3)
Lopinavir	6/328	1.8 (0.7, 3.9)
Indinavir	6/272	2.2 (0.8, 4.7)

APR Advisory Committee Consensus Primary Registry Analysis (Prospective Reports)

- In analyzing individual drugs with sufficient data to warrant a separate analysis, an increased frequency for birth defects has been detected for didanosine only
- For abacavir, efavirenz, 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 with the exception of hypospadias following first trimester exposure to zidovudine from the addition of the Women and Infants Transmission Study (WITS) data**

Table 5. Birth Defect Rates By Trimester of Earliest Exposure to TDF and All ARV Medications in APR

Earliest Exposure to ARVs		TDF	All ARVs
1 st trimester	Number of defects/live births	11/491	117/3951
	Prevalence (95% CI)	2.2% (1.1 - 4.0)	3.0% (2.5 - 3.5)
2 nd /3 rd trimester	Number of defects/live births	4/309	143/5446
	Prevalence (95% CI)	1.3% (0.4 - 3.3)	2.6% (2.2 - 3.1)

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 (i.e., there may be reasons why one report would be provided to the Registry and another would not)
 - Under ascertainment of birth defects (i.e., not every birth defect is identified, e.g., 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., reports where no outcome information is obtained)
 - Data collected is not sufficient to detect an increase in the risk of relatively rare events

Conclusions

- APR overall birth defect prevalence (2.8%) was comparable to that of other large prospective cohort studies of newborns with prenatal exposure to ARVs (2.9% and 1.5%) and to general population-based surveillance data (2.72%)**
- Birth defect prevalence with 1st trimester exposure to NtRTI class (TDF or ADV) was similar to that of 1st trimester exposure to other ARV classes**
- Birth defect prevalence with exposure to TDF was similar to birth defect rate with exposure to all ARVs**
 - Earliest exposure in the first trimester (TDF 2.2%, all ARVs 3.0%)
 - Earliest exposure in the 2nd/3rd trimester (TDF 1.3%, all ARVs 2.6%)
- Monitoring of birth defects among infants born to women with exposure to ARVs during pregnancy is important and should be encouraged**

APR Contact Information

- APR website: www.APRRegistry.com
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Success of the APR depends on reporting of exposures by health care providers

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