

**Watts DH et al.** Assessing the risk of birth defects associated with antiretroviral exposure during pregnancy. *Am J Obstet Gynecol* 191, 985-92, 2004

Type of study	Prospective exposure-registration cohort
Where	US and Canada (international registry)
When	1989-2003
Characteristics of the cohort	Voluntary prospective exposure-registration and follow up cohort: pregnant women with prenatal exposures to antiretroviral drugs included
Characteristics of the disease	- CD4+ cell count at start of pregnancy: <200/mm <sup>3</sup> =16.9%; 200-499/mm <sup>3</sup> =44.3%; ≥500/mm <sup>3</sup> =30.9% - Clinical categories at start of pregnancy: HIV infected: asymptomatic or acute (primary) HIV=73.8%; symptomatic=7.5%; AIDS-indicator conditions=10.3%
Ascertainment of drug exposure	Health care providers registered exposed pregnant women before the pregnancy outcome was known and, shortly after delivery, submitted data on additional antiretroviral exposures in pregnancy and details of pregnancy outcome
Exposure definition	Earliest trimester of exposure to antiretroviral drugs: the first trimester in which the antiretroviral exposure occurred (1 or more antiretroviral drugs)
Size of the studied cohort	Exposed women: 4,328 recruited; 3,782 in follow up (1,587 first-trimester exposures, 2,195 later exposures); 3,635 infants born women lost to follow up did not differ substantially from those with complete data Unexposed reference group: approximately 50,000 births in this 5-county area each year, and 1,500 infants with birth defects.
Exposed cohort	Newborns exposed to a group of drugs
Control cohort	Newborns not exposed to the studied drugs: population-based birth defects surveillance system that includes all infants born to residents of the metropolitan area of Atlanta, Georgia (52% Caucasian). This surveillance system does not capture specific maternal drug exposure data, so infants exposed prenatally to antiretroviral drugs may be included (Centers for Disease Control Metropolitan Atlanta Congenital Defects Program-CDC MACDP)
Malformations ascertainment	If a birth defect was reported, the health care provider was asked to supply more detailed information on the birth defect, concomitant drug exposures during pregnancy, coexisting maternal conditions and family history. All birth defects reported were reviewed and classified by a physician specializing in genetics and dysmorphology, trained by the CDC to use the MACDP system. All birth defects were further reviewed by the independent scientific advisory committee. To increase the sensitivity of the registry, clusters of 2 or more conditional abnormalities were included
Malformations definition	Any major structural or chromosomal abnormality, or any cluster of 2 or more minor abnormalities occurring in infants or fetuses of at least 20 weeks gestational age.
Prevalence of malformations among control offspring	3.1 per 100 livebirths from 1991 through 1995
Analysis	Risk estimates calculated using methods suggested by Kleinbaum et al; 95%CI The prevalence of birth defects was calculated by dividing the number of birth defects in livebirths, stillbirths, and induced

	<p>abortions over 20 weeks of gestation by the total number of livebirths. Pregnancy losses before 20 weeks' gestation with or without defects were excluded from the denominator, although defects noted in these cases were included in the database and analyses for patterns of defects</p>
Strengths	<ul style="list-style-type: none"> <li>- Exposures and outcomes were ascertained prospectively</li> <li>- Thorough definition of the birth defects</li> <li>- Information about characteristics of the disease and women lost to follow up</li> <li>- Evaluation of the study's power analyses</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>- Limits ability to detect an increased risk of rare birth defects and to detect all but large increases in defects for most of the antiretroviral drugs (sample size restrictions)</li> <li>- Clinicians may intentionally or unintentionally select women to enroll based on perceived risk of specific antiretroviral agents (selection bias)</li> <li>- Pregnancies with defects diagnosed early during pregnancy and leading to termination may not be reported (reporting bias)</li> <li>- Defects diagnosed after neonatal hospital discharge may not be made known to the original reporter (ascertainment bias)</li> <li>- The majority of cases reported from providers in the US, the generalizability of the data to other settings needs to be evaluated</li> <li>- No information on concomitant medications used by all women, on additional risk factors for the development of birth defects</li> <li>- Comparison of rates of birth defects after first trimester vs later exposure may not correct for severity bias: sicker women may be more likely to be treated during the first trimester</li> <li>- Differences in racial composition from comparator populations</li> </ul>
Main results	<p>Among 1,391 first trimester exposures, there were a prevalence of birth defects of 2.7%, not significantly higher than the CDC's population surveillance rate, 3.1 per 100 livebirths. No specific pattern of defects was noted. For lamivudine, nevirapine, stavudine, zidovudine, sufficient numbers of livebirths (&gt;200) following first trimester exposures have been monitored to allow detection of a 2-fold increase in risk of birth defects overall: no increases have been detected</p>