Comparative Safety of Antiretroviral Drugs to Treat HIV During Pregnancy

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A Dissertation Submitted to the Faculty of

The Harvard T.H. Chan School of Public Health

in Partial Fulfillment of the Requirements

for the Degree of *Doctor of Science*

in the Department of *Epidemiology*

Harvard University

Boston, Massachusetts

March 2017

Dissertation Advisor: Dr. George R. Seage III Kathryn Rough

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Abstract

Each year, nearly 1.5 million women with HIV become pregnant, and require antiretroviral treatment to reduce risk of perinatal transmission of the virus and improve their own health. The safety of currently approved antiretroviral medications for the fetus is largely unknown; recommendations about preferred regimens during pregnancy are often based on a small body of clinical safety data, expert opinion, and programmatic considerations, including regimen harmonization across sub-populations.

Therefore, there is a public health need to identify the specific antiretroviral drugs and combinations of drugs that are safest for use during pregnancy. Across the papers that comprise this Dissertation, we apply different epidemiological methods to observational data sources in order to provide information on clinically-motivated questions.

In Chapter II, we used descriptive statistics to explore how substance use, one important risk factor for adverse infant birth outcomes, changed over time among pregnant women with HIV in the US. We found that substance use in this population dramatically decreased from 1990 to 2012, and that substance use had correlations with treatment, which means it may act as an important confounder in subsequent antiretroviral safety studies.

In Chapter III, we further investigated the relationship between specific antiretroviral regimens and adverse birth outcomes, providing information on safety questions raised by a recent clinical trial. Pooling data from two prospective cohorts, we compared three antiretroviral regimens and concluded that the use of tenofovir with protease inhibitors not including lopinavir/ritonavir do not increase adverse birth outcomes.

In Chapter IV, we examined the relationship between first trimester use of the antiretroviral zidovudine and congenital malformations. We summarized results of published studies using a systematic review and meta-analysis, and used Bayesian methods to incorporate this information with new data from Medicaid. We concluded that there appears to be a link between first trimester zidovudine use and increased risk of male genital malformations.

We hope that the research undertaken in this Dissertation will substantially contribute to the growing body of antiretroviral safety information available to women with HIV and their clinicians, ultimately allowing them to make more well-informed treatment decisions

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Of the nearly 37 million people living with HIV (human immunodeficiency virus) worldwide,[1] nearly 1.5 women with HIV become pregnant each year,[2] including an estimated 8,700 women in the United States (US).[3,4] Pregnant women with HIV require treatment with antiretroviral drugs for two reasons: (1) to improve their own health and (2) to prevent transmission of HIV to their infant.

Antiretroviral treatment for HIV is essential for individual patient health; untreated HIV infection leads to deterioration of the immune system, opportunistic infections, Acquired Immunodeficiency Syndrome (AIDS), and eventually death.[5] The current standard of care for HIV, combination antiretroviral therapy (cART), is a multi-drug cocktail comprised of medications from different drug classes. The drugs in cART regimens work together to suppress viral growth and replication, leading to increased survival and reduced risk of transmission to others.[6–9]

Treatment of HIV with cART during pregnancy substantially reduces the risk of perinatal transmission of the virus. Over the past two decades, increasing use of cART regimens to treat HIV infection have resulted in dramatic benefits for maternal and infant health. In the US, the number of children born with HIV infection decreased by an order of magnitude, from approximately 1,750 in mid-1990s[10] to less than 115 in 2014.[11] While 20-25% of untreated women transmit the disease to their infants[12,13] the risk of perinatal HIV transmission is reduced to less than 1% for women who receive cART.[14,15] As a result, treatment with cART during pregnancy has become the standard of care, supported by global guidelines from the World Health Organization.[16]

Despite this remarkable advance, the safety of currently approved antiretroviral medications for the fetus is largely unknown. Recommendations about preferred regimens during pregnancy are often based on a small body of clinical safety data, expert opinion, and programmatic considerations, including regimen

harmonization across sub-populations. Experts in the field of perinatal transmission of HIV have repeatedly noted the lack of information on the comparative safety of antiretroviral medications used during pregnancy and called for further research.[17–22] In 2014, the World Health Organization identified cART safety in pregnancy as a priority research area.[23]

Gaps in knowledge of cART safety during pregnancy are troubling, given pharmacological studies that show these medications cross the placenta and result in substantial fetal exposure.[24] Because cART is so effective in preventing perinatal HIV transmission, its proven benefits are likely to outweigh nearly all potential safety risks.[25] Therefore, the clinically relevant questions pertain to identifying which specific combinations of antiretroviral drugs are safest during pregnancy.

Across the papers that comprise this Dissertation, we apply different epidemiological methods to a variety of observational data sources, in order to answer clinically-relevant questions that matter for patients. In Chapter II, we explore how substance use, one important risk factor for adverse infant birth outcomes, changed over time among pregnant women with HIV in the US and how this may impact antiretroviral safety studies. In Chapter III, we further investigate the relationship between specific regimens and adverse birth outcomes, providing information on safety questions raised by a recent clinical trial. In Chapter IV, we examine the relationship between first trimester use of an antiretroviral drug and congenital malformations.

We hope that the research undertaken in this Dissertation will substantially contribute to the growing body of antiretroviral safety information available to women with HIV and their clinicians, ultimately allowing them to make more well-informed treatment decisions.

REFERENCES

1. UNAIDS: Joint United Nations Programme on HIV/AIDS. *Fact Sheet: November 2016*.; 2016. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf.
2. Joint United Nations Program on HIV/AIDS. *UNAIDS Report on the Global AIDS Epidemic 2013*.; 2013.
3. Taylor A, Little K, Zhang X, Borkowf C, Whitmore S, Weidle P. Estimated perinatal antiretroviral exposures, cases prevented, and infected infants in the era of antiretroviral prophylaxis in the United States. In: *19th Conference on Retroviruses and Opportunistic Infections*. Seattle, Washington; 2012.
4. Whitmore SK, Zhang X, Taylor AW, Blair JM. Estimated Number of Infants Born to HIV-Infected Women in the United States and Five Dependent Areas, 2006. *J Acquir Immune Defic Syndr*. 2011;57(3):218-222. doi:10.1097/QAI.0b013e3182167dec.
5. Centers for Disease Control and Prevention. About HIV/AIDS: HIV Basics. http://www.cdc.gov/hiv/basics/whatishiv.html. Published 2016. Accessed November 22, 2016.
6. Braitstein P, Brinkhof MWG, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet*. 2006;367(9513):817-824. doi:10.1016/S0140-6736(06)68337-2.
7. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *N Engl J Med*. 2011;365(6):493-505. doi:10.1056/NEJMoa1105243.
8. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis*. 2014;14(4):281-290. doi:10.1016/S1473-3099(13)70692-3.
9. HIV-CAUSAL Collaboration, Ray M, Logan R, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS*. 2010;24(1):123-137. doi:10.1097/QAD.0b013e3283324283.

10. Gorsky RD, Farnham PG, Straus WL, et al. Preventing perinatal transmission of HIV--costs and effectiveness of a recommended intervention. *Public Heal Rep*. 111(4):335-341.

11. Centers for Disease Control and Prevention. *HIV Surveillance Report, 2014*. Vol 26.; 2015. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-us.pdf. Accessed November 23, 2016.

12. Blanche S, Rouzioux C, Moscato ML, et al. A prospective study of infants born to women seropositive for human immunodeficiency virus type 1. HIV Infection in Newborns French Collaborative Study Group. *N Engl J Med*. 1989;320(25):1643-1648. doi:10.1056/NEJM198906223202502.

13. Landesman SH, Kalish LA, Burns DN, et al. Obstetrical factors and the transmission of human immunodeficiency virus type 1 from mother to child. The Women and Infants Transmission Study. *N Engl J Med*. 1996;334(25):1617-1623. doi:10.1056/NEJM199606203342501.

14. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defici Syndr*. 2002;29(5):484-494.

15. Fowler MG, Qin M, Fiscus SA, et al. PROMISE: Efficacy and safety of 2 strategies to prevent perinatal HIV transmission. In: *Conference on Retroviruses and Opportunistic Infections*. Seattle, Washington; 2015.

16. World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*. World Health Organization; 2016. http://www.who.int/hiv/pub/arv/arv-2016/en/. Accessed July 27, 2016.

17. Heidari S, Mofenson L, Cotton MF, Marlink R, Cahn P, Katabira E. Antiretroviral drugs for preventing mother-to-child transmission of HIV: a review of potential effects on HIV-exposed but uninfected children. *J Acquir Immune Defici Syndr*. 2011;57(4):290-296. doi:10.1097/QAI.0b013e318221c56a.

18. Mofenson LM, Watts DH. Safety of pediatric HIV elimination: the growing population of HIV-

and antiretroviral-exposed but uninfected infants. *PLoS Med*. 2014;11(4):e1001636. doi:10.1371/journal.pmed.1001636.

19. Newell M-L, Bunders MJ. Safety of antiretroviral drugs in pregnancy and breastfeeding for mother and child. *Curr Opin HIV AIDS*. 2013;8(5):504-510. doi:10.1097/COH.0b013e3283632b88.

20. Santini-Oliveira M, Grinsztejn B. Adverse drug reactions associated with antiretroviral therapy during pregnancy. *Expert Opin Drug Saf*. 2014;13(12):1623-1652. doi:10.1517/14740338.2014.975204.

21. Sibiude J, Warszawski J, Blanche S. Tolerance of the newborn to antiretroviral drug exposure in utero. *Expert Opin Drug Saf*. 2015;14(5):643-654. doi:10.1517/14740338.2015.1019462.

22. Thorne C, Newell M-L. Safety of agents used to prevent mother-to-child transmission of HIV: is there any cause for concern? *Drug Saf*. 2007;30(3):203-213.

23. World Health Organization. *Scoping Consultation on Priority Areas and Required Work on ARV Toxicity*. Geneva, Switzerland; 2014. http://www.who.int/hiv/pub/arv/scoping-consultation-report/en/. Accessed November 23, 2016.

24. Mirochnick M, Best BM, Stek AM, et al. Lopinavir exposure with an increased dose during pregnancy. *J Acquir Immune Defic Syndr*. 2008;49(5):485-491. doi:10.1097/QAI.0b013e318186edd0.

25. Ciaranello AL, Seage GR, Freedberg KA, Weinstein MC, Lockman S, Walensky RP. Antiretroviral drugs for preventing mother-to-child transmission of HIV in sub-Saharan Africa: balancing efficacy and infant toxicity. *AIDS*. 2008;22(17):2359-2369. doi:10.1097/QAD.0b013e3283189bd7.

26. Giles ML, Hellard ME, Lewin SR, O'Brien ML. The "work" of women when considering and using interventions to reduce mother-to-child transmission (MTCT) of HIV. *AIDS Care*. 2009;21(10):1230-1237. doi:10.1080/09540120902803166.

27. NAM. HIV Treatments Directory: Side effects and birth defects. 2015; Available from: http://www.aidsmap.com/Side-effects-and-birth-defects/page/1730605/.

Chapter 2. Dramatic decline in substance use by HIV-infected pregnant women in the women in the United States from 1990-2012

INTRODUCTION

It is estimated that approximately 8,700 HIV-infected women give birth in the United States annually [1, 2]. Rates of substance use in this population have historically been high; in the late 1980s and early 1990s, approximately half of HIV-infected pregnant women used illicit substances [3, 4]. Substance use during pregnancy in HIV-infected women has negative implications for transmission, infant outcomes, and the health of the mother. Substance use is associated with increased risk of perinatal transmission[5-8] and lack of viral suppression in pregnant women [9]. HIV-infected substance users are less likely to take [10-12] or adhere to [13, 14] antiretroviral therapy (ART). In addition, prenatal exposure to marijuana, tobacco, alcohol, and cocaine has been linked to low birth weight, behavioral problems, and poorer cognitive functioning [15-25].

The route of HIV acquisition among women has changed over time in the United States. While approximately 50% of female AIDS cases were linked to injection drug use in 1990 [26], it was the suspected source of infection in only 14% of female HIV diagnoses by 2011 [27]. However, to our knowledge, no studies have examined substance use patterns in HIV-infected pregnant women over the last two decades.

Using data from two large US-based cohort studies, we describe the dramatic decrease in maternal substance use during pregnancy from 1990 to 2012 among HIV-infected women, and explore possible explanations for the decrease. In addition, we compare the prevalence of substance use during pregnancy in our study population to prevalence estimates among pregnant women in the general US population.

METHODS

Study participants and design

This study included women who gave birth from January 1, 1990 to December 31, 2012 and were enrolled in either the Women and Infants Transmission Study (WITS) or the Surveillance Monitoring for ART Toxicities (SMARTT) protocol of the Pediatric HIV/AIDS Cohort Study (PHACS). WITS was a prospective, multi-site cohort study designed to determine factors associated with perinatal transmission; it enrolled women who gave birth from 1990 to 2005 and their infants [28]. SMARTT is an ongoing, multi-site cohort study that follows the uninfected children of HIV-infected women longitudinally to evaluate the safety of *in utero* exposure to antiretroviral drugs [29]. The first delivery in SMARTT occurred in 1995. In both WITS and SMARTT, written informed consent was obtained from each participating woman, and the institutional review board at each study center approved the study protocol.

In WITS, women had multiple study visits during pregnancy. At each visit, a physical exam was performed, blood was collected, and medical histories were obtained through chart review. In SMARTT, two groups of women and children (i.e., dynamic and static) were enrolled. In the dynamic cohort, mothers and infants were enrolled during pregnancy (23 weeks of gestation or later) through 72 hours after delivery. The static cohort enrolled women and their children aged 0-12 years. For both WITS and SMARTT, trained study personnel conducted structured interviews at enrollment to assess demographic characteristics (including age, race/ethnicity, education, and marital status).

Women were eligible for this study if they were enrolled in WITS or SMARTT, gave birth from January 1, 1990 to December 31, 2012, and provided self-reported information on substance use during pregnancy. Duplicate pregnancies (e.g. a participant enrolled in both WITS and SMARTT during same pregnancy) were removed for this analysis.

Substance use measures

In WITS, trained nurses administered a questionnaire at each study visit (up to three pre-delivery visits) to ascertain use of alcohol, tobacco, marijuana, heroin, and cocaine during pregnancy, as well as injection drug use. One urine sample for drug testing was collected at the intake visit and one was collected during labor or immediately postpartum. Urine was screened for cocaine, heroin/opiates, marijuana, alcohol or their metabolites using a radioimmunoassay followed by confirmatory gas chromatography and mass spectrometry [7].

Women in the dynamic SMARTT cohort completed a substance use interview within seven days of delivery, and women in the static SMARTT cohort completed this interview at time of enrollment (up to 12 years after pregnancy). The interview collected information on alcohol, tobacco, marijuana, heroin, cocaine, and injection drug use during pregnancy. In a subsample of the dynamic cohort, meconium – the first stool of an infant – was collected from participants' offspring and screened for cocaine, heroin/opiates, marijuana, alcohol, tobacco, or their metabolites using an immunoassay technique followed by confirmatory gas chromatography and mass spectrometry [30].

In these analyses, women were classified as using a substance during pregnancy if they either self-reported or had a positive biological sample for alcohol, tobacco, marijuana, cocaine, or heroin use at any time during pregnancy. Poly-substance use was defined as using two or more of these substances at any time during pregnancy.

Statistical methods

We summarized sociodemographic and clinical characteristics of participants. The proportion of women in each of the substance use categorizations was calculated, stratified by calendar year of delivery. To test whether the proportion of women using substances during pregnancy changed over time, we used log binomial generalized estimating equation (GEE) models. Univariable GEE models were used to account for correlation between repeated pregnancies by the same woman over the course of the study. Because

meconium samples were not available for all mothers in SMARTT, we conducted two sensitivity analyses to ensure that our findings were robust. The first analysis included only WITS pregnancies in the GEE model, while the second also included the SMARTT pregnancies with available meconium data.

Multivariable logistic GEE models were constructed to evaluate predictors of substance use in the pre-highly active ART (HAART) (1990-1995) and HAART (1996-2012) eras. This cut point was chosen to reflect the first reported use of a HAART regimen in WITS. These models included sociodemographic characteristics (race/ethnicity, age, education, household income, and marital status) and clinical factors (diagnosis of HIV during pregnancy, earliest available CD4 count during pregnancy, earliest available HIV RNA during pregnancy, and use of antiretroviral therapy regimens [defined as most intensive regimen used during pregnancy for more than 2 weeks]).

To evaluate trends within individual women, we restricted analysis to the subset of participants who had multiple pregnancies under study observation in either WITS or SMARTT. Log binomial GEE models were used to test whether the risk of substance use changed in successive pregnancies.

We graphically compared substance use prevalence in WITS/SMARTT to prevalence among pregnant women participating in the National Survey on Drug Use and Health (NSDUH), by calendar year. NSDUH is a nationally representative household survey that provides estimates of substance use prevalence in the United States, including in pregnant women. In NSDUH, a woman is considered as using a substance during pregnancy if she reports being pregnant and using the substance in the past month. NSDUH first collected data on pregnancy in 1994; therefore, we compared WITS/SMARTT and NSDUH estimates from 1994-2012 [31-49].

All analyses were performed in SAS version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Of the 5,724 total pregnancies in WITS and SMARTT, 233 were excluded from this analysis because self-reported substance use information was unavailable. An additional 40 pregnancies were excluded because year of delivery was unknown. Therefore, a total of 5,451 pregnancies from 4,408 individual women were included in this analysis. Maternal characteristics for each pregnancy are described in Table 2.1.

Approximately 82% of respondents used at least one substance in 1990; this proportion decreased linearly over time until 2006 (Figure 2.1). From 2006 to 2012 the prevalence was relatively stable, ranging from 21.0% to 26.3%. A similar pattern was observed for each of the individual substances over the 23-year period. The prevalence of tobacco use decreased from 64.9% to 18.2%; alcohol use from 57.4% to 9.3%; marijuana use from 25.5% to 6.7%; cocaine use from 36.2% to 1.3%; and heroin use from 27.7% to 0.0%. The prevalence of injection drug use declined from a peak of 17.1% in 1991 to 0.0% from 2008 onwards, and poly-substance use fell from 64.9% in 1990 to approximately 10% from 2007 onwards.

Each of these observed decreases is statistically significant after accounting for repeated pregnancies by individual women (Table 2.2). Each year, risk of substance use among HIV-infected pregnant women decreased by an average of 6% (Risk ratio [RR], 0.94; 95% Confidence Interval [CI], 0.94-0.95). The largest reductions in risk over the 23-year period were for injection drug use (RR, 0.80; 95% CI, 0.77-0.83), heroin use (RR, 0.87; 95% CI, 0.85-0.88), and cocaine use (RR, 0.87; 95% CI, 0.86-0.88). The smallest reductions in risk were for marijuana (RR, 0.94; 95% CI, 0.93-0.96) and tobacco (RR, 0.94; 95% CI, 0.94-0.95). Both sensitivity analyses produced estimates comparable to those found in the main analysis (Tables 2.4 and 2.5).

In both the pre-HAART and HAART eras, multivariable models showed that non-Hispanic white race, older age, less education, and being unmarried were statistically significantly associated with substance use during pregnancy (Table 2.3). In the pre-HAART era, not receiving any antiretroviral therapy was associated with increased odds of substance use (Odds ratio [OR], 1.42; 95% CI, 1.07-1.88). Similarly, in the HAART era, women receiving no antiretroviral therapy (OR, 2.10; 95% CI, 1.42-3.09), AZT monotherapy (OR, 2.42; 95% CI, 1.90-3.07), or another non-HAART antiretroviral therapy (OR, 1.35; 95% CI, 1.12-1.64) had greater odds of substance use, compared to women receiving HAART.

Of the 4,408 women included in the previous analysis, 824 had two or more pregnancies under study observation. We hypothesized that the observed decreases may be explained in part by the cessation of substance use in women who had multiple pregnancies (i.e., women use substances less in later pregnancies). For most substances, the risk of a woman using the substance did not change with successive pregnancies; the association between pregnancy order and use of tobacco, marijuana, cocaine, heroin, any substance, or multiple substances was not statistically significant. Women had 0.72 times the risk of injecting drugs with each successive pregnancy (95% CI, 0.50-1.03), though this result was not statistically significant. Risk of alcohol use was also slightly reduced in later pregnancies (RR, 0.91; 95% CI, 0.82-1.00). Of note, women who used a substance in their previous pregnancy were at an elevated risk of substance use during their next pregnancy (RR, 5.71; 95% CI, 4.63-7.05).

Figures 2.2a - 2.2e compare prevalence of alcohol, tobacco, marijuana, cocaine, and heroin use during pregnancy among HIV-infected women in the WITS and SMARTT cohorts to estimates from NSDUH, by year. From 1994 through the early 2000s, use of all five of these substances appears substantially higher among HIV-infected pregnant women compared to pregnant women in the general population. However, from the mid-2000s through 2012, prevalence of substance use appears comparable between the two groups.

DISCUSSION

We describe the substantial decline in substance use during pregnancy that occurred between 1990 and 2012 in a population comprised of two large US-based cohorts of HIV-infected women. The use of both licit and illicit substances decreased over the 23-year period. While the prevalence of substance use was initially considerably higher in our study population, it has become similar to that of pregnant women in the general US population. The relatively stable prevalence noted since 2006 suggests that new strategies are needed for further reductions in substance use in both HIV-infected and uninfected pregnant women.

Women who used substances in previous pregnancies had over a 5-fold increased risk of using a substance in future pregnancies. Therefore, we posit that the observed decrease in substance use over time is not due to the cessation of substance use in women who used them previously, but rather that HIV is affecting a different group of women. In other words, it is possible that an epidemiological transition has occurred, in which the types of women becoming infected with HIV in the United States has changed in recent years. This is supported by data from the Centers for Disease Control and Prevention, which shows that the primary route of infection among women has gradually transitioned from injection drug use to heterosexual contact [26, 27].

We identified several factors that were associated with substance use during pregnancy in this population, including non-Hispanic white race, older age, less education, being unmarried, and not receiving antiretroviral therapy/HAART. Our study found that substance use is inversely associated with receiving antiretroviral therapy in pregnant woman, and past studies have shown this association in other HIV-infected groups. In a population of HIV-infected adults, people who used drugs were less likely to receive antiretroviral therapy [11]. Other studies found that current injection drug users were less likely than past users to be receiving antiretroviral therapy [10], and that substance users not enrolled in treatment programs were less likely to receive antiretroviral therapy than those receiving treatment [12].

Because substance use is inversely associated with antiretroviral therapy as well as a number of potential outcomes, it may be an important confounder in antiretroviral safety studies, especially those that use historical comparison data.

Our study has several limitations. First, as with many epidemiological studies, our sample may not represent the larger population of HIV-infected women who gave birth from 1990-2012. Second, different types of biological specimens were used to confirm self-reported substance use in each cohort study (urine in WITS and meconium in SMARTT). These tests have varying sensitivity, specificity, and windows of detection [50-52]. Results from a sensitivity analysis restricted to WITS participants show that differences in biological specimen types do not explain the observed decrease in substance use. Third, only 22% of women in SMARTT had meconium samples analyzed for substances, and some women in the static SMARTT cohort had long recall periods. However, results from an analysis restricted to women with available biological assays suggest that our findings are not explained by recall or social desirability bias. Furthermore, past analyses have shown that underreporting of substance use during pregnancy was minimal in the dynamic SMARTT cohort [30]. Fourth, NSDUH's classification of substance use during pregnancy (being pregnant and using the substance in the past month) differs from that of WITS and SMARTT and was not confirmed by biological assays. Therefore, estimates from NSDUH presented in Figures 2.2a - 2.2e may be underestimates of the true prevalence of substance use among pregnant women in the general US population. Finally, this analysis could not investigate temporal trends in the use of prescription opioids, as WITS did not collect information on prescription opioid use during pregnancy. However, only a small proportion (4.4%) of women in SMARTT reported using prescription opioids during their pregnancy, including both medical and non-medical use.

In conclusion, this study provides important information about temporal trends in substance use among HIV-infected pregnant women in the United States. We documented a dramatic decrease in prevalence of substance use during pregnancy since 1990, which may be due to a shift in the HIV epidemic in the US

among women. The finding that substance use during pregnancy has historically been associated with lack of antiretroviral use is concerning and may warrant further investigation. In addition, our observation that HIV-infected women who used substances in past pregnancies are at increased risk of use during future pregnancies suggests that they may be important to target in efforts to further reduce substance use in this population.

CITATION INFORMATION

This Chapter of the dissertation has been previously published:

Rough K, Tassiopoulos K, Kacanek D, Griner R, Yogev R, Rich KC, Seage GR III. Dramatic decline in substance use by HIV-infected pregnant women in the United States from 1990 to 2012. *AIDS.* 2015;29(1):117-123.

Table 2.1. Maternal Characteristics of the Eligible Pregnancies* of HIV-Infected Pregnant Women in WITS or SMARTT (N = 5,451)

	n	%
Race/ethnicity		
Non-Hispanic black	2,974	54.6
Hispanic	1,734	31.8
Non-Hispanic white	657	12.1
Not available	86	1.6
Age		
15-21	820	15.0
22-34	3,681	67.5
35-47	786	14.4
Not available	164	3.0
Education		
Less than high school	2,107	38.7
High school grad or above	3,292	60.4
Not available	52	1.0
Yearly household income		
Less than $20,000	3,929	72.1
$20,000-$40,000	738	13.5
$40,000 or more	248	4.5
Not available	536	9.8
Marital status		
Married	1,409	25.8
Unmarried	4,007	73.5
Not available	35	0.6
HIV diagnosis during pregnancy		
Diagnosed before pregnancy	3,265	59.9
Diagnosed during pregnancy	1,329	24.4
Not available	857	15.7
CD4 count (cells/mm^3)†		
200 or fewer	707	13.0
201-350	1,210	22.2
351-500	1,260	23.1
More than 500	2,104	38.6
Not available	170	3.1
HIV RNA (copies/mL)†		
400 or fewer	1,650	30.3
401-10,000	1,899	34.8
More than 10,000	1,655	30.4
Not available	247	4.5
ART use during pregnancy‡		
No ART	805	14.8
AZT monotherapy	1,020	18.7
Other ART regimen	599	11.0
HAART	2,977	54.6
Not available	50	0.9

Abbreviations: HIV, human immunodeficiency virus; WITS, Women and Infants Transmission Study; SMARTT, Surveillance Monitoring for Antiretroviral Therapy Toxicities Study; ART, antiretroviral therapy; AZT, zidovudine; HAART, highly active antiretroviral therapy

* Maternal characteristics are listed separately for each pregnancy; 824 women had multiple pregnancies under study observation.

† First available measurement during pregnancy

‡ Most potent antiretroviral therapy regimen used during pregnancy for more than 2 weeks

Table 2.2. Unadjusted Risk Ratios of Substance Use during Pregnancy for a 1-Year Increase in Time

	N	Risk Ratio	95% CI	p-value
Tobacco	5,443	0.94	0.94-0.95	< .001
Alcohol	5,451	0.91	0.90-0.92	< .001
Marijuana	5,396	0.94	0.93-0.96	< .001
Cocaine	5,396	0.87	0.86-0.88	< .001
Heroin	5,396	0.87	0.85-0.88	< .001
Any substance	5,396	0.94	0.94-0.95	< .001
Poly-substance	5,451	0.91	0.90-0.91	< .001
Injection drug use	5,228	0.80	0.77-0.83	< .001

Table 2.3. Odds Ratios of Substance Use during Pregnancy (Multivariable Model)

	Pre-HAART era* (N = 1,093)				HAART era† (N = 3,754)			
	n	% using substances	Odds Ratio	95% CI	n	% using substances	Odds Ratio	95% CI
Race/ethnicity								
Non-Hispanic black	460	69.4	0.42	0.27-0.66	2,184	34.9	0.34	0.27-0.44
Hispanic	414	65.5	0.38	0.24-0.59	1,185	34.9	0.32	0.25-0.41
Non-Hispanic white	219	83.6	Ref		385	60.0	Ref	
Age								
15-21	146	48.0	Ref		590	32.4	Ref	
22-34	828	73.9	3.97	2.60-6.05	2,554	37.7	1.57	1.28-1.93
35-47	119	76.5	5.16	2.82-9.44	610	41.5	1.99	1.54-2.58
Education								
Less than high school	508	78.7	2.40	1.76-3.28	1,362	43.4	1.35	1.16-1.57
High school grad or above	585	63.8	Ref		2,392	34.1	Ref	
Yearly household income								
Less than $20,000	885	71.0	Ref		2,610	40.3	Ref	
$20,000-$40,000	79	62.0	0.84	0.51-1.37	589	28.9	0.77	0.63-0.94
$40,000 or more	21	66.7	0.83	0.31-2.28	208	29.8	0.83	0.59-1.17
Not available	108	75.9	1.12	0.70-1.81	347	35.7	0.86	0.68-1.09
Marital status								
Married	303	61.7	Ref		965	27.6	Ref	
Unmarried	790	74.2	1.71	1.23-2.36	2,789	40.9	1.96	1.65-2.34
HIV diagnosis during pregnancy								
Diagnosed before pregnancy	677	75.8	Ref		753	40.6	Ref	
Diagnosed during pregnancy	416	62.5	0.58	0.44-0.77	2,234	40.8	0.90	0.75-1.08
Not available	n/a	--	n/a	--	767	24.8	0.56	0.47-0.66
CD4 count (cells/mm^3)‡								
200 or fewer	150	66.7	0.63	0.40-0.99	504	38.3	0.99	0.78-1.24
201-350	240	70.8	0.79	0.53-1.17	864	37.3	0.99	0.82-1.19
351-500	264	70.5	0.87	0.61-1.25	878	37.2	0.99	0.83-1.18
More than 500	439	72.2	Ref		1,508	37.5	Ref	
HIV RNA (copies/mL)‡								
400 or fewer	88	67.1	Ref		1,453	33.4	Ref	
401-10,000	462	71.7	1.22	0.70-2.10	1,297	39.3	1.20	1.02-1.41
More than 10,000	543	70.5	1.19	0.68-2.09	1,004	41.0	1.30	1.07-1.58
ART use during pregnancy§								
No ART	533	73.9	1.42	1.07-1.88	89	56.2	2.10	1.42-3.09
Any ART	560	67.7	Ref		n/a	--	n/a	--
AZT monotherapy	n/a	--	n/a	--	378	61.4	2.42	1.90-3.07
Other ART regimen	n/a	--	n/a	--	509	41.3	1.35	1.12-1.64
HAART	n/a	--	n/a	--	2,778	32.9	Ref	

Abbreviations: HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; ART, antiretroviral therapy; AZT, zidovudine
Note: Pregnancies with missing covariate information were excluded from this model
* Deliveries in the "pre-HAART era" occurred between 1990 and 1995
† Deliveries in the "HAART era" occurred between 1996 and 2012
‡ First available measurement during pregnancy
§ Most potent antiretroviral therapy regimen used during pregnancy for more than 2 weeks

Figure 2.1. Proportion of HIV-Infected Women Using Substances during Pregnancy, by Delivery Year (N = 5,451)

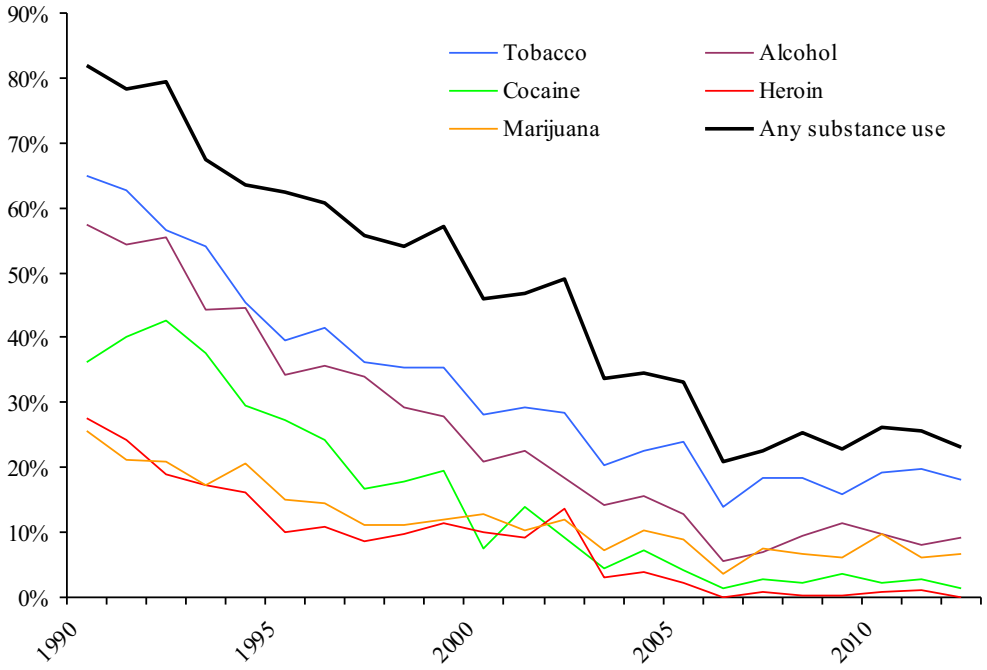
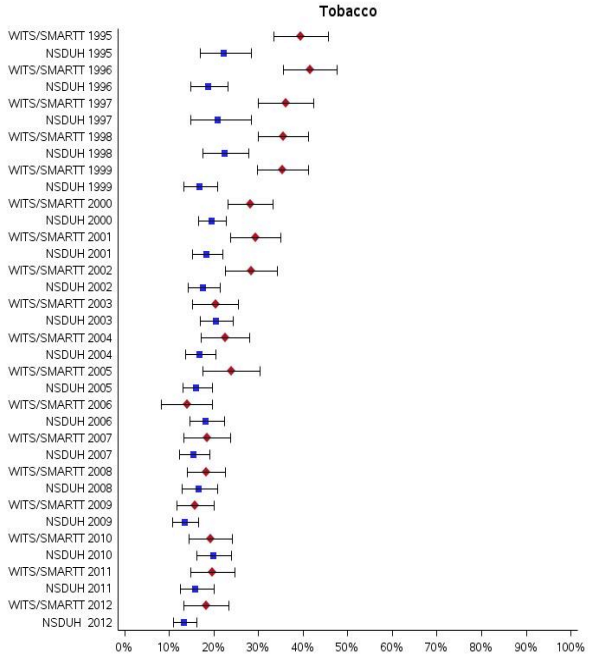


Figure 2.2a-2.2e. Prevalence of Substance Use During Pregnancy in WITS/SMARTT and NSDUH, by Delivery Year


Tobacco
WITS/SMARTT 1995
NSDUH 1995
WITS/SMARTT 1996
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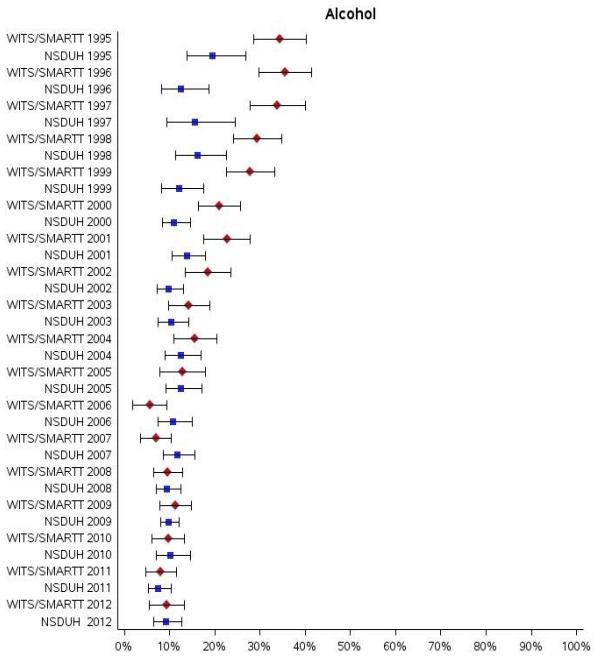
Alcohol
WITS/SMARTT 1995
NSDUH 1995
WITS/SMARTT 1996
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WITS/SMARTT 1999
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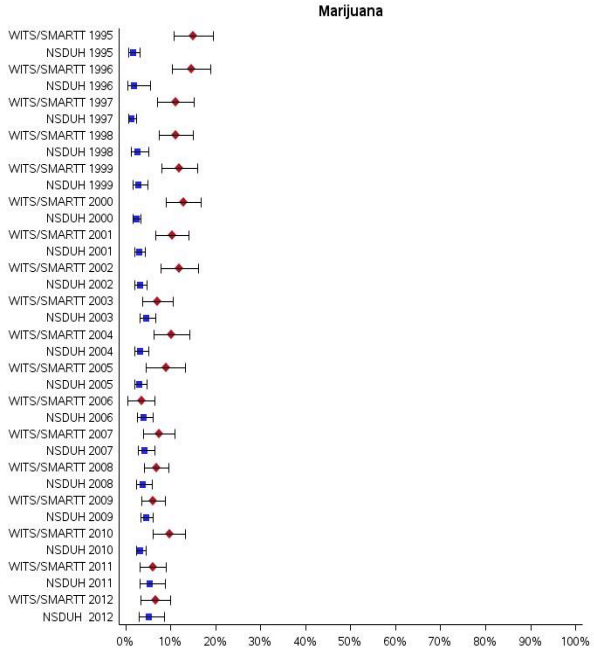
Marijuana
WITS/SMARTT 1995
NSDUH 1995
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WITS/SMARTT 1999
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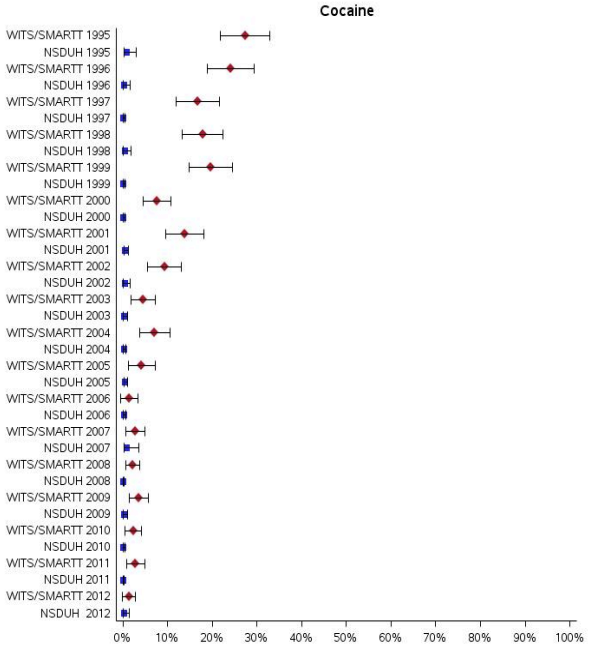
Cocaine
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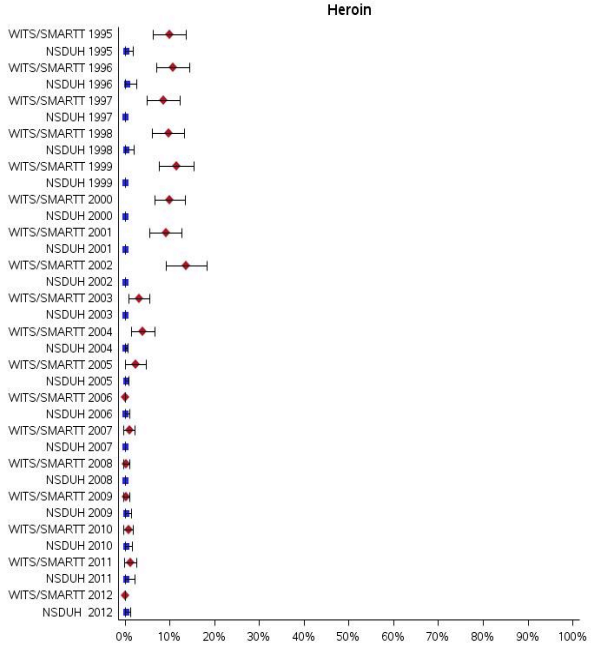
Heroin
WITS/SMARTT 1995
NSDUH 1995
WITS/SMARTT 1996
NSDUH 1996
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NSDUH 1997
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NSDUH 1998
WITS/SMARTT 1999
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0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Figure 2.2 Legend.

Abbreviations: WITS, Women and Infants Transmission Study; SMARTT, Surveillance Monitoring for Antiretroviral Therapy Toxicities Study; NSDUH, National Survey on Drug Use and Health

Table 2.4. Sensitivity Analysis: Unadjusted Risk Ratios of Substance Use during Pregnancy for a 1-Year Increase in Time (WITS Participants Only)

	N	Risk Ratio	95% CI	p-value
Tobacco	3,224	0.95	(0.94, 0.96)	< .001
Alcohol	3,232	0.92	(0.91, 0.93)	< .001
Marijuana	3,177	0.94	(0.92, 0.96)	< .001
Cocaine	3,177	0.90	(0.88, 0.91)	< .001
Heroin	3,177	0.93	(0.91, 0.95)	< .001
Any substance	3,177	0.96	(0.95, 0.97)	< .001
Poly-substance	3,232	0.92	(0.90, 0.93)	< .001
Injection drug use	3,009	0.83	(0.79, 0.87)	< .001

Abbreviations: WITS, Women and Infants Transmission Study

Table 2.5. Sensitivity Analysis: Unadjusted Risk Ratios of Substance Use during Pregnancy for a 1-Year Increase in Time (WITS Participants and SMARTT Participants with Meconium Samples)

	N	Risk Ratio	95% CI	p-value
Tobacco	3,712	0.93	(0.92, 0.94)	< .001
Alcohol	3,567	0.92	(0.91, 0.93)	< .001
Marijuana	3,720	0.94	(0.92, 0.96)	< .001
Cocaine	3,725	0.85	(0.84, 0.87)	< .001
Heroin	3,726	0.90	(0.88, 0.92)	< .001
Any substance	3,799	0.92	(0.91, 0.93)	< .001

Abbreviations: WITS, Women and Infants Transmission Study; SMARTT, Surveillance Monitoring for Antiretroviral Therapy Toxicities Study

References

1. Taylor AW, Little KM, Zhang X, Borkowf CB, Whitmore SK, Weidle PJ*, et al.* Estimated perinatal antiretroviral exposures, cases prevented and infected infants in the era of antiretroviral prophylaxis in the United States. *19th Conference on Retroviruses and Opportunistic Infections*. Seattle, WA; 2012.
2. Whitmore SK, Zhang X, Taylor AW, Blair JM. Estimated number of infants born to HIV-infected women in the United States and five dependent areas, 2006. *J Acquir Immune Defic Syndr* 2011;**57**:218-222.
3. Nair P, Alger L, Hines S, Seiden S, Hebel R, Johnson JP. Maternal and neonatal characteristics associated with HIV infection in infants of seropositive women. *J Acquir Immune Defic Syndr* 1993;**6**:298-302.
4. Rodriguez EM, Mendez H, Rich K, Sheon A, Fox H, Green K*, et al.* Maternal drug use in perinatal HIV studies. The Women and Infants Transmission Study. *Ann N Y Acad Sci* 1993;**693**:245-248.
5. Landesman SH, Kalish LA, Burns DN, Minkoff H, Fox HE, Zorrilla C*, et al.* Obstetrical factors and the transmission of human immunodeficiency virus type 1 from mother to child. The Women and Infants Transmission Study. *N Engl J Med* 1996;**334**:1617-1623.
6. Purohit V, Rapaka RS, Schnur P, Shurtleff D. Potential impact of drugs of abuse on mother-to-child transmission (MTCT) of HIV in the era of highly active antiretroviral therapy (HAART). *Life Sci* 2011;**88**:909-916.
7. Rodriguez EM, Mofenson LM, Chang BH, Rich KC, Fowler MG, Smeriglio V*, et al.* Association of maternal drug use during pregnancy with maternal HIV culture positivity and perinatal HIV transmission. *AIDS* 1996;**10**:273-282.
8. Whitmore SK, Taylor AW, Espinoza L, Shouse RL, Lampe MA, Nesheim S. Correlates of mother-to-child transmission of HIV in the United States and Puerto Rico. *Pediatrics* 2012;**129**:e74-81.

9. Katz IT, Shapiro R, Li D, Govindarajulu U, Thompson B, Watts DH*, et al.* Risk factors for detectable HIV-1 RNA at delivery among women receiving highly active antiretroviral therapy in the Women and Infants Transmission Study. *J Acquir Immune Defic Syndr* 2010;**54**:27-34.

10. Celentano DD, Vlahov D, Cohn S, Shadle VM, Obasanjo O, Moore RD. Self-reported antiretroviral therapy in injection drug users. *JAMA* 1998;**280**:544-546.

11. Sohler NL, Wong MD, Cunningham WE, Cabral H, Drainoni ML, Cunningham CO. Type and pattern of illicit drug use and access to health care services for HIV-infected people. *AIDS Patient Care STDS* 2007;**21 Suppl 1**:S68-76.

12. Strathdee SA, Palepu A, Cornelisse PG, Yip B, O'Shaughnessy MV, Montaner JS*, et al.* Barriers to use of free antiretroviral therapy in injection drug users. *JAMA* 1998;**280**:547-549.

13. Arnsten JH, Demas PA, Grant RW, Gourevitch MN, Farzadegan H, Howard AA*, et al.* Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. *J Gen Intern Med* 2002;**17**:377-381.

14. Tucker JS, Burnam MA, Sherbourne CD, Kung FY, Gifford AL. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *Am J Med* 2003;**114**:573-580.

15. Bateman DA, Ng SK, Hansen CA, Heagarty MC. The effects of intrauterine cocaine exposure in newborns. *Am J Public Health* 1993;**83**:190-193.

16. Day NL, Richardson GA, Geva D, Robles N. Alcohol, marijuana, and tobacco: effects of prenatal exposure on offspring growth and morphology at age six. *Alcohol Clin Exp Res* 1994;**18**:786-794.

17. Day NL, Richardson GA, Goldschmidt L, Robles N, Taylor PM, Stoffer DS*, et al.* Effect of prenatal marijuana exposure on the cognitive development of offspring at age three. *Neurotoxicol Teratol* 1994;**16**:169-175.

18. Goldschmidt L, Richardson GA, Willford J, Day NL. Prenatal marijuana exposure and intelligence test performance at age 6. *J Am Acad Child Adolesc Psychiatry* 2008;**47**:254-263.

19. Levine TP, Liu J, Das A, Lester B, Lagasse L, Shankaran S*, et al.* Effects of prenatal cocaine exposure on special education in school-aged children. *Pediatrics* 2008;**122**:e83-91.

20. Lightwood JM, Phibbs CS, Glantz SA. Short-term health and economic benefits of smoking cessation: low birth weight. *Pediatrics* 1999;**104**:1312-1320.

21. Richardson GA, Goldschmidt L, Larkby C. Effects of prenatal cocaine exposure on growth: a longitudinal analysis. *Pediatrics* 2007;**120**:e1017-1027.

22. Riley EP, McGee CL. Fetal alcohol spectrum disorders: an overview with emphasis on changes in brain and behavior. *Exp Biol Med* 2005;**230**:357-365.

23. Sexton M, Fox NL, Hebel JR. Prenatal exposure to tobacco: II. Effects on cognitive functioning at age three. *Int J Epidemiol* 1990;**19**:72-77.

24. Stroud LR, Paster RL, Goodwin MS, Shenassa E, Buka S, Niaura R*, et al.* Maternal smoking during pregnancy and neonatal behavior: a large-scale community study. *Pediatrics* 2009;**123**:e842-848.

25. Zuckerman B, Frank DA, Hingson R, Amaro H, Levenson SM, Kayne H*, et al.* Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med* 1989;**320**:762-768.

26. Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 1990. 1991.

27. Centers for Disease Control and Prevention. HIV Surveillance Report, 2011. 2013.

28. Sheon AR, Fox HE, Rich KC, Stratton P, Diaz C, Tuomala R*, et al.* The Women and Infants Transmission Study (WITS) of maternal-infant HIV transmission: study design, methods, and baseline data. *J Womens Health* 1996;**5**:69-78.

29. Williams PL, Seage GR, 3rd, Van Dyke RB, Siberry GK, Griner R, Tassiopoulos K*, et al.* A trigger-based design for evaluating the safety of in utero antiretroviral exposure in uninfected children of human immunodeficiency virus-infected mothers. *Am J Epidemiol* 2012;**175**:950-961.

30. Tassiopoulos K, Read JS, Brogly S, Rich K, Lester B, Spector SA*, et al.* Substance use in HIV-infected women during pregnancy: self-report versus meconium analysis. *AIDS Behav* 2010;**14**:1269-1278.

31. Substance Abuse and Mental Health Services Administration. Results from the 1994 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 1995.

32. Substance Abuse and Mental Health Services Administration. Results from the 1995 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 1996.

33. Substance Abuse and Mental Health Services Administration. Results from the 1996 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 1997.

34. Substance Abuse and Mental Health Services Administration. Results from the 1997 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 1998.

35. Substance Abuse and Mental Health Services Administration. Results from the 1998 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 1999.

36. Substance Abuse and Mental Health Services Administration. Results from the 1999 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2000.

37. Substance Abuse and Mental Health Services Administration. Results from the 2000 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2001.

38. Substance Abuse and Mental Health Services Administration. Results from the 2001 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2002.

39. Substance Abuse and Mental Health Services Administration. Results from the 2002 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2003.

40. Substance Abuse and Mental Health Services Administration. Results from the 2003 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2004.

41. Substance Abuse and Mental Health Services Administration. Results from the 2004 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2005.

42. Substance Abuse and Mental Health Services Administration. Results from the 2005 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2006.

43. Substance Abuse and Mental Health Services Administration. Results from the 2006 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2007.

44. Substance Abuse and Mental Health Services Administration. Results from the 2007 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2008.

45. Substance Abuse and Mental Health Services Administration. Results from the 2008 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2009.

46. Substance Abuse and Mental Health Services Administration. Results from the 2009 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2010.

47. Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2011.

48. Substance Abuse and Mental Health Services Administration. Results from the 2011 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2012.

49. Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: national findings. Rockville, MD: Office of Applied Studies; 2013.

50. Halstead AC, Godolphin W, Lockitch G, Segal S. Timing of specimen collection is crucial in urine screening of drug dependent mothers and newborns. *Clin Biochem* 1988;**21**:59-61.

51. Ostrea EM, Brady M, Gause S, Raymundo AL, Stevens M. Drug screening of newborns by meconium analysis: a large-scale, prospective, epidemiologic study. *Pediatrics* 1992;**89**:107-113.

52. Ostrea EM, Jr., Knapp DK, Tannenbaum L, Ostrea AR, Romero A, Salari V*, et al.* Estimates of illicit drug use during pregnancy by maternal interview, hair analysis, and meconium analysis. *J Pediatr* 2001;**138**:344-348.

Chapter 3. Risk of adverse infant birth outcomes with use of tenofovir/emtricitabine-based regimens among HIV-infected pregnant women in the US

INTRODUCTION

The use of three-drug antiretroviral therapy (ART) during pregnancy has reduced the risk of perinatal HIV transmission to <1%,[1,2] becoming the standard of care in the United States (US) and globally.[3,4] While US and World Health Organization (WHO) perinatal guidelines specify which ART regimens are preferred for use during pregnancy, recommendations are based on a small body of clinical safety data, expert opinion, and programmatic considerations, including regimen harmonization across sub-populations.

Recently, the PROMISE (Promoting Maternal and Infant Survival Everywhere) trial, conducted across multiple sites in sub-Saharan Africa and India, identified potential safety concerns for one ART regimen.[2] During the trial's Period 2, pregnant women randomized to receive tenofovir disoproxil fumarate, emtricitabine, and ritonavir-boosted lopinavir (TDF/FTC/LPV/r) were twice as likely to have infants born very prematurely (<34 weeks) or at very low birth weight (<1,500g), compared to women randomized to receive zidovudine, lamivudine, and ritonavir-boosted lopinavir (ZDV/3TC/LPV/r).[2] Infants with *in utero* exposure to TDF/FTC/LPV/r were also found to have substantially greater risk of death within 14 days postpartum.

The PROMISE results were unexpected given numerous observational studies have found use of TDF/FTC-based regimens during pregnancy to be safe for most infant outcomes.[5–18] Understanding the safety of *in utero* exposure to TDF/FTC-based regimens is critical, as the WHO recommends a once-daily TDF/FTC-based regimen as first-line therapy for all HIV-infected adults, including pregnant women.[4] It

is unclear whether the risks observed in PROMISE are shared by all TDF/FTC-based regimens or how the findings will translate to other settings. Of particular interest is the safety of TDF/FTC with ritonavir-boosted atazanavir (ATV/r), as it is one of the most commonly used regimens among HIV-infected pregnant women in the US.

Using data from two large US-based perinatal cohort studies, we compared the risk of adverse birth outcomes for infants with *in utero* exposure to three specific ART regimens: ZDV/3TC/LPV/r, TDF/FTC/LPV/r, and TDF/FTC/ATV/r.

METHODS

Study participants and design

This study used data from two US-based multi-site observational cohorts of pregnant women living with HIV and their infants: the Surveillance Monitoring for ART Toxicities (SMARTT) protocol of the Pediatric HIV/AIDS Cohort Study (PHACS) and the P1025 protocol of the International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) Network. We included mother-infant pairs enrolled between April 2007 and March 2016 in the Dynamic cohort of SMARTT, which enrolls women with HIV and their infants at ≥23 weeks gestation through 72 hours postpartum. P1025 was active from 2002 through 2013, and enrolled pregnant women from either 8 (2007-2013) or 14 (2002-2006) weeks gestation through 14 days postpartum. Detailed descriptions of each study have been published previously.[19,20]

This analysis included all infants with an observed birth outcome in SMARTT or P1025, where the first ART regimen used during pregnancy was one of the three being investigated: TDF/FTC/LPV/r, TDF/FTC/ATV/r or ZDC/3TC/LPV/r. Because mother-infant pairs could be enrolled in both SMARTT and P1025, duplicate observations were removed during pooling of the datasets.

The SMARTT and P1025 protocols were approved by Institutional Review Boards at each participating site and the Harvard T.H. Chan School of Public Health. Written informed consent was obtained from all participating mothers.

Antiretroviral exposure and confounder classification

Information on maternal antiretroviral exposure, including regimen start and stop dates, was abstracted from medical records in SMARTT and P1025. For this study, participant's antiretroviral exposure was classified as the first regimen taken during pregnancy, mimicking the intention-to-treat principle. We further classified antiretroviral exposure based on timing of therapy initiation as pre-conception, first trimester, or second/third trimester.

Maternal demographic and behavioral characteristics, including age, education, race/ethnicity, and substance use, were based on maternal self-report. CD4 cell count, HIV viral load, and information on diagnoses (pre-gestational diabetes, hepatitis [B and C], sexually transmitted infections) were abstracted from medical charts and recorded lab results.

For participants co-enrolled in both SMARTT and P1025, data from P1025 was generally more complete and was prioritized, with several exceptions. Information on substance use was used preferentially from SMARTT (where it was collected more thoroughly),[21] and if covariate or outcome values were missing in P1025, data from SMARTT were used when available.

Outcome classification

In both SMARTT and P1025, gestational age was assessed using obstetric estimates based on ultrasound, physical exam, or date of last menstrual period.[22,23] In accordance with definitions used in PROMISE, deliveries occurring <37 completed weeks of gestation were considered preterm and those occurring <34 completed weeks were considered very preterm. We classified birth weights <2,500g as low birth weight

and those <1,500g as very low birthweight. We analyzed a composite adverse outcome (preterm birth, low birth weight, fetal demise, or death <14 days postpartum), and a composite severe adverse outcome (very preterm birth, very low birth weight, fetal demise, or death <14 days post-partum).

Statistical methods

Maternal characteristics were summarized, stratified by initial regimen during pregnancy. The unadjusted risk of each outcome by regimen was calculated along with the corresponding 95% Wald confidence intervals (CIs).

In primary analyses, we made three separate pairwise comparisons of ART regimens: TDF/FTC/LPV/r versus ZDV/3TC/LPV/r (the comparison made in the PROMISE trial), TDF/FTC/ATV/r versus ZDV/3TC/LPV/r (a comparison between two common regimens used during pregnancy in the US), and TDF/FTC/LPV/r versus TDF/FTC/ATV/r (a comparison between two different protease inhibitors used with TDF/FTC). For gestational age and birth weight analyses, comparisons were limited to live born infants. Log-binomial models were used to estimate risk ratios (RRs) and corresponding 95% CIs. In adjusted analyses, four risk factors with consistently strong associations with the outcomes across multiple studies were included in the models (race/ethnicity, smoking, diabetes, and sexually transmitted infection).[24] We also examined potential confounders listed in Table 3.1 and included variables substantially associated with the exposures and outcomes of interest. Due to sparse numbers for very preterm birth, very low birth weight, and severe adverse outcomes, multivariable adjustment was not feasible for these outcomes.

We conducted four subgroup analyses to ensure findings were robust and identify potential effect modification; we restricted our sample to: (1) women who initiated ART during pregnancy, (2) women who continued an ART regimen initiated before conception, (3) the first singleton pregnancy for a woman

observed in either study, and (4) women who did not switch their regimen during pregnancy. Due to sample size limitations, subgroup analyses were not adjusted for potential confounders.

In secondary analyses, we compared the use of TDF/FTC with any PI to ZDV/3TC with any PI using the same methodology described above. We also summarized risks of our outcomes by timing of regimen initiation.

All analyses were conducted in SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Of the 2,389 infants enrolled in the Dynamic SMARTT cohort and 3,146 infants enrolled in the P1025 cohort, 4,646 birth outcomes to 3,847 unique women were observed (Figure 3.3). Among these infants, 128 (2.8%) were exposed to TDF/FTC/LPV/r as the initial regimen during pregnancy, 539 (11.6%) were exposed to TDF/FTC/ATV/r, and 954 (20.5%) were exposed to ZDV/3TC/LPV/r. The percentage of women who switched regimens during pregnancy varied; 48% whose initial regimen was TDF/FTC/LPV/r changed regimens before delivery, compared to 32% in the TDF/FTC/ATV/r group and 36% in the ZDV/3TC/LPV/r group.

The distribution of most maternal characteristics was similar across the three regimens (Table 3.1). TDF/FTC/ATV/r was used more frequently in later calendar years compared to the other two regimens, and women on TDF/FTC/ATV/r as their initial regimen during pregnancy tended to be older. The timing of regimen initiation also differed between regimens; 76% of women whose first regimen was ZDV/3TC/LPV/r initiated therapy in Trimester 2 or 3 (compared to 41% for TDF/FTC/LPV/r and 36% for TDF/FTC/ATV/r), while TDF/FTC-based regimens were more likely to be started before conception (45% for TDF/FTC/LPV/r and 49% for TDF/FTC/ATV/r versus 12% for ZDV/3TC/LPV/r). Correspondingly, women on ZDV/3TC/LPV/r were more likely to be diagnosed with HIV-infection

during pregnancy, and women on the TDF/FTC-based regimens were more likely to have their first viral load measurement below 400 copies/mL.

There were 10 recorded fetal losses in our sample: 2 (1.6%) among women who received TDF/FTC/LPV/r as their first regimen during pregnancy, 2 (0.4%) among those receiving TDF/FTC/ATV/r, and 6 (0.6%) among those receiving ZDV/3TC/LPV/r. One infant each in the TDF/FTC/ATV/r and ZDV/3TC/LPV/r groups died within 14 days after delivery (0.2% and 0.1%, respectively); in both cases, the cause of death was extreme prematurity. The risks of preterm birth, low birth weight, and any adverse outcomes across the three regimens ranged from 16.1-21.4%, 16.2-23.8%, and 23.7-28.1% respectively (Table 3.2). The risks of these outcomes were lowest in the TDF/FTC/ATV/r group, though there were only slight differences between regimens for severe adverse outcomes. In unadjusted analyses, the 95% CIs for all comparisons of TDF/FTC/LPV/r to ZDV/3TC/LPV/r included the null value of 1 (Table 3.3). TDF/FTC/ATV/r appeared to be associated with a lower risk of preterm birth, low birth weight, and any adverse outcome, though only the comparison to TDF/FTC/LPV/r for low birth weight had a 95% CI that excluded the null value (RR=0.68 [0.47, 0.98]).

After adjustment, the comparison of TDF/FTC/LPV/r to ZDV/3TC/LPV/r yielded estimates close to the null value for preterm birth, low birth weight, and any adverse outcomes (RR=0.95 [0.66, 1.39]; RR=1.08 [0.76, 1.54]; RR=0.90 [0.66, 1.23], respectively; Table 3.3). For the outcomes of preterm birth, low birth weight, and any adverse outcome, TDF/FTC/ATV/r had consistently lower risks compared to the LPV/r-based regimens; however, the 95% CIs for many of these associations included the null value of 1. Secondary analyses comparing TDF/FTC/any PI to ZDV/3TC/any PI found that TDF/FTC-based regimens were associated with lower risks for preterm birth (RR=0.81 [0.68, 0.98]) and any adverse outcome (RR=0.85 [0.73, 0.99], Tables 3.4-3.7).

Results of the subgroup analyses for the outcomes of preterm birth and low birth weight are presented in Figure 3.1 (for other outcomes, see Figures 3.4-3.7). For all regimen comparisons, subgroup restriction to first singleton pregnancies and to women who did not switch regimens during pregnancy did not substantially shift estimates from crude or adjusted estimates in the overall population. However, among those who initiated therapy before conception, unadjusted risks of preterm birth and low birth weight were elevated in the TDF/FTC/LPV/r group compared to both ZDV/3TC/LPV/r (preterm RR=1.30 [0.77, 2.20]; low birth weight RR=1.79 [1.03, 3.14]) and TDF/FTC/ATV/r (preterm RR=1.71 [1.06, 2.75]; low birth weight RR=1.97 [1.23, 3.16]).

We observed a higher risk of preterm birth and very preterm birth among women who initiated any of the three regimens before conception compared to women who initiated regimens in the second or third trimester (Figure 3.2). Risks of very low birth weight and severe adverse outcomes also were slightly higher among women initiating ART before pregnancy or in the first trimester.

DISCUSSION

In two large US-based multi-site cohorts of pregnant women with HIV and their infants, the use of TDF/FTC/LPV/r during pregnancy was not associated with increased risk of adverse infant birth outcomes when compared to ZDV/3TC/LPV/r or TDF/FTC/ATV/r. In unadjusted subgroup analyses, we did observe increased risks of preterm birth, low birth weight, and a composite adverse outcome among women who initiated TDF/FTC/LPV/r before conception. Additional analyses comparing TDF/FTC/any PI to ZDV/3TC/any PI indicated slightly lower risks of preterm birth and any adverse outcome for the TDF/FTC-containing regimens.

Consistent with the PROMISE trial, we did not observe differences in risks of preterm birth and low birth weight between TDF/FTC/LPV/r and ZDV/3TC/LPV/r. Contrary to PROMISE, we were unable to replicate an increased risk of very preterm and very low birth weight deliveries for TDF/FTC/LPV/r

compared to ZDV/3TC/LPV/r. Given the small number of women who received TDF/FTC/LPV/r and the rarity of these outcomes in the sample, some comparisons involving this group were underpowered, and the upper bound of the 95% confidence intervals for the estimated RRs of very preterm birth, very low birth weight, and severe adverse outcomes included the values estimated in PROMISE. Dosing of TDF/FTC/LPV/r may also have differed between PROMISE and SMARTT/P1025; to compensate for reduced plasma levels observed in pharmacokinetic studies,[25–27] the PROMISE protocol specified 1.5 times the normal dosing of LPV/r during the third trimester. Because dosing information was not collected in SMARTT and P1025, it is unclear whether women received similar doses in this study. Another potential explanation for the lack of an association could be the relatively high rate of switching off TDF/FTC/LPV/r before delivery; however, subgroup analyses restricted to women who did not switch regimens did not alter our conclusions. Because our study lacked randomization, residual confounding could explain the discrepancy in findings, yet, for most measured characteristics, there were limited differences between women taking each ART regimen. Due to limited sample sizes for some regimens, we were unable to emulate the PROMISE eligibility criterion of including only women with CD4 counts >350 cells/mm^3 prior to regimen initiation. Finally, there are important differences in the care provided to pregnant women and their infants in the US compared to the low resource settings where PROMISE was conducted, and there may be underlying differences between the types of women in enrolled in each setting.

TDF/FTC/LPV/r was rarely used by pregnant women living with HIV in either of the two large US-based cohort studies, and use of this regimen in other settings is also limited, as it is not among WHO's recommended first line regimens.[4] Concerns regarding the use of TDF/FTC/LPV/r during pregnancy still remain; further investigation is warranted to understand why women who initiated TDF/FTC/LPV/r before conception had higher risks for preterm birth, low birth weight, and any adverse outcomes compared to women who initiated ZDV/3TC/LPV/r or TDF/FTC/ATV/r before conception.

The use of ATV/r with TDF/FTC was associated with lower risk of adverse infant birth outcomes relative to the other regimens studied. However, our results must be interpreted alongside other safety findings related to TDF, FTC, and ATV/r use in pregnancy. Several studies have shown relationships between ATV and delayed language development[28–30] and social emotional development.[30] First trimester ATV use has also been linked with increased risk of skin and musculoskeletal malformations,[16] and *in utero* TDF exposure may be linked to reduced infant bone mineral content.[14]

Several studies have evaluated the association between timing of ART and infant birth outcomes,[31–34] with the majority reporting increased risks associated with preconception ART compared to initiation later in pregnancy.[31–33] Our study adds to the limited number of studies reporting on risks of severe adverse infant birth outcomes including very preterm birth and very low birth weight by timing of regimen initiation. We observed higher risks of these outcomes among women who initiated ART before conception or in the first trimester compared to women who initiated regimens in the second or third trimester, suggesting that these women may require more careful monitoring. However, a more thorough investigation of this relationship is needed.

This study has several important limitations. First, because enrollment late in pregnancy and shortly after delivery was allowed in both P1025 and SMARTT, stillbirths and very preterm births may not be well captured. While we do not expect under-ascertainment to be differential between regimens, presence of differential measurement could cause selection bias. Second, there was limited information on some important predictors of preterm birth and low birth weight, including parity, previous preterm delivery, and hypertension. Because these variables could not be controlled for in analyses, estimates could be confounded if the distribution of these predictors varied by ART regimen. Third, because of the rare occurrence of severe adverse outcomes in the sample, some comparisons, especially those involving TDF/FTC/LPV/r, had limited power to detect safety signals. Finally, it is unclear how generalizable our finding are outside of the US; interactions between host genetics, pharmacokinetics of antiretroviral

drugs, and risks of specific outcomes have been reported, which may modify associations observed in different contexts.[35–37]

In conclusion, we did not observe increased risk of adverse or severe adverse birth outcomes for infants with *in utero* exposure to TDF/FTC/LPV/r when compared to ZDV/3TC/LPV/r or TDF/FTC/ATV/r. However, given the results of the PROMISE trial, it may be advisable to limit the use of TDF/FTC/LPV/r during pregnancy, especially given its already infrequent use and the availability of a variety of safe ARV combinations. Our findings additionally support the use of TDF/FTC-based regimens with other protease inhibitors during pregnancy, as they appear to carry similar or slightly less risk of preterm birth and low birth weight than ZDV/3TC-based regimens.

CITATION INFORMATION

Suggested reference:

Rough K, Seage GR III, Williams PL, Hernandez-Diaz S, Huo Y, Chadwick EG, Currier JS, Hoffman RM, Barr E, Shapiro DE, Patel K for the Pediatric HIV/AIDS Cohort Study (PHACS) and the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1025 Study Teams. Risk of Adverse Infant Birth Outcomes with use of tenofovir/emtricitabine-based regimens among HIV-infected pregnant women in the US [dissertation]. Boston: Harvard University; 2017.

Table 3.1. Maternal characteristics[1] by initial antiretroviral regimen during pregnancy

	Initial regimen during pregnancy					
	TDF/FTC/LPV/r n = 128		TDF/FTC/ATV/r n = 539		ZDV/3TC/LPV/r n = 954	
	n	%	n	%	n	%
Year of delivery						
2002-2004	0	0.0	0	0.0	29	3.0
2005-2008	38	29.7	92	17.1	260	27.3
2009-2012	76	59.4	290	53.8	554	58.1
2012-2016	14	10.9	157	29.1	111	11.6
Age						
24 years or less	50	39.1	136	25.2	355	37.2
25 to 34 years	67	52.3	293	54.4	473	49.6
35 years or more	11	8.6	109	20.2	125	13.1
Missing	*0*	*0.0*	*1*	*0.2*	*1*	*0.1*
Education						
Less than high school	34	26.6	188	34.9	331	34.7
High school diploma	61	47.7	240	44.5	427	44.8
College or more	33	25.8	109	20.2	194	20.3
Missing	*0*	*0.0*	*2*	*0.4*	*2*	*0.2*
Race/ethnicity						
Non-Hispanic White	15	11.7	44	8.2	68	7.1
Non-Hispanic Black	81	63.3	365	67.7	611	64.0
Hispanic	30	23.4	120	22.3	258	27.0
Other	1	0.8	9	1.7	11	1.2
Missing	*1*	*0.8*	*1*	*0.2*	*6*	*0.6*
First CD4 in pregnancy						
Less than 250 cells/mm^3	30	23.4	100	18.6	194	20.3
250 to 500 cells/mm^3	47	36.7	205	38.0	381	39.9
More than 500 cells/mm^3	47	36.7	225	41.7	365	38.3
Missing	*4*	*3.1*	*9*	*1.7*	*14*	*1.5*
First viral RNA in pregnancy						
Less than 400 copies/mL	61	47.7	277	51.4	281	29.5
400 to 10,000 copies/mL	33	25.8	137	25.4	361	37.8
More than 10,000 copies/mL	33	25.8	122	22.6	305	32.0
Missing	*1*	*0.8*	*3*	*0.6*	*7*	*0.7*
Timing of HIV diagnosis						
Before pregnancy	107	83.6	470	87.2	673	70.5
During pregnancy	21	16.4	69	12.8	278	29.1
Missing	*0*	*0.0*	*0*	*0.0*	*3*	*0.3*
Timing of regimen initiation						
Before pregnancy	58	45.3	265	49.2	111	11.6
Trimester 1	18	14.1	82	15.2	115	12.1
Trimester 2 or 3	52	40.6	192	35.6	728	76.3
Alcohol use during pregnancy						
Yes	25	19.5	92	17.1	182	19.1
No	91	71.1	432	80.1	705	73.9
Missing	*12*	*9.4*	*15*	*2.8*	*67*	*7.0*

Table 3.1 (continued). Maternal characteristics[1] by initial antiretroviral regimen during pregnancy

	Initial regimen during pregnancy					
	TDF/FTC/LPV/r n = 128		TDF/FTC/ATV/r n = 539		ZDV/3TC/LPV/r n = 954	
	n	%	n	%	n	%
Tobacco use during pregnancy						
Yes	30	23.4	105	19.5	182	19.1
No	77	60.2	387	71.8	628	65.8
Missing	*21*	*16.4*	*47*	*8.7*	*144*	*15.1*
Illicit drug use during pregnancy						
Yes	21	16.4	61	11.3	115	12.1
No	85	66.4	427	79.2	687	72.0
Missing	*22*	*17.2*	*51*	*9.5*	*152*	*15.9*
Pregestational diabetes						
Yes	1	0.8	10	1.9	12	1.3
No	126	98.4	527	97.8	939	98.4
Missing	*1*	*0.8*	*2*	*0.4*	*3*	*0.3*
Hepatitis B or C during pregnancy						
Yes	20	15.6	71	13.2	99	10.4
No	108	84.4	468	86.8	855	89.6
Sexually transmitted infection[2] during pregnancy						
Yes	36	28.1	208	38.6	373	39.1
No	78	60.9	297	55.1	513	53.8
Missing	*14*	*10.9*	*34*	6.3	*68*	*7.1*

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinivir; ATV/r, ritonavir-boosted atazanavir; ZDV, zidovudine; 3TC, lamivudine

[1] Mothers may not be unique. Some women had multiple pregnancies under study observation.

[2]Sexually transmitted infections include syphilis, gonorrhea, chlamydia, genital herpes, or "other" sexually transmitted infections noted in the medical chart.

Table 3.2. Risk of infant outcomes by initial antiretroviral regimen during pregnancy

	Initial antiretroviral regimen during pregnancy								
	TDF/FTC/LPV/r			TDF/FTC/ATV/r			ZDV/3TC/LPV/r		
Outcome	n	Risk (%)	95% CI	n	Risk (%)	95% CI	n	Risk (%)	95% CI
Preterm birth[1]	27	21.4	(14.3, 28.6)	86	16.1	(13.0, 19.2)	184	19.5	(16.9, 22.0)
Very preterm birth[2]	5	4.0	(0.6, 7.4)	26	4.9	(3.0, 6.7)	44	4.7	(3.3, 6.0)
Low birth weight[3]	30	23.8	(16.4, 31.2)	86	16.2	(13.0, 19.3)	175	18.8	(16.3, 21.3)
Very low birth weight[4]	1	0.8	(0.0, 2.3)	10	1.9	(0.7, 3.0)	18	1.9	(1.0, 2.8)
Adverse outcome[5]	36	28.1	(20.3, 35.9)	127	23.7	(20.1, 27.3)	256	27.2	(24.4, 30.1)
Severe adverse outcome[6]	7	5.5	(1.5, 9.4)	28	5.2	(3.3, 7.1)	51	5.4	(4.0, 6.9)

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinivir; ATV/r, ritonavir-boosted atazanavir; ZDV, zidovudine; 3TC, lamivudine; CI, confidence interval

[1]Preterm birth defined as <37 weeks gestational age

[2]Very preterm birth defined as <34 weeks gestational age

[3]Low birth weight defined as <2,500g

[4]Very low birth weight defined as <1,500g

[5]Adverse outcome defined as preterm birth, low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

[6]Severe adverse outcome defined as very preterm birth, very low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

Table 3.3. Risk ratios for infant outcomes based on comparison of initial antiretroviral regimen during pregnancy

	TDF/FTC/LPV/r vs ZDV/3TC/LPV/r				TDF/FTC/ATV/r vs ZDV/3TC/LPV/r				TDF/FTC/LPV/r vs TDF/FTC/ATV/r			
	Crude		Adjusted[1]		Crude		Adjusted[1]		Crude		Adjusted[1]	
Outcome	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Preterm birth[2]	1.10	(0.77, 1.58)	0.95	(0.66, 1.39)	0.83	(0.65, 1.04)	0.76	(0.59, 0.99)	1.33	(0.91, 1.96)	1.23	(0.84, 1.82)
Very preterm birth[3]	0.85	(0.19, 2.11)			1.04	(0.65, 1.68)			0.82	(0.32, 2.08)		
Low birth weight[4]	1.27	(0.90, 1.78)	1.08	(0.76, 1.54)	0.86	(0.68, 1.09)	0.83	(0.64, 1.09)	1.47	(1.02, 2.13)	1.40	(0.97, 2.03)
Very low birth weight[5]	0.41	(0.06, 3.06)			0.97	(0.45, 2.10)			0.42	(0.05, 3.27)		
Adverse outcome[6]	1.03	(0.77, 1.39)	0.90	(0.66, 1.23)	0.87	(0.72, 1.05)	0.83	(0.67, 1.02)	1.18	(0.86, 1.62)	1.11	(0.81, 1.52)
Severe adverse outcome[7]	1.01	(0.47, 2.17)			0.96	(0.61, 1.51)			1.04	(0.47, 2.34)		

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinivir; ZDV, zidovudine; 3TC, lamivudine; ATV/r, ritonavir-boosted atazanavir; RR, risk ratio; CI, confidence interval

[1]Log-binomial models adjusted for race/ethnicity, smoking, diabetes, sexually transmitted infection, and timing of antiretroviral therapy initiation

[2]Preterm birth defined as <37 weeks gestational age

[3]Very preterm birth defined as <34 weeks gestational age

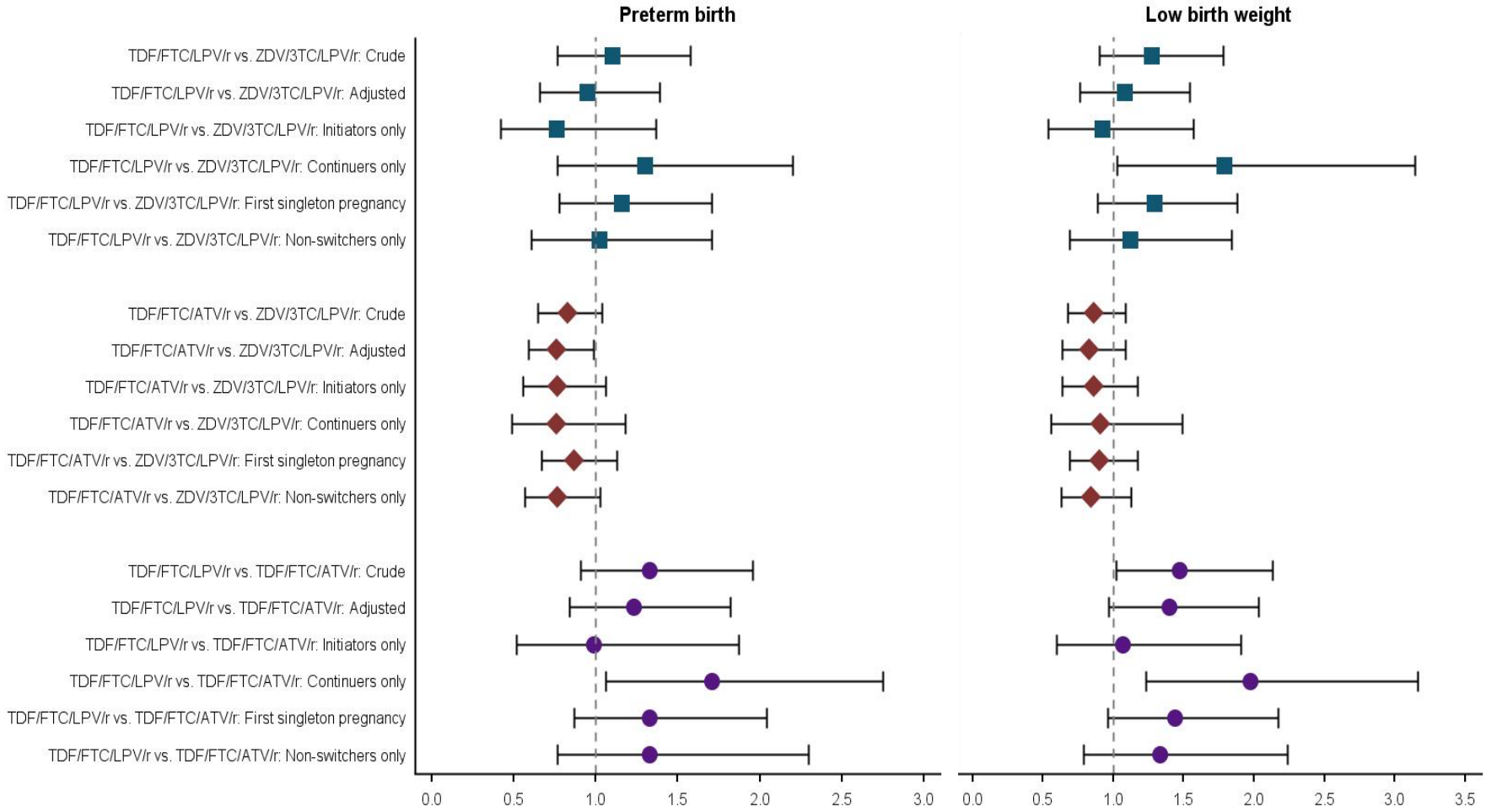
[4]Low birth weight defined as <2,500g

[5]Very low birth weight defined as <1,500g

[6]Adverse outcome defined as preterm birth, low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

[7]Severe adverse outcome defined as very preterm birth, very low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

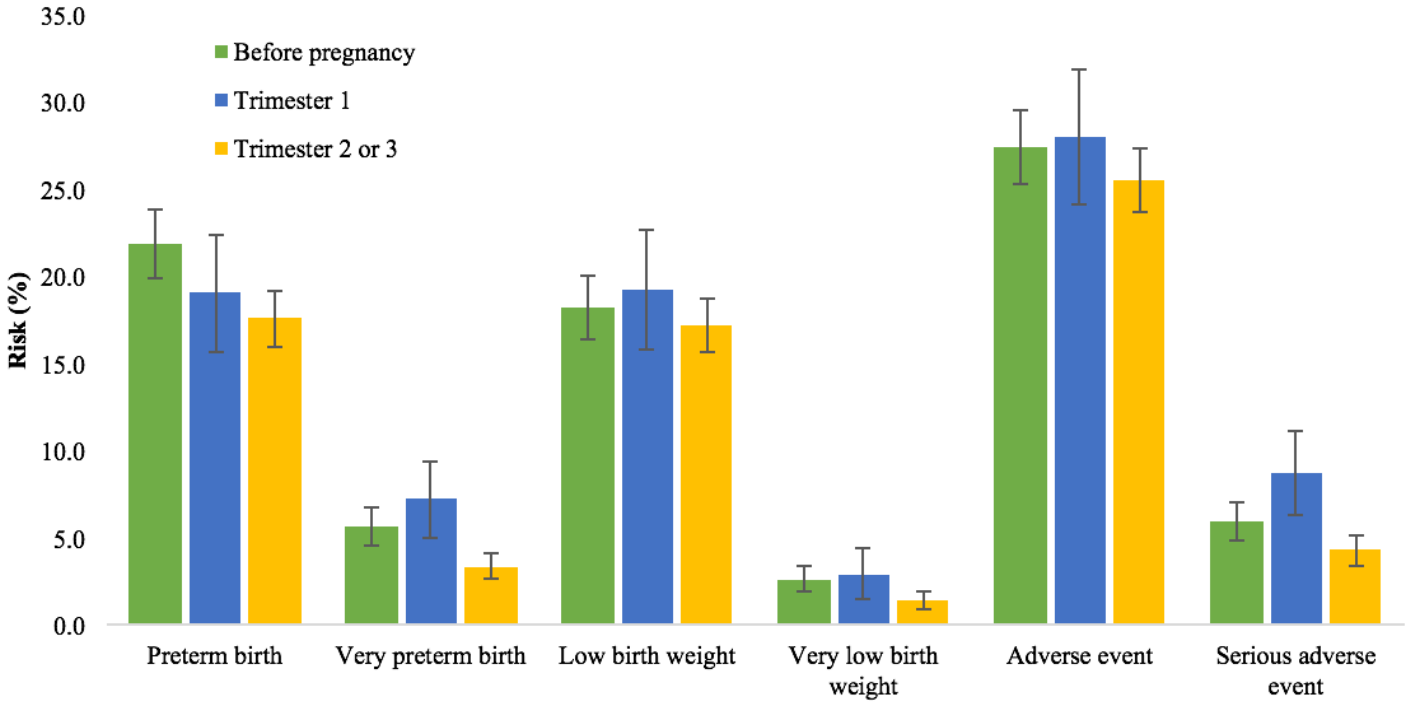
Figure 3.1. Subgroup analyses for comparison of initial antiretroviral regimen during pregnancy and risk of preterm birth[1] and low birth weight[2]: Risk ratios and corresponding 95% confidence intervals



Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinivir; ZDV, zidovudine; 3TC, lamivudine; ATV/r, ritonavir-boosted atazanavir
Note: "Adjusted" risk ratios obtained from log-binomial models adjusted for race/ethnicity, smoking, diabetes, sexually transmitted infection, and timing of antiretroviral therapy initiation

"Initiators" defined as women who initiated ART regimen during pregnancy
"Continuers" defined as women who initiated ART prior to conception
[1]Preterm birth defined as <37 weeks gestational age
[2]Low birth weight defined as <2,500g

Figure 3.2. Risk of birth outcomes by timing of antiretroviral therapy initiation, with 95% confidence intervals



	Preterm birth		Very preterm birth		Low birth weight		Very low birth weight		Adverse event		Serious adverse event	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Before pregnancy	22.0	(19.0, 25.0)	5.7	(4.0, 7.4)	18.2	(15.4, 21.1)	2.7	(1.5, 3.9)	27.5	(24.2, 30.7)	6.0	(4.3, 7.8)
Trimester 1	19.1	(14.7, 23.5)	7.2	(4.3, 10.2)	19.3	(14.8, 23.7)	3.0	(1.1, 4.9)	28.0	(23.0, 33.0)	8.8	(5.6, 12.0)
Trimester 2/3	17.6	(15.7, 19.5)	3.4	(2.5, 4.3)	17.2	(15.3, 19.1)	1.4	(0.8, 2.0)	25.6	(23.4, 27.8)	4.3	(3.3, 5.4)

Abbreviations: CI, confidence interval

Figure 3.3. Flowchart of study pooling and inclusion criteria

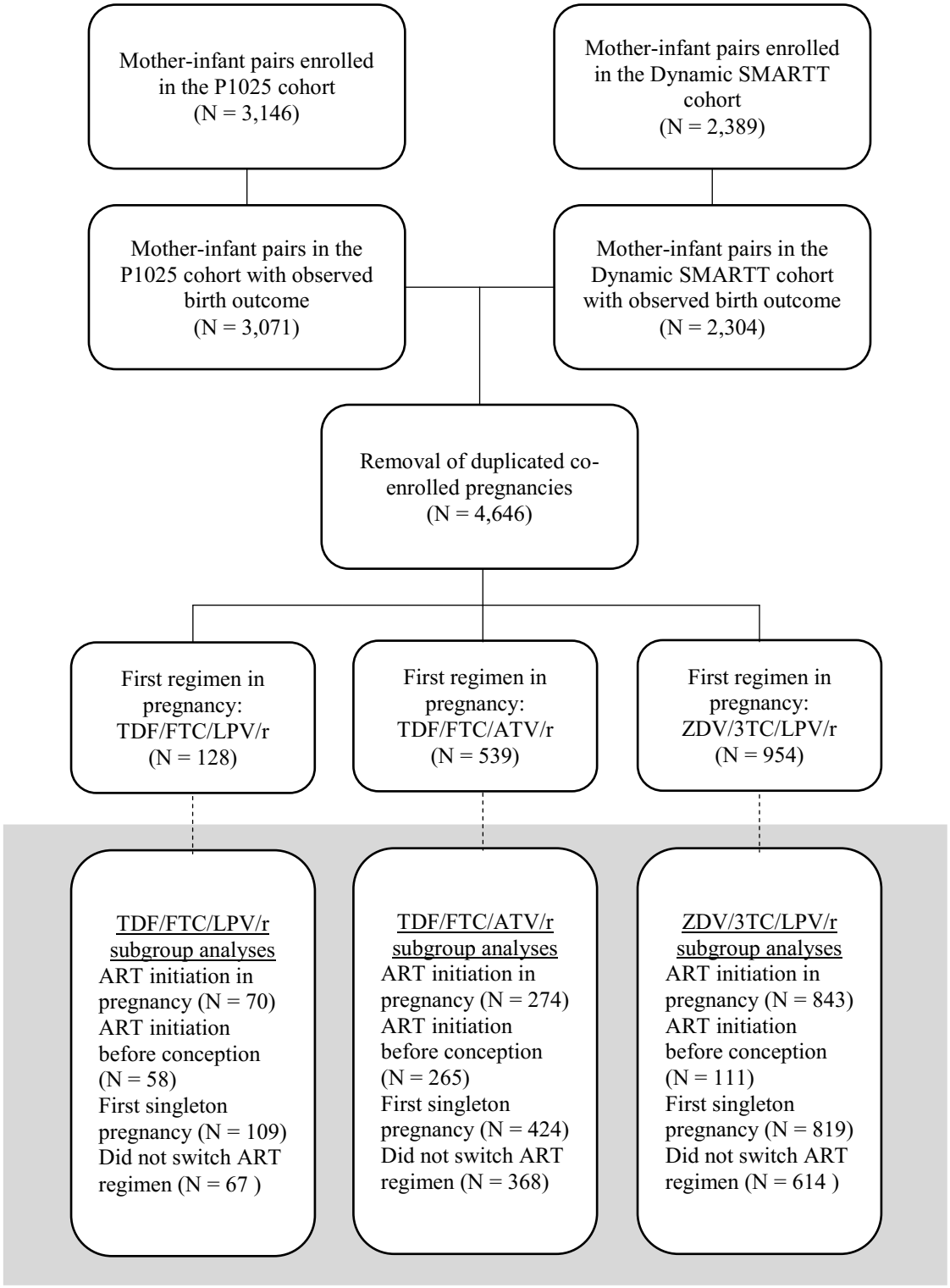


Table 3.4. Maternal characteristics[1] by initial antiretroviral regimen during pregnancy: TDF/FTC/Any PI versus ZDV/3TC/Any PI

	Initial regimen during pregnancy			
	TDF/FTC/Any PI N = 960		ZDV/3TC/Any PI N = 1,593	
	n	%	n	%
Year of delivery				
2002-2004	0	0.0	138	8.7
2005-2008	178	18.5	610	38.3
2009-2012	514	53.5	693	43.5
2012-2016	268	27.9	152	9.5
Age				
24 years or less	254	26.5	592	37.2
25 to 34 years	533	55.5	785	49.3
35 years or more	170	17.7	214	13.4
Missing	*3*	*0.3*	*2*	*0.1*
Education				
Less than high school	313	32.6	570	35.8
High school diploma	434	45.2	690	43.3
College or more	209	21.8	327	20.5
Missing	*4*	*0.4*	*6*	*0.4*
Race/ethnicity				
Non-Hispanic White	81	8.4	113	7.1
Non-Hispanic Black	629	65.5	966	60.6
Hispanic	233	24.3	484	30.4
Other	15	1.6	19	1.2
Missing	*2*	*0.2*	*11*	*0.7*
First CD4 in pregnancy				
Less than 250 cells/mm^3	187	19.5	293	18.4
250 to 500 cells/mm^3	374	39.0	676	42.4
More than 500 cells/mm^3	379	39.5	591	37.1
Missing	*20*	*2.1*	*33*	*2.1*
First viral RNA in pregnancy				
Less than 400 copies/mL	503	52.4	469	29.4
400 to 10,000 copies/mL	224	23.3	601	37.7
More than 10,000 copies/mL	223	23.2	500	31.4
Missing	*10*	*1.0*	*23*	*1.4*
Timing of HIV diagnosis				
Before pregnancy	834	86.9	1,112	69.8
During pregnancy	124	12.9	478	30.0
Missing	2	0.2	3	0.2

Table 3.4 (continued). Maternal characteristics[1] by initial antiretroviral regimen during pregnancy: TDF/FTC/Any PI versus ZDV/3TC/Any PI

	Initial regimen during pregnancy			
	TDF/FTC/Any PI N = 960		ZDV/3TC/Any PI N = 1,593	
	n	%	n	%
Timing of regimen initiation				
Before pregnancy	490	51.0	240	15.1
Trimester 1	135	14.1	177	11.1
Trimester 2 or 3	335	34.9	1,176	73.8
Alcohol use during pregnancy				
Yes	156	16.3	298	18.7
No	767	79.9	1,166	73.2
Missing	*37*	*3.9*	*129*	*8.1*
Tobacco use during pregnancy				
Yes	188	19.6	295	18.5
No	676	70.4	997	62.6
Missing	*96*	*10.0*	*301*	*18.9*
Illicit drug use during pregnancy				
Yes	115	12.0	191	12.0
No	741	77.2	1,079	67.7
Missing	*104*	*10.8*	*323*	*20.3*
Pregestational diabetes				
Yes	15	1.6	24	1.5
No	939	97.8	1,564	98.2
Missing	*6*	*0.6*	*5*	*0.3*
Hepatitis B or C during pregnancy				
Yes	135	14.1	153	9.6
No	825	85.9	1,440	90.4
Sexually transmitted infection[2] during pregnancy				
Yes	338	35.2	586	36.8
No	553	57.6	849	53.3
Missing	*69*	*7.2*	*158*	*9.9*

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; PI, protease inhibitor; ZDV, zidovudine; 3TC, lamivudine
[1]Mothers may not be unique. Some women had multiple pregnancies under study observation.
[2]Sexually transmitted infections include syphilis, gonorrhea, chlamydia, genital herpes, or "other" sexually transmitted infections noted in the medical chart.

Table 3.5. Risk of infant outcomes by initial antiretroviral regimen during pregnancy: TDF/FTC/Any PI versus ZDV/3TC/Any PI

	Initial antiretroviral regimen during pregnancy					
	TDF/FTC/Any PI			ZDV/3TC/Any PI		
Outcome	n	Risk (%)	95% CI	n	Risk (%)	95% CI
Preterm birth[1]	170	17.9	(15.4, 20.3)	311	19.7	(17.8, 21.7)
Very preterm birth[2]	47	4.9	(3.6, 6.3)	67	4.3	(3.3, 5.3)
Low birth weight[3]	167	17.7	(15.2, 20.1)	275	17.8	(15.9, 19.7)
Very low birth weight[4]	17	1.8	(1.0, 2.6)	32	2.1	(1.4, 2.8)
Adverse outcome[5]	237	24.9	(22.2, 27.7)	426	27.3	(25.1, 29.5)
Severe adverse outome[6]	51	5.4	(3.9, 6.8)	83	5.3	(4.2, 6.5)

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; PI, protease inhibitor; ZDV, zidovudine; 3TC, lamivudine; CI, confidence interval

[1]Preterm birth defined as <37 weeks gestational age

[2]Very preterm birth defined as <34 weeks gestational age

[3]Low birth weight defined as <2,500g

[4]Very low birth weight defined as <1,500g

[5]Adverse outcome defined as preterm birth, low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

[6]Serious adverse outcome defined as very preterm birth, very low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

Table 3.6. Risk ratios for infant outcomes: TDF/FTC/Any PI versus ZDV/3TC/Any PI

	Crude		Adjusted[1]	
	RR	95% CI	RR	95% CI
Preterm birth[2]	0.90	(0.76, 1.07)	0.81	(0.68, 0.98)
Very preterm birth[3]	1.16	(0.81, 1.67)		
Low birth weight[4]	0.86	(0.68, 1.09)	0.94	(0.78, 1.14)
Very low birth weight[5]	0.87	(0.49, 1.56)		
Adverse outcome[6]	0.87	(0.72, 1.05)	0.85	(0.73, 0.99)
Serious adverse outcome[7]	1.01	(0.72, 1.41)		

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; PI, protease inhibitor; ZDV, zidovudine; 3TC, lamivudine; RR, risk ratio; CI, confidence interval

[1]Log-binomial models adjusted for race/ethnicity, smoking, diabetes, sexually transmitted infection, and timing of antiretroviral therapy initiation

[2]Preterm birth defined as <37 weeks gestational age

[3]Very preterm birth defined as <34 weeks gestational age

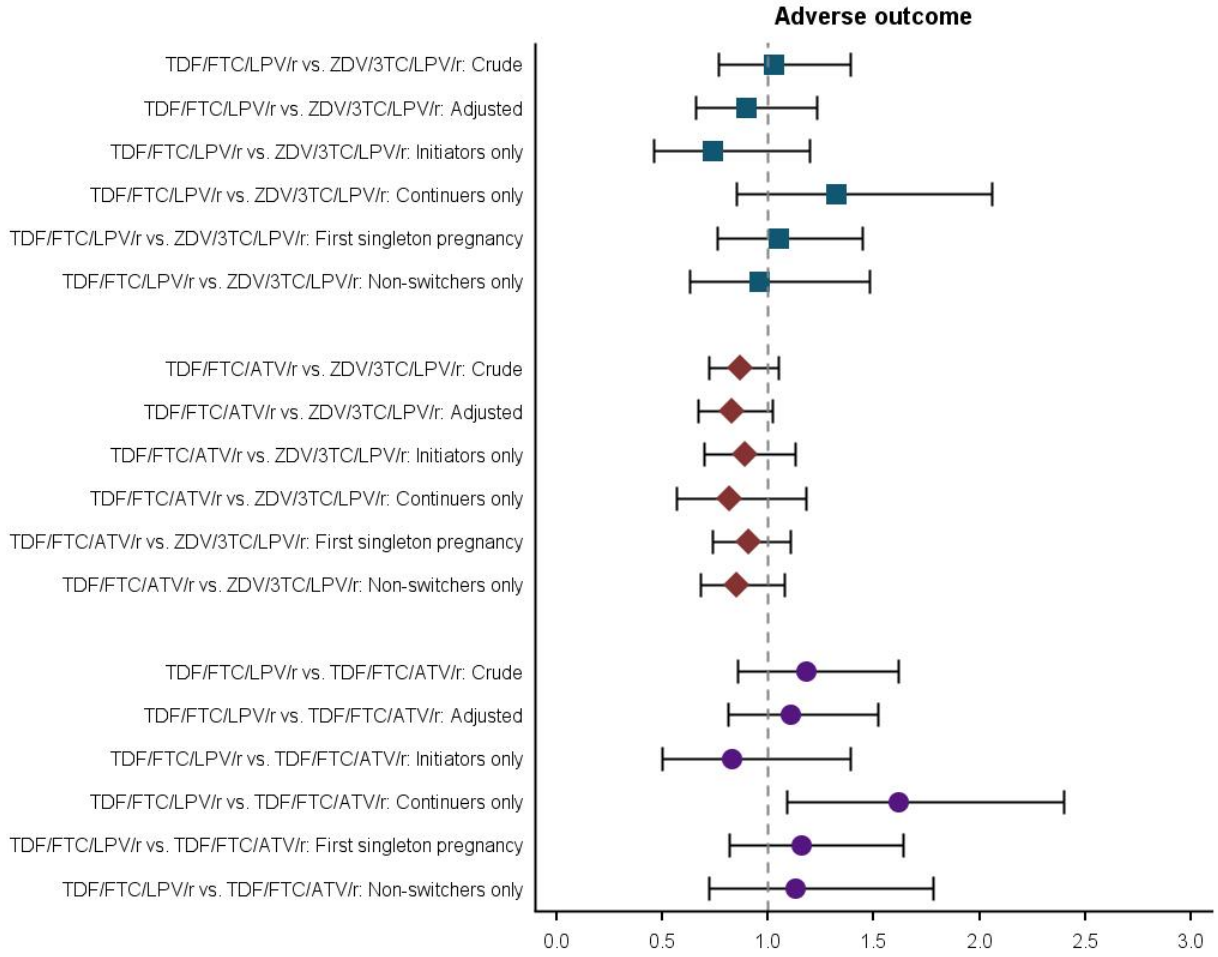
[4]Low birth weight defined as <2,500g

[5]Very low birth weight defined as <1,500g

[6]Adverse outcome defined as preterm birth, low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

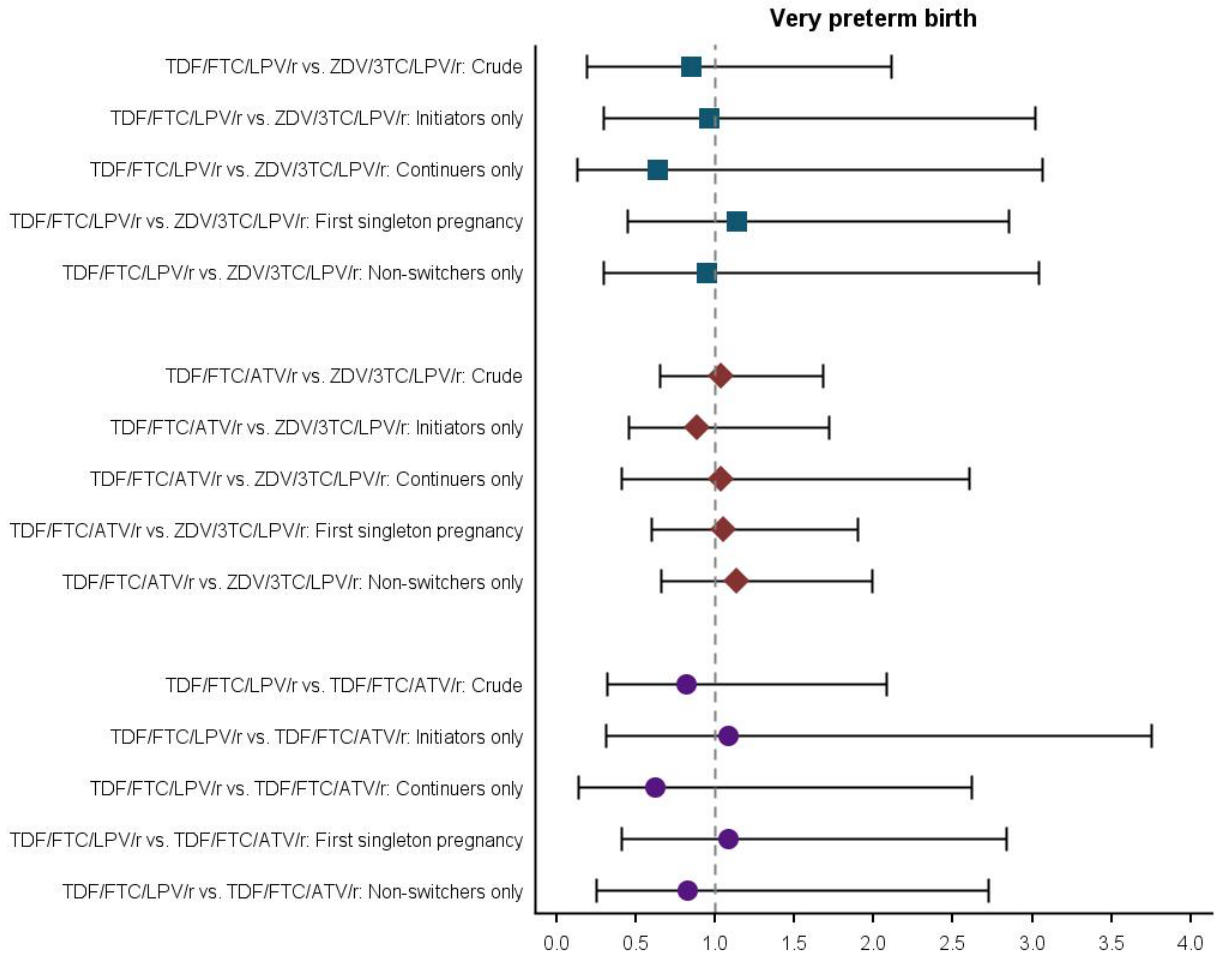
[7]Serious adverse outcome defined as very preterm birth, very low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

Figure 3.4. Subgroup analyses for comparison of initial antiretroviral regimen during pregnancy and risk of any adverse outcome[1]: Risk ratios and corresponding 95% confidence intervals



Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinivir; ZDV, zidovudine; 3TC, lamivudine; ATV/r, ritonavir-boosted atazanavir
Note: "Adjusted" risk ratios obtained from log-binomial models adjusted for race/ethnicity, smoking, diabetes, sexually transmitted infection, and timing of antiretroviral therapy initiation
[1]Adverse outcome defined as preterm birth, low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

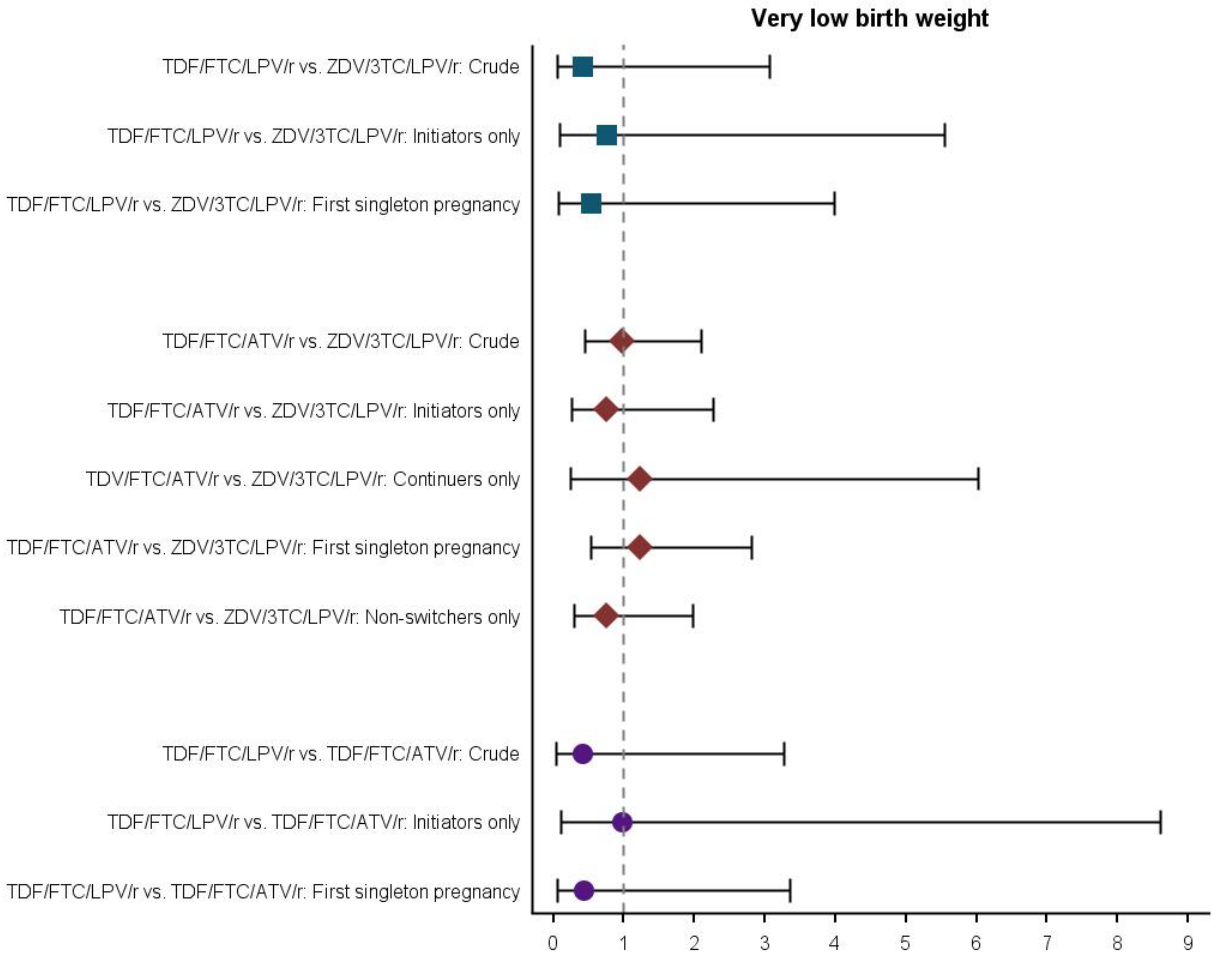
Figure 3.5. Subgroup analyses for comparison of initial antiretroviral regimen during pregnancy and risk of very preterm birth[1]: Risk ratios and corresponding 95% confidence intervals



Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinivir; ZDV, zidovudine; 3TC, lamivudine; ATV/r, ritonavir-boosted atazanavir

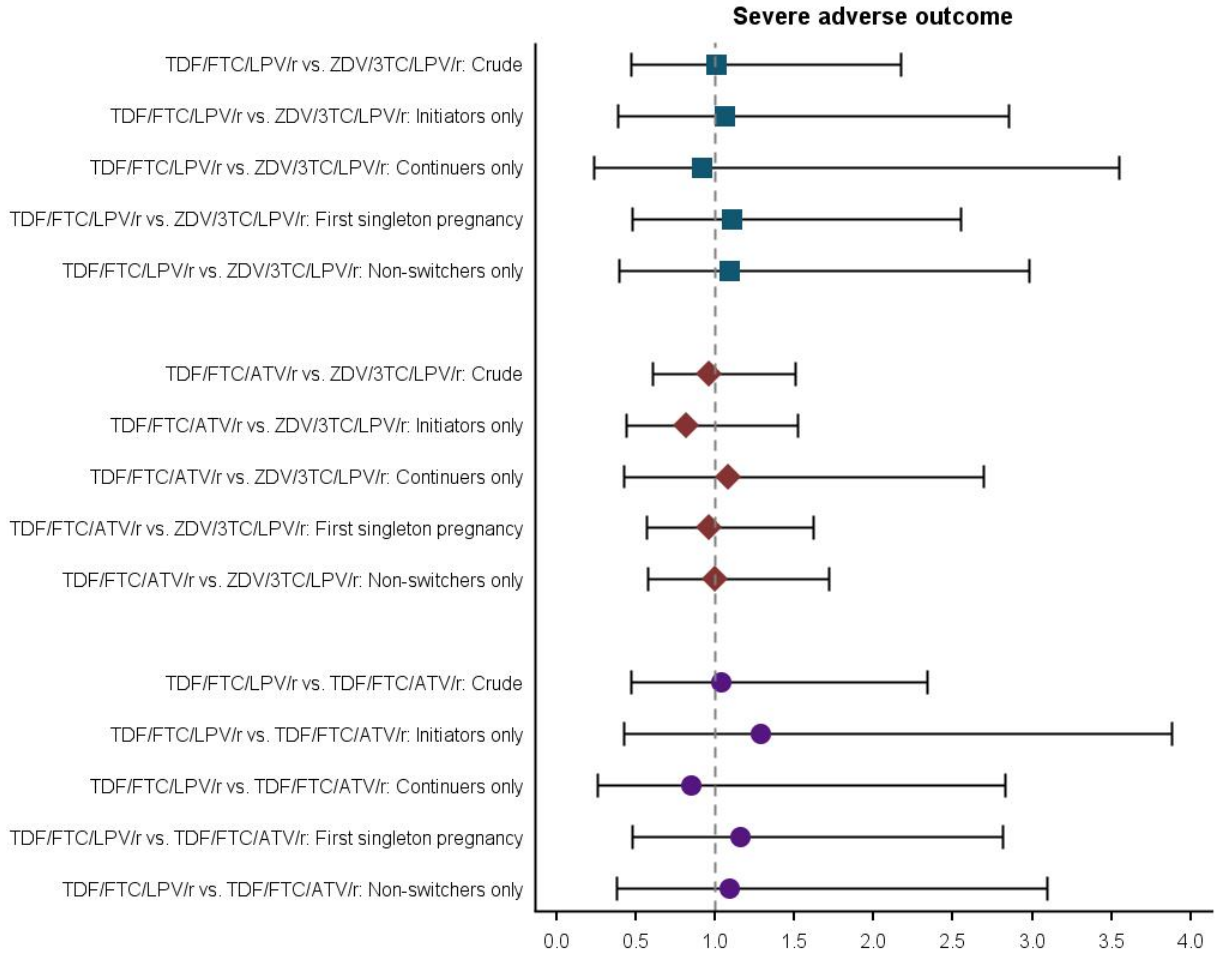
[1]Very preterm birth defined as <34 weeks gestational age

Figure 3.6. Subgroup analyses for comparison of initial antiretroviral regimen during pregnancy and risk of very low birth weight[1]: Risk ratios and corresponding 95% confidence intervals



Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinivir; ZDV, zidovudine; 3TC, lamivudine; ATV/r, ritonavir-boosted atazanavir
[1]Very low birth weight defined as <1,500g

Figure 3.7. Subgroup analyses for comparison of initial antiretroviral regimen during pregnancy and risk of serious adverse outcome[1]: Risk ratios and corresponding 95% confidence intervals



Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinivir; ZDV, zidovudine; 3TC, lamivudine; ATV/r, ritonavir-boosted atazanavir

[1]Serious adverse outcome defined as very preterm birth, very low birth weight, fetal loss, or neonatal mortality (within 14 days after delivery)

REFERENCES

1. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defici Syndr*. 2002;29(5):484-494.
2. Fowler MG, Qin M, Fiscus SA, et al. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. *N Engl J Med*. 2016;375(18):1726-1737. doi:10.1056/NEJMoa1511691.
3. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.*; 2016. https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0.
4. World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*. World Health Organization; 2016. http://www.who.int/hiv/pub/arv/arv-2016/en/. Accessed July 27, 2016.
5. Nurutdinova D, Onen NF, Hayes E, Mondy K, Overton ET. Adverse effects of tenofovir use in HIV-infected pregnant women and their infants. *Ann Pharmacother*. 2008;42(11):1581-1585. doi:10.1345/aph.1L083.
6. Kinai E, Hosokawa S, Gomibuchi H, Gatanaga H, Kikuchi Y, Oka S. Blunted fetal growth by tenofovir in late pregnancy. *AIDS*. 2012;26(16):2119-2120. doi:10.1097/QAD.0b013e328358ccaa.
7. Viganò A, Mora S, Giacomet V, et al. In utero exposure to tenofovir disoproxil fumarate does not impair growth and bone health in HIV-uninfected children born to HIV-infected mothers. *Antivir Ther*. 2011;16(8):1259-1266. doi:10.3851/IMP1909.
8. Siberry GK, Williams PL, Mendez H, et al. Safety of tenofovir use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. *AIDS*. 2012;26(9):1151-1159. doi:10.1097/QAD.0b013e328352d135.
9. Gibb DM, Kizito H, Russell EC, et al. Pregnancy and infant outcomes among HIV-infected women taking long-term ART with and without tenofovir in the DART trial. *PLoS Med*.

2012;9(5):e1001217. doi:10.1371/journal.pmed.1001217.

10. Ransom CE, Huo Y, Patel K, et al. Infant growth outcomes after maternal tenofovir disoproxil fumarate use during pregnancy. *J Acquir Immune Defic Syndr*. 2013;64(4):374-381. doi:10.1097/QAI.0b013e3182a7adb2.

11. Celen MK, Mert D, Ay M, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection. *World J Gastroenterol*. 2013;19(48):9377-9382. doi:10.3748/wjg.v19.i48.9377.

12. Greenup AJ, Tan PK, Nguyen V, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. *J Hepatol*. 2014;61(3):502-507.

13. Vivanti A, Soheili TS, Cuccuini W, et al. Comparing genotoxic signatures in cord blood cells from neonates exposed in utero to zidovudine or tenofovir. *AIDS*. 2015;29(11):1319-1324. doi:10.1097/QAD.0000000000000564.

14. Siberry GK, Jacobson DL, Kalkwarf HJ, et al. Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate During Pregnancy. *Clin Infect Dis*. 2015;61(6):996-1003. doi:10.1093/cid/civ437.

15. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. *Pediatr Infect Dis J*. 2012;31(2):164-170. doi:10.1097/INF.0b013e318235c7aa.

16. Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and in utero antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):48-55. doi:10.1001/jamapediatrics.2014.1889.

17. Brogly SB, Abzug MJ, Watts DH, et al. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. *Pediatr Infect Dis J*. 2010;29(8):721-727. doi:10.1097/INF.0b013e3181e74a2f.

18. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11).

PLoS Med. 2014;11(4):e1001635. doi:10.1371/journal.pmed.1001635.

19. Williams PL, Seage GR, Van Dyke RB, et al. A trigger-based design for evaluating the safety of in utero antiretroviral exposure in uninfected children of human immunodeficiency virus-infected mothers. *Am J Epidemiol*. 2012;175(9):950-961. doi:10.1093/aje/kwr401.

20. Livingston EG, Huo Y, Patel K, et al. Complications and route of delivery in a large cohort study of HIV-1-infected Women- IMPAACT P1025. *J Acquir Immune Defic Syndr*. April 2016. doi:10.1097/QAI.0000000000001021.

21. Tassiopoulos K, Read JS, Brogly S, et al. Substance use in HIV-Infected women during pregnancy: self-report versus meconium analysis. *AIDS Behav*. 2010;14(6):1269-1278. doi:10.1007/s10461-010-9705-0.

22. Patel K, Shapiro DE, Brogly SB, et al. Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. *J Infect Dis*. 2010;201(7):1035-1044. doi:10.1086/651232.

23. Watts DH, Williams PL, Kacanek D, et al. Combination antiretroviral use and preterm birth. *J Infect Dis*. 2013;207(4):612-621. doi:10.1093/infdis/jis728.

24. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75-84.

25. Stek AM, Mirochnick M, Capparelli E, et al. Reduced lopinavir exposure during pregnancy. *AIDS*. 2006;20(15):1931-1939. doi:10.1097/01.aids.0000247114.43714.90.

26. Mirochnick M, Best BM, Stek AM, et al. Lopinavir exposure with an increased dose during pregnancy. *J Acquir Immune Defic Syndr*. 2008;49(5):485-491. doi:10.1097/QAI.0b013e318186edd0.

27. Best BM, Stek AM, Mirochnick M, et al. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. *J Acquir Immune Defic Syndr*. 2010;54(4):381-388. http://www.ncbi.nlm.nih.gov/pubmed/20632458.

28. Sirois PA, Huo Y, Williams PL, et al. Safety of perinatal exposure to antiretroviral medications:

developmental outcomes in infants. *Pediatr Infect Dis J*. 2013;32(6):648-655. doi:10.1097/INF.0b013e318284129a.

29. Rice ML, Zeldow B, Siberry GK, et al. Evaluation of risk for late language emergence after in utero antiretroviral drug exposure in HIV-exposed uninfected infants. *Pediatr Infect Dis J*. 2013;32(10):e406-13. doi:10.1097/INF.0b013e31829b80ee.
30. Caniglia EC, Patel K, Huo Y, et al. Atazanavir exposure in utero and neurodevelopment in infants: a comparative safety study. *AIDS*. 2016;30(8):1267-1278. doi:10.1097/QAD.0000000000001052.
31. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. *J Infect Dis*. 2012;206(11):1695-1705. doi:10.1093/infdis/jis553.
32. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis*. 2015;61(11):1715-1725. doi:10.1093/cid/civ578.
33. Sibiude J, Warszawski J, Tubiana R, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? *Clin Infect Dis*. 2012;54(9):1348-1360. doi:10.1093/cid/cis198.
34. Short CE, Douglas M, Smith JH, Taylor GP. Preterm delivery risk in women initiating antiretroviral therapy to prevent HIV mother-to-child transmission. *HIV Med*. 2014;15(4):233-238. doi:10.1111/hiv.12083.
35. Elens L, Vandercam B, Yombi J-C, Lison D, Wallemacq P, Haufroid V. Influence of host genetic factors on efavirenz plasma and intracellular pharmacokinetics in HIV-1-infected patients. *Pharmacogenomics*. 2010;11(9):1223-1234. doi:10.2217/pgs.10.94.
36. López Aspiroz E, Cabrera Figueroa SE, Porras Hurtado GL, et al. Pharmacogenetic analysis of SNPs in genes involved in the pharmacokinetics and response to lopinavir/ritonavir therapy. *Curr Drug Metab*. 2013;14(7):729-737.
37. Purswani MU, Patel K, Winkler CA, et al. Brief Report: APOL1 Renal Risk Variants Are

Associated With Chronic Kidney Disease in Children and Youth With Perinatal HIV Infection. *J Acquir Immune Defic Syndr*. 2016;73(1):63-68. doi:10.1097/QAI.0000000000001010.

Chapter 4. Zidovudine use in pregnancy and congenital malformations: A Bayesian analysis

INTRODUCTION

Use of antiretroviral drugs during pregnancy has dramatically reduced the risk of perinatal transmission of HIV to less than 1%.[1,2] However, there are lingering concerns about the safety of specific antiretroviral agents when used during pregnancy,[3] and careful evaluation of the risks associated with specific drugs are needed to inform treatment decisions. Zidovudine is one antiretroviral agent that has frequently been used to treat HIV during pregnancy, though it is no longer a component of the preferred first-line treatment, largely for programmatic reasons unrelated to safety.[4]

Some epidemiological studies have found that zidovudine use, especially in the first trimester, is associated with modest elevations in the risk of overall malformations,[5] cardiac malformations,[6–8] and male genital malformations.[9,10] However, a number of other studies have not replicated the increased risk.[11–18] There are several potential explanations for these seemingly inconsistent results, including heterogeneity in study design, exposure definition and outcome measurement. Further, because malformations are rare events, individual studies may lack the power to detect differences in risk, especially for specific malformation subgroups.

To provide more robust estimates of the association between zidovudine and overall, cardiac, and male genital malformations, we used Bayesian methods, which allow us to formally incorporate existing knowledge about an association into an analysis of new data. We conducted a systematic review and meta-analysis to develop a prior distribution for the risk of defects associated with zidovudine, and incorporated data from the Medicaid Analytic eXtract (MAX) to provide the most updated evidence available on this safety concern.

METHODS

Study population

This study used data from the Medicaid Analytic eXtract (MAX), a collection of enrollment information and healthcare claims for Medicaid beneficiaries nationwide in the United States. We had access to claims for inpatient and outpatient diagnoses and procedures, as well as outpatient pharmacy dispensing, from 2000-2010. An estimated 45% of all deliveries that occur in the United States are covered by Medicaid.[19]

We identified a cohort of pregnancies in MAX where distinct mothers and infants could be matched. The creation of this cohort has previously been described in detail.[20] Briefly, women between the ages of 12 and 55 years old with a code indicating delivery were identified and linked to live-born infants based on shared family Case Numbers. We removed infants linked to more than one woman, as well as deliveries that were unreasonably close in time. The sample was restricted to women continuously enrolled in Medicaid, without supplementary private insurance or restricted benefits, for 3 months prior to estimated last menstrual period (LMP) through 30 days after delivery, and infants were required to be continuously enrolled for 90 days after delivery or until death, whichever occurred sooner.

We included women who met any of our diagnostic criteria for HIV infection: (a) ≥2 claims for an HIV diagnosis; (b) ≥1 claim for HIV diagnosis and ≥1 HIV-related procedure; or (c) ≥1 claim for HIV diagnosis and ≥2 dispensings of antiretroviral drugs. We further limited the sample to women who received some form of antiretroviral therapy (ART) during pregnancy, defined by at least one dispensing of an antiretroviral medication between LMP and delivery. We applied this restriction to produce a comparative safety study design with an active comparator group to produce results would be useful for clinical decision making and less susceptible to confounding by indication.[21]

Exposure and outcome definitions

For infants who had no diagnosis or procedure codes that indicated prematurity, we estimated the date of LMP by subtracting 270 days from the delivery date. For preterm deliveries, LMP was estimated by subtracting 245 days from the delivery date. The first trimester was defined as the 90-day period after LMP, the second trimester as the period from 91 to 180 days after LMP, and the third trimester as the period from 181 days after LMP through delivery.

A pregnancy was defined as having zidovudine exposure during the first trimester if at least one prescription for the drug was dispensed during the first trimester. The comparison group was comprised of pregnancies where the ART received did not include any dispensings of zidovudine during the first trimester.

Infant malformations were identified in the 90-day post-delivery period. An organ system was said to have a malformation if there were two recorded diagnostic codes for an anomaly in the organ system, either from maternal or infant records, or one code and a recorded infant death within three months of delivery. In this analysis, we focused on three outcomes: malformations from any organ system, cardiac malformations, and male genital malformations. A validation study found that cardiac malformations identified in MAX had a positive predictive value of 78%.[22]

Confounding and adjustment

We considered a variety of risk factors for malformations as potential confounders, including maternal demographic characteristics, markers of HIV disease severity, comorbid medical conditions (including the Obstetric Comorbidity Index[23]), obstetric characteristics, and prescription drugs dispensed (Table 4.2). Confounders were defined in the 3-month baseline period prior to LMP and the first trimester.

To adjust for confounding, propensity scores were used to match each exposed pregnancy to an unexposed pregnancy. Propensity scores were calculated using a logistic regression model that estimated the probability of being dispensed zidovudine in the first trimester based on confounder values. All variables listed in Table 4.2 were included in the propensity score. We performed 1:1 fixed-ratio matching using a greedy algorithm,[24] based on the logit transformation of the propensity score. To minimize residual confounding, we used a caliper of 0.2 times the standard deviation of the logit transformation of the propensity score.[25]

Development of a Bayesian prior

Bayesian methods require specification of a prior probability distribution for each parameter included in the model. This prior can be conceptualized as a summary of beliefs about the true value of a variable before considering any new data. In this way, Bayesian analyses allowed us to incorporate existing evidence about zidovudine exposure and risk of congenital malformations into our analysis using the MAX data.

To develop our prior, we conducted a systematic review and meta-analysis for studies that examined the relationship between use of zidovudine in pregnancy and three outcomes: any congenital malformation, cardiac malformation, and male genital malformation. We searched MEDLINE via PubMed, EMBASE, and Cochrane CENTRAL for abstracts with terms related to "zidovudine" and "pregnancy/congenital malformations." The references cited in all included studies were reviewed to identify additional articles.

Articles were included if they were written in English and reported adequate information to calculate an odds ratio (OR) for zidovudine exposure during pregnancy and one of the outcomes of interest (any, cardiac, and/or male genital malformation). We excluded conference abstracts, animal studies, basic science research, case reports, case series, and commentaries were excluded. When reports were published on the same cohort, we only included the most recent publication, to avoid duplication. In

secondary analyses, we further restricted the meta-analysis to studies that defined exposure to zidovudine in the first trimester, had a comparison group that received ART, and controlled for confounding.

Two authors (KR, JS) screened the titles and abstracts of all identified articles according to the inclusion and exclusion criteria listed above. For articles passing the initial screen, the two authors independently performed full text review, finalized inclusion decisions, and extracted the relevant information using a standardized form. All discrepancies were discussed and resolved consensus.

A random-effects meta-analysis was performed using the DerSimonian and Laird method[26] to summarize findings and construct a prior, and results were reported in Forest plots. The I^2 metric was computed to quantify between-study heterogeneity, and Egger's test was performed to identify publication bias. The meta-analysis was conducted using user-written packages in Stata.[27,28]

Statistical analysis

The risk of each outcome was summarized in the full and matched samples. Within the matched sample, we used a Bayesian approach to build a logistic model for the risk of malformation by exposure to zidovudine in pregnancy. Separate models were created for each malformation outcome. The prior distributions for the zidovudine-malformation relationships were set according to results of the meta-analysis, and a non-informative prior was specified for the model intercept term. Posterior estimates of the ORs and an accompanying 95% credible intervals were developed using Markov Chain Monte Carlo methods. Because malformations are a rare outcome, the estimated OR closely approximates a risk ratio.[29,30] Bayesian analyses were performed in SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

After removing duplicate references, the search strategy identified 4,673 unique citations, whose titles and abstracts were screened (Figure 4.1). After screening, 48 citations underwent a full-text review, and

results from 17 articles were included in the meta-analysis.[6–11,13–18,31–35] For the outcome of any malformation, 14 articles contributed information on over 27,239 infants with an *in utero* zidovudine exposure and over 36,501 infants without zidovudine exposure. Of these, 7 studies contributed information on cardiac malformations (n=8,956 zidovudine exposed, n=15,100 unexposed), and 5 contributed information on male genital malformations (n=8,630 zidovudine exposed, n=4,643 unexposed). Study designs varied between articles: one study was a randomized controlled trial, while the remainder were observational cohorts; 14 defined exposure to zidovudine specifically in the first trimester; and 12 had control groups who received other ART (Table 4.1). Nearly all studies were conducted in the United States or Europe.

For the zidovudine exposure during pregnancy, results from the meta-analysis indicated slightly increased odds of any malformation and cardiac malformation (Figure 4.2). Odds of a male genital malformation more than doubled with zidovudine exposure during pregnancy (OR=2.57, 95% CI:1.26-5.24; Figure 4.2). Between-study heterogeneity was low to moderate for each of the malformation outcomes. I^2, which represents the percentage of variance in meta-analysis that is attributable to between-study heterogeneity, ranged from 0 to 28 (any malformation: I^2=0, 95% confidence interval [CI]=0-55; cardiac malformation: I^2=28, 95% CI=0-69; male genital malformation: I^2= 0, 95% CI: 0-79). There was also some evidence of publication bias according to Egger's test for small study effects, where a small p-value indicates asymmetry in the funnel plot[36] (p=0.04 for any malformation; p=0.08 for cardiac malformation; p=0.26 for male genital malformation).

In the MAX cohort, 824 women were dispensed zidovudine in the first trimester and 1,998 were dispensed ART that did not include zidovudine in the first trimester. Before matching, there were some small differences in baseline characteristics between the exposure groups; women with first trimester zidovudine exposures were slightly older, less likely to be black, had deliveries earlier in the study period, had more psychiatric diagnoses and antidepressant use, and were more likely to be dispensed an

antiretroviral medication in the 3 months prior to pregnancy (Table 4.2). The 1:1 matching procedure resulted in a sample of 735 women each in the zidovudine and comparator groups. In the matched sample, these differences between baseline characteristics decreased (Table 4.2).

Prior to matching, women with a first trimester dispensing of zidovudine group had slightly elevated risk of any malformation (4.6% versus 4.0%), but these risks became similar after implementing the matching procedure (4.6% versus 4.9%) (Table 4.3). In both the full sample and the matched sample, women with first trimester zidovudine exposure and those without had similar risk of cardiac defects (1.5% versus 1.5% in the full sample; 1.5% versus 1.6% in the matched sample). Among women with first trimester zidovudine exposure, there were no male genital malformations in either the full or matched samples.

When comparing ART with first trimester zidovudine to ART without first trimester zidovudine, the Bayesian modeling procedure yielded OR estimates slightly above the null for any malformation (OR=1.11; 95% credible interval: 0.80-1.55) and cardiac malformation (OR=1.30; 95% credible interval: 0.63-2.71). Because there were no exposed cases of male genital malformations in either the full or matched cohorts, the Bayesian model did not converge for that outcome. When the meta-analysis used to specify the prior distribution for the outcome of any malformation was restricted to studies with similar designs to what was implemented in the MAX cohort (i.e., classified zidovudine exposure during the first trimester, required that women in the comparison group received ART, and controlled for confounding), the OR estimate was very similar, though the credible interval became wider. We were unable to conduct similar sensitivity analyses for the cardiac and male genital malformation outcomes because there were a prohibitively small number of studies that met the more restrictive criteria.

DISCUSSION

In a nationwide cohort of Medicaid-enrolled pregnant women with HIV from the years 2000 to 2010, we found that first trimester exposure to zidovudine was relatively common. Our Bayesian analysis

incorporated novel information from Medicaid alongside a prior that captured the results of a systematic review and meta-analysis. Compared to women with ART regimens that did not include zidovudine in the first trimester, those with first trimester exposure had a modest increase in the odds of any anomaly and cardiac anomaly, though the 95% credible intervals included the null value of 1. Results from the meta-analysis for the outcome of male genital malformation indicate a substantial increase in risk for infants with *in utero* zidovudine exposures, though estimates were imprecise due to the limited sample size and the rare nature of the outcome.

The severity of the clinical impact of the specific malformations observed is unclear. The cardiac malformations identified in this study, as well as studies included in the meta-analysis, were primarily ventricular septal defects which are often managed non-surgically.[37] The 2015 study by Sibiude et al found that most identified cardiac malformations were minor and less than 10% required a surgical intervention.[8] The male genital malformations identified in previous studies were predominantly hypospadias, which has a generally good prognosis.[38]

Findings from this study must also be interpreted within the context of existing knowledge about the use of zidovudine and other antiretroviral drugs during pregnancy. In addition to potential teratogenicity, many considerations influence treatment decisions for pregnant women with HIV, including treatment availability, tolerability of side effects, interactions with other medications, drug resistance, and other maternal and infant safety signals.

Our study has several limitations. First, it is possible that some children were enrolled in multiple studies included in the meta-analysis, which would artificially increase the sample size and decrease the variance. However, we do not expect bias in our estimates because of the prospective nature of nearly all included studies makes it unlikely that repeated observations are differential with respect to exposure or outcome. Second, classification of exposure to zidovudine during the first trimester was based on an algorithm to

estimate LMP. This may result in some non-differential misclassification of the exposure, which would bias estimates towards the null. Third, we were only able to follow infants for 3 months after delivery, limiting outcome sensitivity, and were not able to review medical records for cases of suspected malformations, limiting outcome specificity. However, a previous validation study showed good positive predictive value for claims-based definitions of cardiac malformations in MAX.[22] We expect any outcome misclassification to be non-differential, and therefore biased towards the null. Fourth, the MAX dataset, along with all but one study included in the meta-analysis, is an observational cohort, and there is always some potential for residual confounding, though this should be limited by use of propensity score matching and an active comparator group. Fourth, because MAX and some studies in the meta-analysis are restricted to only include live births, there is a potential for selection bias if malformations due to first trimester zidovudine were so severe that pregnancies ended in miscarriage or stillbirth. Finally, the data from MAX and most studies included in the meta-analysis were conducted in high-income countries in North America and Europe. However, most women receiving ART during pregnancy are from low-income countries, and it is unclear how our results may generalize to these settings.

Our study also has multiple strengths. Because exposure was measured through pharmacy dispensing records, our measurements will not be impacted by inconsistencies in recall or memory. In addition, the active comparator design also makes our results clinically interpretable and minimizes the potential for bias due to confounding. Finally, our posterior estimates summarize all currently available information, and are especially useful in this context because of rare nature of organ-specific malformations.

In conclusion, these findings provide reassurance that for most types of congenital malformations, first trimester exposure to zidovudine results in minimal differences in risk compared to other treatment strategies. The potential increase in male genital malformations appears small in absolute magnitude, but should continue to be monitored. It will be increasingly important to conduct similar analyses to monitor adverse events associated with other antiretroviral agents used during pregnancy, especially more novel

agents with limited safety data. Due to the Bayesian approach used, estimates from this study reflect the most updated available evidence on zidovudine and malformations that can be used as a resource for women with HIV, their healthcare providers, and policy makers to assess options for treatment of HIV during pregnancy to minimize risk of birth defects.

CITATION INFORMATION

Suggested reference:

Rough K, Sun J, Seage GR III, Williams PL, Huybrechts KF, Bateman BT, Hernadez-Diaz S. Zidovudine use in pregnancy and congenital malformations: A Bayesian analysis [dissertation]. Boston: Harvard University; 2017.

Figure 4.1. Flowchart of article inclusion in meta-analysis

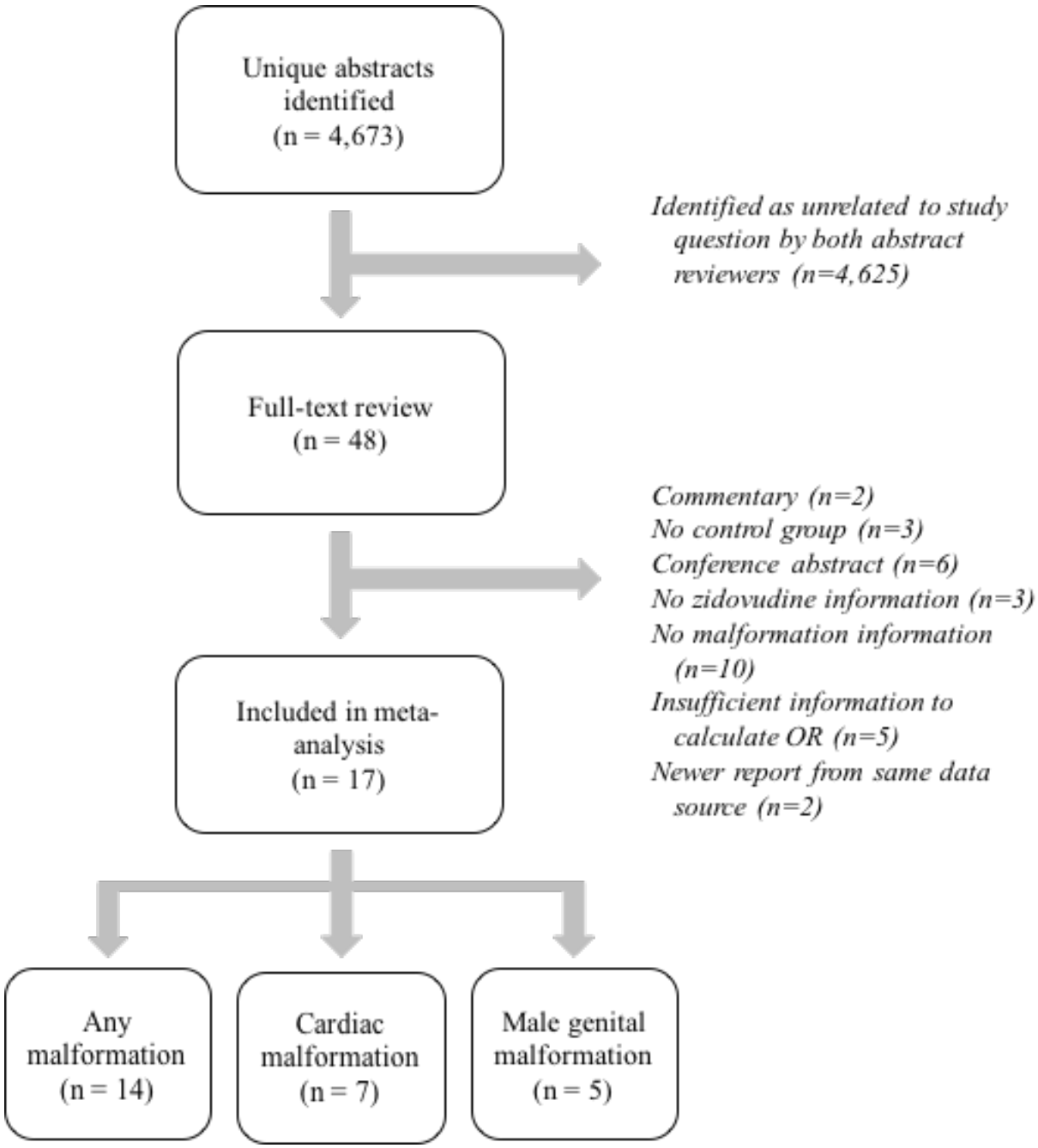


Table 4.1. Description of studies included in meta-analyses

Citation	Cohort	Geographic setting	Years	Exposure comparison	Definition of malformations	Number with zidovudine exposure	Number in comparison group	Malformation outcomes
Sperling et al 1998	ACTG 076	France, USA	1991-1994	Zidovudine in Trimester 2/3 versus placebo*	Not reported	214	210	Any malformation, cardiac malformation, male genital malformation
Newschaffer et al 2000	New York Medicaid	New York, USA	1993-1996	Zidovudine in Trimester 1 versus no zidovudine during pregnancy*	ICD-9 coding; blinded clinician review	Not reported	Not reported	Any malformation, cardiac malformation
Watts et al 2007	WITS	USA	1990-2004	Zidovudine in Trimester 1 versus no zidovudine in Trimester 1	MACDP guidelines & APR criteria	621	1,289	Any malformation, male genital malformation
Townsend et al 2009	NSHPC	Ireland, UK	1990-2007	Zidovudine during pregnancy versus no zidovudine during pregnancy	Reported by treating physician / ICD??	6,711	792	Male genital malformation
Brogly et al 2010	PACTG 219/219C	USA	1993-2006	Zidovudine in Trimester 1 versus no zidovudine in Trimester 1*	MACDP guidelines & APR criteria; blinded clinican review	605	1,428	Any malformation, cardiac malformation
Joao et al 2010	NISDI Perinatal Study	Argentina, Brazil	2002-2007	Zidovudine during pregnancy versus no zidovudine during pregnancy	MACDP guidelines & APR criteria	954	41	Any malformation
Watts et al 2011	PACTG 316	Brazil, Bahamas, Europe, USA	1997-2000	Zidovudine in Trimester 1 versus no zidovudine in Trimester 1	MACDP guidelines & APR criteria; blinded clinican review	517	897	Any malformation, cardiac malformation
Tariq et all 2011	NSHPC and ECS	Europe	2000-2009	Zidovudine in Trimester 1 versus no zidovudine in Trimester 1	ICD-10 coding	1,077	1,477	Any malformation

Table 4.1 (continued). Description of studies included in meta-analyses

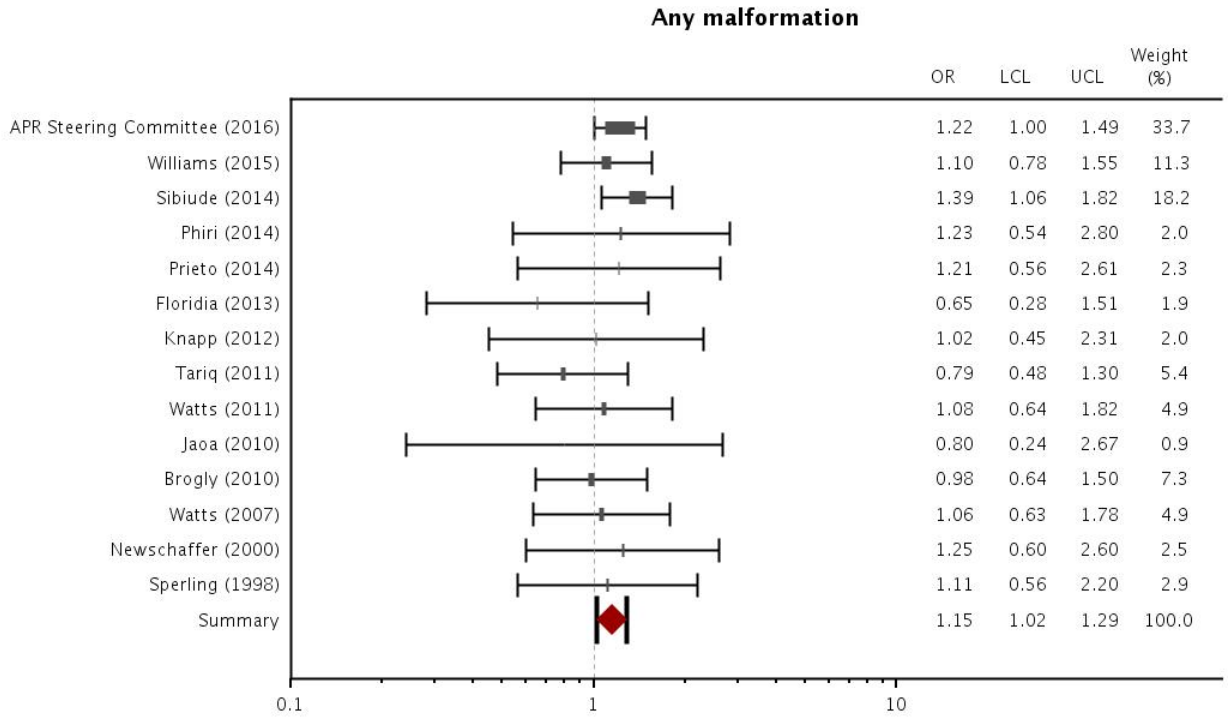
Citation	Cohort	Geographic setting	Years	Exposure comparison	Definition of malformations	Number with zidovudine exposure	Number in comparison group	Malformation outcomes
Knapp et al 2012	IMPAACT P1025	USA	2002-2007	Zidovudine in Trimester 1 versus no zidovudine during pregnancy	MACDP guidelines; blinded clinician review	356	187	Any malformation
Floridia et al 2013	Italian National Programme on Surveillance on Antiretroviral Treatment in Pregnancy	Italy	2001-2011	Zidovudine in Trimester 1 versus no ART in Trimester 1	MACDP guidelines & APR criteria	358	561	Any malformation, cardiac malformation, male genital malformation
Prieto et al 2014	The Madrid Cohort	Madrid, Spain	2000-2009	Zidovudine Trimester 1 versus no zidovudine during pregnancy*	EUROCAT criteria	287	189	Any malformation
Sibiude et al 2014	EPF ANRS CO1/CO11	France	1994-2010	Zidovudine in Trimester 1 versus no zidovudine during pregnancy	ICD-10 coding according to EUROCAT criteria	3,267	2152	Any malformation
Phiri et al 2014	Tennessee Medicaid	Tennessee, USA	1994-2009	Zidovudine in Trimester 1 versus no zidovudine in Trimester 1*	ICD-9 coding & vital record data according to MACDP guidelines; blinded clinician review	156	650	Any malformation
Sibiude et al 2015	EPF ANRS CO1/CO11	France	1994-2010	Zidovudine in Trimester 1 versus no zidovudine in Trimester 1	Previously identified cardiac defects reviewed by pediatric cardiologist	3,262	9626	Cardiac malformation

Table 4.1 (continued). Description of studies included in meta-analyses

Citation	Cohort	Geographic setting	Years	Exposure comparison	Definition of malformations	Number with zidovudine exposure	Number in comparison group	Malformation outcomes
Williams et al 2015	PHACS SMARTT	USA	1995-2012	Zidovudine in Trimester 1 versus no zidovudine in Trimester 1	MACDP guidelines & APR criteria; blinded clinican review	726	1,791	Any malformation, male genital malformation
Vannappagari et al 2016	APR	USA (majority), 65 additional countries	1989-2013	Zidovudine in Trimester 1 versus no zidovudine during pregnancy	MACDP guidelines & APR criteria	4,000	2,378	Cardiac malformation
Antiretroviral Pregnancy Registry Steering Committee 2016	APR	USA (majority), 65 additional countries	1989-2016	Zidovudine in Trimester 1 versus no zidovudine in Trimester 1	MACDP guidelines & APR criteria	4,128	12,833	Any malformation

Figure 4.2. Forest plot of meta-analysis results: odds ratios for zidovudine use in pregnancy and outcomes of any malformation, cardiac malformation, and male genital malformation

Panel A



Panel B

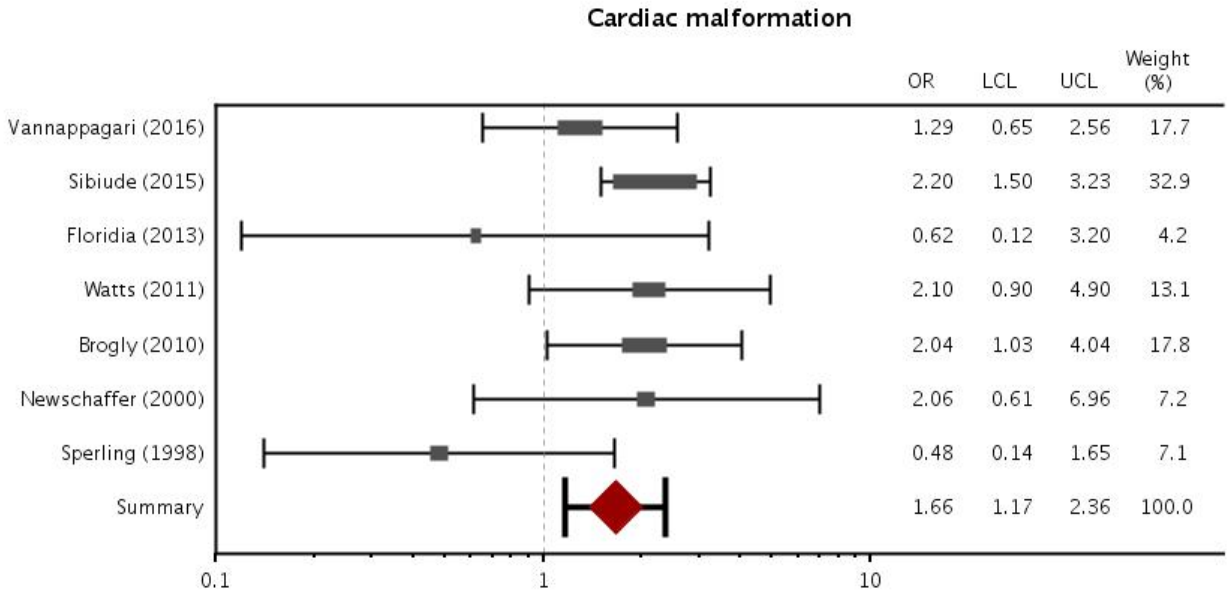
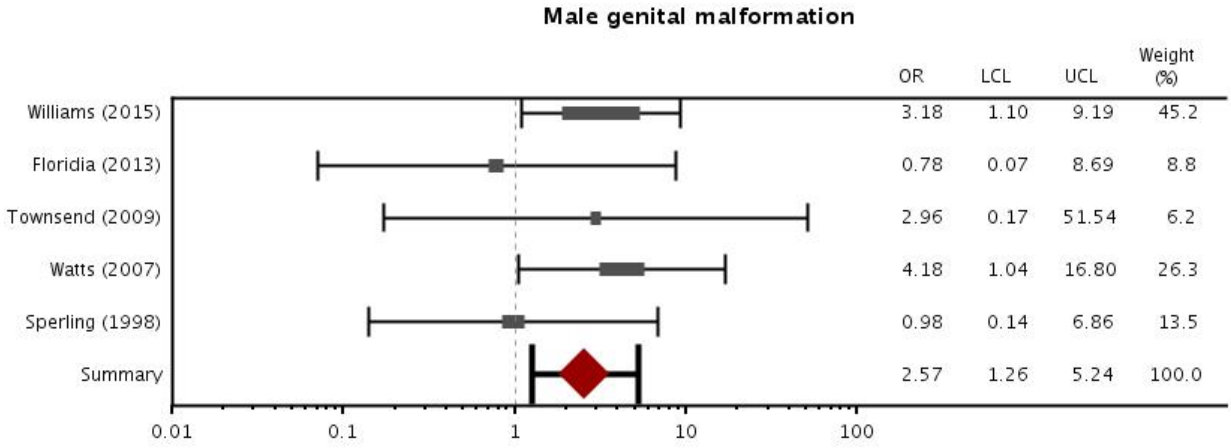


Figure 4.2 (continued). Forest plot of meta-analysis results: odds ratios for zidovudine use in pregnancy and outcomes of any malformation, cardiac malformation, and male genital malformation

Panel C



Abbreviations: APR, Antiretroviral Pregnancy Registry; OR, odds ratio; LCL, lower 95% confidence limit; UCL, upper 95% confidence limit

Table 4.2. Baseline characteristics for pregnant women living with HIV in Medicaid Analytic eXtract sample

	Full cohort				Matched cohort			
	Treated with zidovudine in Trimester 1 (N = 824)		Treated without zidovudine in Trimester 1 (N = 1,998)		Treated with zidovudine in Trimester 1 (N = 735)		Treated without zidovudine in Trimester 1 (N = 735)	
Categorical variables	n	%	n	%	n	%	n	%
Age								
12-18 years	29	3.5	122	6.1	28	3.8	26	3.5
19-25 years	289	35.1	813	40.7	261	35.5	267	36.3
26-35 years	390	47.3	841	42.1	343	46.7	357	48.6
36-55 years	116	14.1	222	11.1	103	14.0	85	11.6
Race/ethnicity								
White	125	15.2	251	12.6	111	15.1	113	15.4
Black/African American	527	64.0	1,465	73.3	481	65.4	483	65.7
Hispanic/Latino	45	5.5	54	2.7	32	4.4	30	4.1
Other/Unknown	127	15.4	228	11.4	111	15.1	109	14.8
Year of delivery								
2000-2003	171	20.8	366	18.3	148	20.1	135	18.4
2004-2006	352	42.7	717	35.9	313	42.6	312	42.4
2007-2010	301	36.5	915	45.8	274	37.3	288	39.2
Multifetal gestation	169	20.5	298	14.9	136	18.5	129	17.6
Baseline antiretroviral dispensing	481	58.4	460	23.0	394	53.6	383	52.1
Diarrhea	19	2.3	38	1.9	14	1.9	19	2.6
Parasitic/fungal infection	42	5.1	97	4.9	39	5.3	38	5.2
Hepatitis C	13	1.6	24	1.2	11	1.5	14	1.9
Herpes simplex virus	14	1.7	41	2.1	13	1.8	12	1.6
Sexually transmitted infection	54	6.6	163	8.2	51	6.9	51	6.9
Overweight/obese	21	2.5	38	1.9	17	2.3	17	2.3
Hypertension	42	5.1	98	4.9	35	4.8	41	5.6
Diabetes	32	3.9	50	2.5	27	3.7	30	4.1
Dyslipidemia	13	1.6	22	1.1	11	1.5	11	1.5
Bipolar disorder	25	3.0	37	1.9	18	2.4	24	3.3
Anxiety disorder	28	3.4	50	2.5	25	3.4	25	3.4
Depression	111	13.5	162	8.1	93	12.7	86	11.7
Other psychiatric disorder	42	5.1	69	3.5	36	4.9	32	4.4
Alcohol abuse	28	3.4	34	1.7	22	3.0	20	2.7
Tobacco use	29	3.5	66	3.3	25	3.4	28	3.8
Illicit drug abuse	65	7.9	97	4.9	52	7.1	49	6.7
Antidepressant dispensing	164	19.9	190	9.5	125	17.0	127	17.3
Anticonvulsant dispensing	39	4.7	59	3.0	30	4.1	30	4.1
Stimulant dispensing	11	1.3	14	0.7	<11[1]	--	<11[1]	--
Antibiotic dispensing	500	60.7	1,080	54.1	443	60.3	454	61.8
Antihypertensive dispensing	54	6.6	110	5.5	46	6.3	50	6.8
Insulin dispensing	20	2.4	25	1.3	15	2.0	15	2.0
Antidiabetes medication dispensing	18	2.2	21	1.1	15	2.0	13	1.8

Table 4.2 (continued). Baseline characteristics for pregnant women living with HIV in Medicaid Analytic eXtract sample

	Full cohort				Matched cohort			
	Treated with zidovudine in Trimester 1 (N = 824)		Treated without zidovudine in Trimester 1 (N = 1,998)		Treated with zidovudine in Trimester 1 (N = 735)		Treated without zidovudine in Trimester 1 (N = 735)	
Categorical variables	n	%	n	%	n	%	n	%
NSAID dispensing	201	24.4	405	20.3	176	23.9	192	26.1
Acetaminophen dispensing	219	26.6	486	24.3	194	26.4	200	27.2
Benzodiazapine dispensing	34	4.1	50	2.5	28	3.8	32	4.4
Opioid dispensing	192	23.3	423	21.2	173	23.5	175	23.8
Progestins dispensing	14	1.7	28	1.4	12	1.6	12	1.6
Corticosteroid dispensing	208	25.2	341	17.1	169	23.0	174	23.7
Fluconazole dispensing	119	14.4	209	10.5	103	14.0	117	15.9
ACE inhibitor dispensing	16	1.9	31	1.6	13	1.8	15	2.0
Continuous variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Generic medications (excluding ARVs)	7.34	6.64	5.09	5.00	6.85	6.08	7.09	5.71
Distinct diagnoses	11.84	7.68	9.48	7.19	11.44	7.42	12.04	7.94
Outpatient visits	8.36	7.75	6.48	7.64	8.16	7.45	8.60	9.66
Emergency department visits	1.12	4.73	1.05	1.75	1.13	4.98	1.28	2.01
Inpatient hospitalizations	0.13	0.43	0.13	0.55	0.13	0.44	0.12	0.39
HIV-related procedures	0.02	0.15	0.02	0.13	0.03	0.16	0.02	0.16
Obstetric Comorbidity Index	1.84	1.38	1.17	1.35	1.75	1.34	1.77	0.43

[1] Cell sizes of 10 or less have been suppressed in accordance with Centers for Medicare and Medicaid Services cell size suppression policy.

Table 4.3. Risk of malformations in MAX and results of Bayesian analysis

	Risk in original sample: treated with zidovudine in Trimester 1 (N=823)		Risk in original sample: treated without zidovudine in Trimester 1 (N-1,998)		Risk in matched sample: treated with zidovudine in Trimester 1 (N=735)		Risk in matched sample: treated without zidovudine in Trimester 1 (N=735)		Posterior estimates: Bayesian analysis results		
	n	%	n	%	n	%	n	%	OR	95% credible interval	
Any malformation	38	4.6	79	4.0	34	4.6	36	4.9	1.11	0.80	1.55
Cardiac malformation	12	1.5	29	1.5	11	1.5	12	1.6	1.30	0.63	2.71
Male genital malformation	0	0.0	<11[1]	--	0	0.0	<11[1]	--	N/A	--	--

Abbreviations: OR, odds ratio

[1] Cell sizes of 10 or less have been suppressed in accordance with Centers for Medicare and Medicaid Services cell size suppression policy.

REFERENCES

1. Fowler MG, Qin M, Fiscus SA, et al. PROMISE: Efficacy and safety of 2 strategies to prevent perinatal HIV transmission. In: *Conference on Retroviruses and Opportunistic Infections*. Seattle, Washington; 2015.
2. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defici Syndr*. 2002;29(5):484-494.
3. Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2014;28 Suppl 2:S123-31. doi:10.1097/QAD.0000000000000231.
4. World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*. World Health Organization; 2016. http://www.who.int/hiv/pub/arv/arv-2016/en/. Accessed July 27, 2016.
5. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. doi:10.1371/journal.pmed.1001635.
6. Brogly SB, Abzug MJ, Watts DH, et al. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. *Pediatr Infect Dis J*. 2010;29(8):721-727. doi:10.1097/INF.0b013e3181e74a2f.
7. Watts DH, Huang S, Culnane M, et al. Birth defects among a cohort of infants born to HIV-infected women on antiretroviral medication. *J Perinat Med*. 2011;39(2):163-170. doi:10.1515/JPM.2010.139.
8. Sibiude J, Le Chenadec J, Bonnet D, et al. In utero exposure to zidovudine and heart anomalies in the ANRS French perinatal cohort and the nested PRIMEVA randomized trial. *Clin Infect Dis*. 2015;61(2):270-280. doi:10.1093/cid/civ260.
9. Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and in utero antiretroviral

exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):48-55. doi:10.1001/jamapediatrics.2014.1889.

10. Watts DH, Li D, Handelsman E, et al. Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. *J Acquir Immune Defic Syndr*. 2007;44(3):299-305. doi:10.1097/QAI.0b013e31802e2229.

11. Antiretroviral Pregnancy Registry Steering Committee. *Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2016*. Wilmington, NC; 2016.

12. Phiri K, Fischer MA, Mogun H, et al. Trends in antiretroviral drug use during pregnancy among HIV-infected women on medicaid: 2000-2007. *AIDS Patient Care STDS*. 2014;28(2):56-65. doi:10.1089/apc.2013.0165.

13. Prieto LM, González-Tomé MI, Muñoz E, et al. Birth defects in a cohort of infants born to HIV-infected women in Spain, 2000-2009. *BMC Infect Dis*. 2014;14:700. doi:10.1186/s12879-014-0700-3.

14. Floridia M, Mastroiacovo P, Tamburrini E, et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001-2011. *BJOG*. 2013;120(12):1466-1475. doi:10.1111/1471-0528.12285.

15. Vannappagari V, Albano JD, Koram N, Tilson H, Scheuerle AE, Napier MD. Prenatal exposure to zidovudine and risk for ventricular septal defects and congenital heart defects: data from the Antiretroviral Pregnancy Registry. *Eur J Obs Gynecol Reprod Biol*. 2016;197:6-10. doi:10.1016/j.ejogrb.2015.11.015.

16. Sperling RS, Shapiro DE, McSherry GD, et al. Safety of the maternal-infant zidovudine regimen utilized in the Pediatric AIDS Clinical Trial Group 076 Study. *AIDS*. 1998;12(14):1805-1813. http://www.ncbi.nlm.nih.gov/pubmed/9792381. Accessed October 5, 2016.

17. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. *Pediatr Infect Dis J*. 2012;31(2):164-170.

doi:10.1097/INF.0b013e318235c7aa.

18. Tariq S, Townsend CL, Cortina-Borja M, et al. Use of zidovudine-sparing HAART in pregnant HIV-infected women in Europe: 2000-2009. *J Acquir Immune Defic Syndr*. 2011;57(4):326-333. doi:10.1097/QAI.0b013e31821d34d0.

19. National Governors Association. *2014 Maternal and Child Health Update: States Are Using Medicaid and CHIP to Improve Health Outcomes for Mothers and Children*. Washington, D.C.; 2015. http://www.nga.org/files/live/sites/NGA/files/pdf/MCHUPDATE2014.PDF. Accessed March 16, 2016.

20. Palmsten K, Huybrechts KF, Mogun H, et al. Harnessing the Medicaid Analytic eXtract (MAX) to Evaluate Medications in Pregnancy: Design Considerations. *PLoS One*. 2013;8(6):e67405. doi:10.1371/journal.pone.0067405.

21. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol*. 2005;58(4):323-337. doi:10.1016/j.jclinepi.2004.10.012.

22. Palmsten K, Huybrechts KF, Kowal MK, Mogun H, Hernández-Díaz S. Validity of maternal and infant outcomes within nationwide Medicaid data. *Pharmacoepidemiol Drug Saf*. 2014;23(6):646-655. doi:10.1002/pds.3627.

23. Bateman BT, Mhyre JM, Hernandez-Diaz S, et al. Development of a Comorbidity Index for Use in Obstetric Patients. *Obs Gynecol*. 2013;122(5):957-965. doi:10.1097/AOG.0b013e3182a603bb.

24. Bergstralh E, Kosanke J. Gmatch SAS macro. 1995.

25. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10(2):150-161. doi:10.1002/pst.433.

26. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. http://www.ncbi.nlm.nih.gov/pubmed/3802833. Accessed November 7, 2016.

27. StataCorp. Stata Statistical Software: Release 13. 2013.

28. Sterne JAC, Harris RJ, Harbord RM, Steichen TJ. *Meta-Analysis in Stata: An Updated Collection from the Stata Journal, Second Edition*. (Palmer TM, Sterne JAC, eds.). College Station, TX: StataCorp LP; 2016.

29. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.

30. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol*. 2002;155(2):176-184. http://www.ncbi.nlm.nih.gov/pubmed/11790682. Accessed November 25, 2016.

31. Newschaffer CJ, Cocroft J, Anderson CE, Hauck WW, Turner BJ. Prenatal zidovudine use and congenital anomalies in a medicaid population. *J Acquir Immune Defic Syndr*. 2000;24(3):249-256. http://www.ncbi.nlm.nih.gov/pubmed/10969349. Accessed October 5, 2016.

32. Townsend CL, Willey BA, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990-2007. *AIDS*. 2009;23(4):519-524. doi:10.1097/QAD.0b013e328326ca8e.

33. Joao EC, Calvet GA, Krauss MR, et al. Maternal antiretroviral use during pregnancy and infant congenital anomalies: the NISDI perinatal study. *J Acquir Immune Defic Syndr*. 2010;53(2):176-185. doi:10.1097/QAI.0b013e3181c5c81f.

34. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. doi:10.1371/journal.pmed.1001635.

35. Phiri K, Hernandez-Diaz S, Dugan KB, et al. First Trimester Exposure to Antiretroviral Therapy and Risk of Birth Defects. *Pediatr Infect Dis J*. 2014;33(7):741-746. doi:10.1097/INF.0000000000000251.

36. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. http://www.ncbi.nlm.nih.gov/pubmed/9310563.

Accessed November 7, 2016.

37. Penny DJ, Vick GW. Ventricular septal defect. *Lancent*. 2011;377(9771):1103-1112. doi:10.1016/S0140-6736(10)61339-6.

38. Baskins L. Hypospadias. In: Stringer O, Mouriquand P, eds. *Pediatric Surgery and Urology: Long Term Outcomes*. Cambridge: University Press; 2006:611-620.