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Zidovudine use in pregnancy and congenital malformations

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Abstract

Objective—There is inconsistent evidence that zidovudine use during pregnancy increases overall, cardiac, and male genital malformations.

Design—We conducted a systematic review and meta-analysis of zidovudine use and malformations and, using Bayesian methods, combined it with data from a cohort study of mother-infant pairs in the nationwide Medicaid Analytic eXtract (MAX).

Methods—Using MAX data (2000–2010), we identified pregnant women with HIV treated with antiretroviral therapy (ART). Women with ≥1 zidovudine dispensing during the first trimester were compared to women receiving ART without zidovudine in the first trimester. Malformation outcomes were defined using diagnosis/procedure codes. To adjust for confounding, we performed 1:1 propensity score matching. Bayesian methods require specification of a prior, which we developed in the meta-analysis. Logistic regression models combined MAX data with the prior, estimating odds ratios (ORs) and 95% credible intervals.

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Author contributions: KR, GRS, PLW, and SHD were the authors who conceived and designed the study. KR and JWS conducted the systematic review. KR had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. KR was responsible for conducting statistical analyses, and led the drafting of the manuscript. KFH, BTB, and SHD provided leadership and oversight of the creation of the MAX pregnancy cohort. All authors provided input on the study design, interpretation of analyses, and revisions to manuscript.

CONFLICTS OF INTEREST

KH is co-investigator of a grant to the Brigham and Women's Hospital from Eli Lilly and from Pfizer, unrelated to the topic of this manuscript. BTB is co-investigator of a grant to the Brigham and Women's Hospital or Massachusetts General Hospital from Eli Lilly, GSK, Pacira, Baxalta, and Pfizer. SHD received salary support from the North American AED Pregnancy Registry; and consulted for UCB, Teva, and Boehringer-Ingelheim; her institution received training grants from Pfizer, Takeda, Bayer, and Asisa. She is co-investigator grants to the Harvard T.H. Chan School of Public Health from Eli Lilly, GSK and Pfizer, unrelated to the topic of this manuscript.

Results—Fourteen articles contributed information on overall malformations, 7 on cardiac malformations, and 5 on male genital malformations. In MAX, matching led to a sample of 735 women each in the zidovudine and comparator groups. When comparing first trimester zidovudine use to other ART, the Bayesian procedure yielded OR estimates slightly above the null for overall (OR=1.11, 95% credible interval [0.80–1.55]) and cardiac (OR=1.30 [0.63–2.71]) malformations. There were no zidovudine-exposed cases of male genital malformations in MAX, but the meta-analysis yielded elevated OR estimates (OR=2.57 [1.26–5.24]).

Conclusions—For most malformations, first trimester zidovudine was not associated with increased risk. The potential increase in male genital malformations was small in absolute terms, and should be evaluated further.

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, and careful evaluation of the risks associated with specific drugs is needed to inform treatment decisions. Zidovudine is one antiretroviral agent that is frequently used to treat HIV during pregnancy, though it is no longer a component of the preferred first-line treatment, largely due to programmatic reasons unrelated to safety.[3]

Some epidemiological studies have found that zidovudine use, especially in the first trimester, is associated with modest elevations in the risk of overall malformations,[4] cardiac malformations,[5–7] and male genital malformations.[8,9] However, a number of other studies have not replicated the increased risk.[10–15] 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 malformations associated with zidovudine, and incorporated data from the Medicaid Analytic eXtract (MAX) to provide a comprehensive assessment of the 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.[16]

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,[17] and has been used in multiple studies of prescription drug safety during pregnancy[18–21]. Briefly, women between the ages of 12 and 55 years old with a code indicating a 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 the 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 estimated LMP using an algorithm which correctly classifies pregnancy duration within 2 weeks in 99% of term and 75% of preterm deliveries.[22] For infants without diagnosis or procedure codes that indicated prematurity, date of LMP was 270 days prior to the delivery date. For preterm deliveries, date of LMP was 245 days prior to 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.

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 (see Supplemental Digital Content Table S1 for diagnostic and procedure codes). 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 create a comparative safety study design with an active comparator group, which produces results that are useful for clinical decision making and less susceptible to confounding by indication.[23]

Exposure and outcome definitions

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. Women in the exposed group were commonly co-prescribed other antiretroviral drugs in addition to zidovudine. 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 defined as having a malformation if there were at least two recorded diagnostic codes on separate dates for an anomaly in the organ system (or a diagnostic code and a surgical code), either from maternal or infant records, or one code and a recorded infant death within three months of delivery (see Supplemental Digital Content Table S2 for full list of codes). In this analysis, we focused on three outcomes: overall 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%.[24]

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[25]), obstetric characteristics, and prescription drugs. 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 2 were included in the propensity score. We performed 1:1 fixed-ratio matching using a greedy algorithm,[26] 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.[27]

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 of 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 our three outcomes of interest: overall 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 eligible articles. Search criteria are described in detail in Supplemental Digital Content Table S3.

Articles were included if they were written in English and reported sufficient information to calculate an odds ratio (OR) for zidovudine exposure during pregnancy and one of the outcomes of interest (overall, cardiac, and/or male genital malformation). We excluded conference abstracts, animal studies, basic science research, case reports, case series, and commentaries. When multiple reports were published from the same study, 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, JWS) each 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 resolved through discussion until reaching a consensus.

A random-effects meta-analysis was performed using the DerSimonian and Laird method[28] 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.[29,30] The meta-analysis was conducted using publically available user-written packages in Stata.[31,32]

Statistical analysis

The risk of each outcome was summarized in the full and matched MAX samples. Within the matched sample, we used a Bayesian approach to build a logistic model for the risk of malformation from 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 interval were developed using Markov Chain Monte Carlo methods. Because malformations are a rare outcome, the estimated OR closely approximates a risk ratio.[33,34] 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 1). After screening, 48 citations underwent a full-text review, and results from 17 articles were included in the meta-analysis.[4–15,35–39] For the outcome of overall malformation, 14 articles contributed information on over 27,239 infants with *in utero* zidovudine exposure and over 36,501 infants without zidovudine exposure. Seven 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 forms of ART (Table 1). Nearly all studies were conducted in the United States or Europe.

For zidovudine exposure during pregnancy, results from the meta-analysis indicated slightly increased odds of overall malformation and cardiac malformation (overall malformation: OR=1.15, 95% CI [1.02–1.29]; cardiac malformation: OR=1.66 [1.17–2.36]; Figure 2). Odds of a male genital malformation more than doubled with zidovudine exposure during pregnancy (OR=2.57 [1.26–5.24]; Figure 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 (overall malformation: I^2=0 [0–55]; cardiac malformation: I^2=28 [0–69]; male genital malformation: I^2= 0 [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 (p=0.04 for overall 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 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 2). Women with first trimester zidovudine exposure who were unmatched, and thus dropped from the analysis, were slightly more likely to receive antiretroviral drugs in the baseline period (59% in unmatched group versus 54% in matched group) and were dispensed more prescriptions overall (mean=7.34 in unmatched group versus mean=6.85 in the matched group).

Prior to matching, women with a first trimester dispensing of zidovudine had a 4.6% risk of overall malformations, compared to 4.0% in the comparison group (Table 3). After implementing the matching procedure, these risks shifted to 4.6% and 4.9%, respectively. In both the full sample and the matched sample, women with first trimester zidovudine exposure and those without had similar risk of cardiac malformations (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 the full sample.

Among infants with first trimester exposure to zidovudine, cardiac malformations were the most common type of malformation. The remainder of malformations were heterogeneous, with no more than five linked to any single organ system. Within the category of cardiac malformations, there was also considerable diversity, including diagnoses of patent ductus arteriosus, right ventricular outflow tract obstruction, left ventricular outflow tract obstruction, secundum atrial septal defects, single ventricle defects, and conotruncal defects.

When comparing ART with first trimester zidovudine to ART without first trimester zidovudine, the Bayesian posterior OR estimates were slightly above the null for overall 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 the MAX cohort, the Bayesian model did not converge for that outcome.

For the outcome of overall malformation, restricting the meta-analysis 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) resulted in very similar posterior OR estimates, though the credible interval became wider (OR=1.08; 95% credible interval: 0.70–1.69). 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

The use of antiretroviral agents, including zidovudine, has dramatically lowered the risk of perinatal HIV transmission. 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, comprising 30% of deliveries for ART-treated women with HIV. Our systematic review and meta-analysis captured existing information in the literature, which used Bayesian methods to incorporate novel information from Medicaid. Compared to women with ART regimens that did not include zidovudine in the first trimester, those with first trimester zidovudine exposure had a modest increase in the odds of overall malformation and cardiac malformation, though the 95% credible intervals in the Bayesian analysis included the null value of 1. No exposed cases of male genital malformation were observed in the MAX cohort. However, our meta-analysis of previous studies reporting estimates for this outcome indicate that there may be a substantial increase in risk of male genital malformations for infants with *in utero* zidovudine exposure, though estimates were imprecise due to the limited sample size and the rare nature of the outcome.

The severity and clinical impact of the specific malformations observed is unclear. In the MAX data, the cardiac malformations identified among infants with first trimester zidovudine exposure were largely heterogeneous. Studies included in the meta-analysis identified an excess of ventricular septal defects among infants with *in utero* zidovudine exposure, and these defects are often managed non-surgically[40]. A 2015 study in France found that most identified cardiac malformations were minor and less than 10% required a surgical intervention.[7] The male genital malformations identified in previous studies were predominantly hypospadias, which generally has a good prognosis.[41]

Because of the relatively smaller size of MAX compared to the number of women included across all studies in the meta-analysis, posterior credible intervals from the Bayesian analysis were wider than confidence intervals from the meta-analysis alone. In sensitivity analyses, we undertook an alternative analytical approach, treating the MAX data as another entry in the meta-analysis. This led to odds ratio estimates of 1.13 [1.01, 1.27] for overall malformations and 1.53 [1.08, 2.17] for cardiac malformations, which are similar to the findings of the meta-analysis before including the MAX data.

When interpreting the results of the meta-analysis, it is important to be aware of substantial diversity in the designs of the included studies. In addition to random error, heterogeneity in results may be due to a number of important differences, including timing of exposure measurement (e.g., zidovudine use in first trimester versus any time in pregnancy), comparator group (e.g., no antiretroviral therapy in pregnancy versus no zidovudine exposure in the first trimester), outcome definitions (e.g., MACDP versus EUROCAT), internal study validity (e.g., amount of confounding control), or geographic differences (e.g. Europe versus United States).

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 concerns.

An important infant safety concern for zidovudine use in pregnancy is its possible link to mitochondrial dysfunction, a debilitating disorder caused by disturbances in the mitochondrial oxidative phosphorylation system. Animal models have suggested zidovudine causes transplacental mitochondrial toxicity,[42] and studies of mitochondrial function biomarkers have found inverse relationships with *in utero* exposure to zidovudine [43] and nucleoside drugs [44]. Epidemiological evidence of zidovudine use during pregnancy leading to mitochondrial dysfunction has been mixed, with some studies supporting the link, [45,46] but others finding no relationship.[47–50] We did not examine mitochondrial dysfunction in this study but, alongside malformations, it is a key safety consideration when contemplating the use of zidovudine during pregnancy.

Our study has several limitations. First, it is possible that some children were enrolled in multiple studies, including MAX, which would artificially increase the sample size and decrease the variance. However, we do not expect bias in our estimates because the prospective nature of nearly all included studies makes it unlikely that repeated observations are differential with respect to 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 a good positive predictive value for claims-based definitions of cardiac malformations in MAX.[24] We expect any outcome misclassification to be non-differential, and therefore biased towards the null. Fourth, the MAX dataset and nearly all studies included in the meta-analysis were observational cohorts, and there is potential for residual confounding. However, this should be limited by use of propensity score matching and an active comparator group. Fifth, 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 the 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 important to conduct similar analyses to monitor adverse events associated with other antiretroviral agents used during pregnancy, including other nucleoside agents and newer agents from other classes with limited safety data. Due to the Bayesian approach used, estimates from this study reflect the most comprehensive evidence available 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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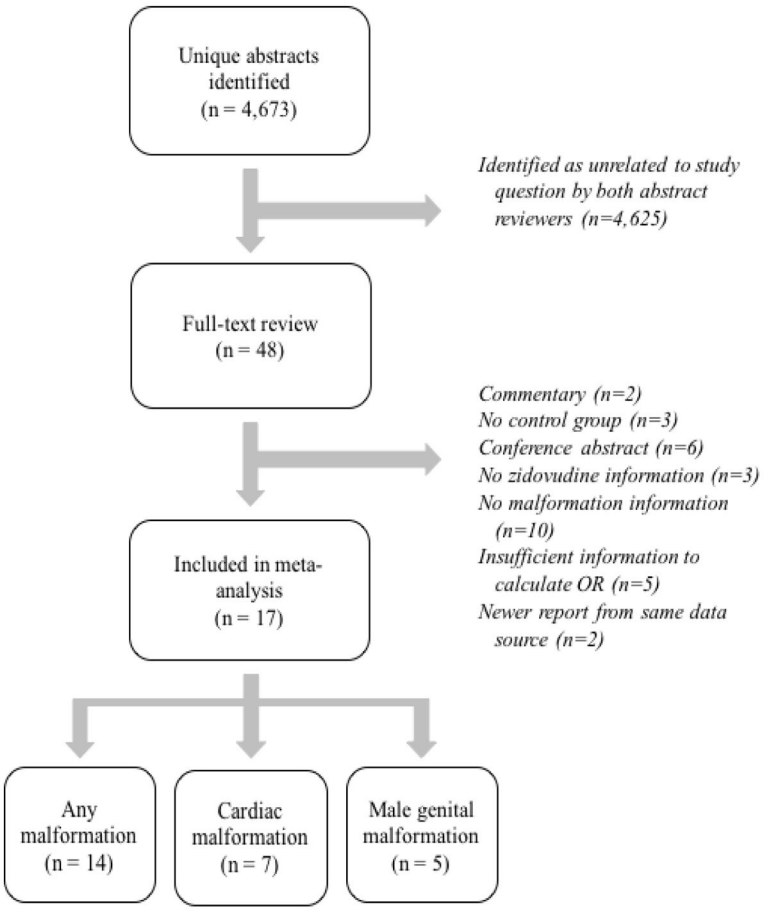
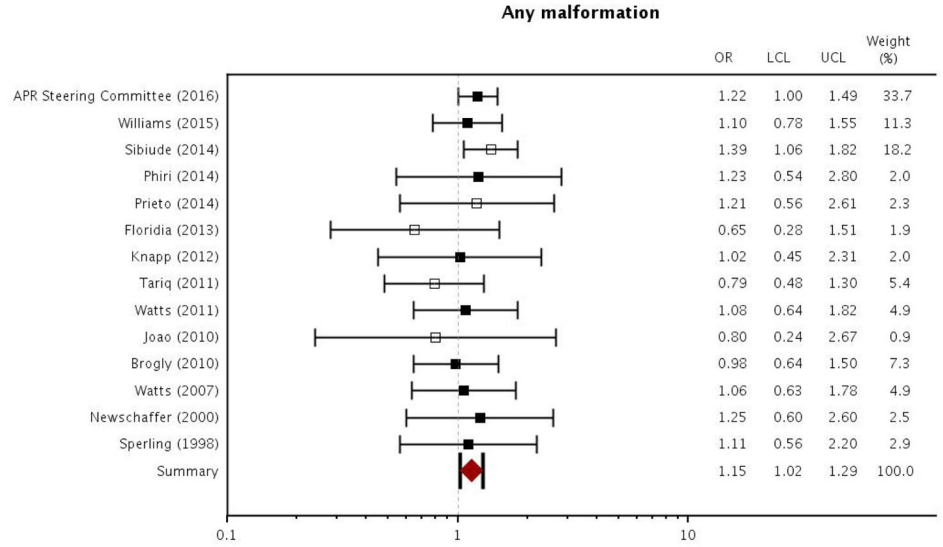
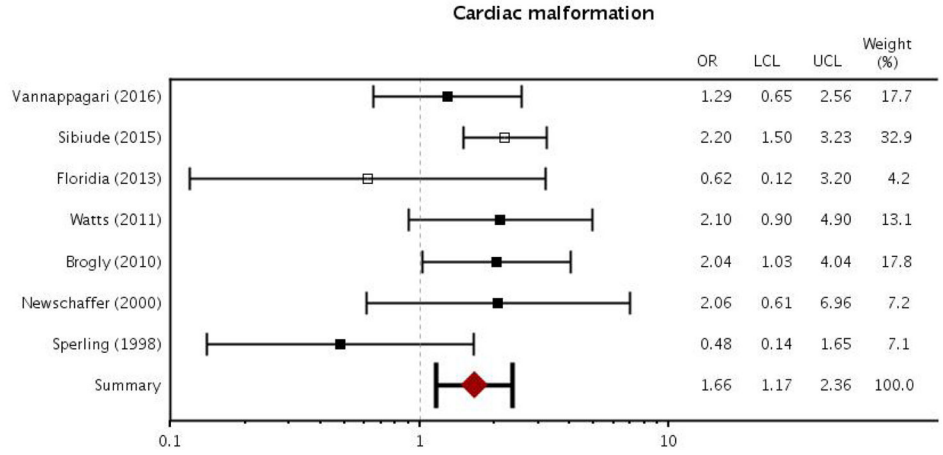


Figure 1.
Flowchart of article inclusion in meta-analysis

Panel A



Panel B



Panel C

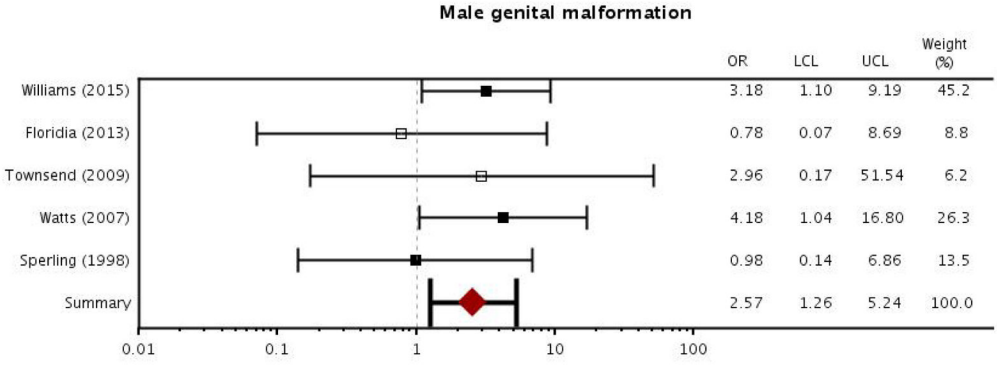


Figure 2.

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

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

Filled boxes indicate studies that recruited participants from the US and may have some overlap with Medicaid data. Empty boxes indicate studies that did not recruit participants from the US.

Table 1

Description of studies identified in systematic review and included in meta-analyses

Citation	Cohort	Geographic setting	Years	Timing of zidovudine exposure	Comparison group	Malformation definitions	Number exposed	Number unexposed	Malformation outcomes
Sperling et al 1998	ACTG 076	France, USA	1991–1994	T2/T3	Placebo in T2/T3[1]	Not reported	214	210	Overall, Cardiac, Male genital
Newschaffer et al 2000	New York Medicaid	New York, USA	1993–1996	T1	No zidovudine in pregnancy[1]	ICD-9 coding[2]	Not reported	Not reported	Overall, Cardiac
Watts et al 2007	WITS	USA	1990–2004	T1	No zidovudine in T1	MACDP guidelines & APR criteria	621	1,289	Overall, Male genital
Townsend et al 2009	NSHPC	Ireland, UK	1990–2007	Anytime in pregnancy	No zidovudine in pregnancy	Reported by treating physician	6,711	792	Male genital
Brogly et al 2010	PACTG 219/219C	USA	1993–2006	T1	No zidovudine in T1[1]	MACDP guidelines & APR criteria[2]	605	1,428	Overall, Cardiac
Joao et al 2010	NISDI Perinatal Study	Argentina, Brazil	2002–2007	Anytime in pregnancy	No zidovudine in pregnancy	MACDP guidelines & APR criteria	954	41	Overall
Watts et al 2011	PACTG 316	Brazil, Bahamas, Europe, USA	1997–2000	T1	No zidovudine in T1	MACDP guidelines & APR criteria[2]	517	897	Overall, Cardiac
Tariq et all 2011	NSHPC and ECS	Europe	2000–2009	T1	No zidovudine in T1	ICD-10 coding	1,077	1,477	Overall
Knapp et al 2012	IMPAACT P1025	USA	2002–2007	T1	No zidovudine in pregnancy	MACDP guidelines[2]	356	187	Overall
Floridia et al 2013	Italian NPSATP	Italy	2001–2011	T1	No ART in T1	MACDP guidelines & APR criteria	358	561	Overall, Cardiac, Male genital
Prieto et al 2014	The Madrid Cohort	Madrid, Spain	2000–2009	T1	No zidovudine in pregnancy[1]	EUROCAT criteria	287	189	Overall
Sibiude et al 2014	EPF ANRS CO1/CO11	France	1994–2010	T1	No zidovudine in pregnancy	ICD-10 coding according to EUROCAT criteria	3,267	2152	Overall
Phiri et al 2014	Tennessee Medicaid	Tennessee, USA	1994–2009	T1	No zidovudine in T1[1]	ICD-9 coding & vital record data according to MACDP guidelines[2]	156	650	Overall
Sibiude et al 2015	EPF ANRS CO1/CO11	France	1994–2010	T1	No zidovudine in T1	Previously identified cardiac defects reviewed by pediatric cardiologist[2]	3,262	9626	Cardiac
Williams et al 2015	PHACS SMARTT	USA	1995–2012	T1	No zidovudine in T1	MACDP guidelines & APR criteria[2]	726	1,791	Overall, Male genital
Vannappagari et al 2016	APR	USA, 65 additional countries	1989–2013	T1	No zidovudine in pregnancy	MACDP guidelines & APR criteria	4,000	2,378	Cardiac
APR Steering Committee 2016	APR	USA, 65 additional countries	1989–2016	T1	No zidovudine in T1	MACDP guidelines & APR criteria	4,128	12,833	Overall

Abbreviations: APR, Antiretroviral Pregnancy Registry; ACTG, AIDS Clinical Trials Group; WITS, Women and Infants Transmission Study; NSHPC, National Study of HIV in Pregnancy and Childhood; PACTG, Pediatric AIDS Clinical Trials Group; NISDI, NICHD International Site Development Initiative; NSHPC, National Study of HIV in Pregnancy and Childhood; ECS, European Collaborative Study; IMPAACT, International Maternal, Pediatric, Adolescent Clinical Trials Network; NPSATP, National Programme on Surveillance on Antiretroviral Treatment in Pregnancy; EPF, Enquete Perinatale Francaise; PHACS, Pediatric HIV/AIDS Cohort Study; SMARTT, Surveillance Monitoring for ART Toxicities; ART, antiretroviral therapy; T1, first trimester; T2, second trimester; T3, third trimester; EUROCAT, European Surveillance of Congenital Anomalies; MACDP, Metropolitan Atlanta Congenital Defects Program

[1]Comparison group included women who were not treated during pregnancy

[2]Case determination included blinded clinician review

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Table 2

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

	Full cohort				Matched cohort			
	Zidovudine in Trimester 1 (N = 824)		No zidovudine in Trimester 1 (N = 1,998)		Zidovudine in Trimester 1 (N = 735)		No 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
Evidence of parity	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

	Full cohort				Matched cohort			
	Zidovudine in Trimester 1 (N = 824)		No zidovudine in Trimester 1 (N = 1,998)		Zidovudine in Trimester 1 (N = 735)		No zidovudine in Trimester 1 (N = 735)	
Categorical variables	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
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
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

	Full cohort				Matched cohort			
	Zidovudine in Trimester 1 (N = 824)		No zidovudine in Trimester 1 (N = 1,998)		Zidovudine in Trimester 1 (N = 735)		No zidovudine in Trimester 1 (N = 735)	
Categorical variables	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
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 3

First trimester zidovudine exposure and risk of malformations: MAX and posterior Bayesian analysis results

	Risk in full sample: zidovudine in Trimester 1 (N=823)		Risk in full sample: no zidovudine in Trimester 1 (N=1,998)		Risk in matched sample: zidovudine in Trimester 1 (N=735)		Risk in matched sample: no zidovudine in Trimester 1 (N=735)		Posterior estimates: Bayesian analysis results		
	n	%	n	%	n	%	n	%	OR	95% credible interval	
Overall 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: MAX, Medicaid Analytic eXtract; 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.