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EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Hepatitis B virus and human immunodeficiency virus drugs in pregnancy: Findings from the Antiretroviral Pregnancy Registry

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Background & Aims: Fetal safety of antiviral therapies is important given the long-term treatment of women with chronic hepatitis B (CHB) infection who may become pregnant. We analyzed neonatal safety data from the Antiretroviral Pregnancy Registry (APR), the largest safety database in pregnancy for antivirals used for HIV and CHB.

Methods: Data were extracted from APR cases prospectively enrolled between 1989 and 2011. Primary outcomes were major birth defects rates with exposure to all antivirals, individual classes, and drugs compared to population-based controls. Relevant to CHB, only lamivudine (LAM) and tenofovir disoproxil fumarate (TDF) had sufficient individual data for review ($\geqslant$200 cases).

Results: Of 13,711 cases analyzed, the overall birth defect prevalence (2.8%, 95% CI 2.6–3.1%) was comparable to Centers for Disease Control population-based data (2.72%, 2.68–2.76%, $p = 0.87$) and two prospective antiretroviral exposed newborn cohorts (2.8%, 2.5–3.2%, $p = 0.90$ and 1.5%, 1.1–2.0%, $p < 0.001$). The birth defects prevalence between first and second/third trimesters exposure was similar (3.0% *vs.* 2.7%). No increased risk of major birth defects with LAM or TDF exposure compared to population-based controls was observed. No specific pattern of major birth defects was observed for individual antivirals or overall.

Conclusions: No increased risk of major birth defects including in non-live births was observed for pregnant women exposed to antivirals relevant to CHB treatment overall or to LAM or TDF compared to population-based controls. Continued safety and efficacy reporting on antivirals in pregnancy are essential to inform patients on their risks and benefits during pregnancy.

Keywords: Antiretroviral Pregnancy Registry; Hepatitis B; Birth defects.
Received 14 March 2012; received in revised form 14 June 2012; accepted 26 June 2012; available online 2 July 2012

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Abbreviations: CDC, Centers for Disease Control and Prevention; CHB, chronic hepatitis B; HIV, human immunodeficiency virus; APR, Antiretroviral Pregnancy Registry; LAM, lamivudine; TDF, tenofovir disoproxil fumarate; MTCT, mother-to-child transmission; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; NRTI, nucleoside reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase inhibitor; FDA, Food and Drug Administration; PI, protease inhibitor; MACDP, Metropolitan Atlanta Congenital Defects Program; NNRTI, non-nucleoside reverse transcriptase inhibitor.

Introduction

Chronic hepatitis B (CHB) remains an important global health problem. Up to one million of the approximately 350 million carriers worldwide die annually due to CHB-related disease [1]. Mother-to-child transmission (MTCT) is the most common form of transmission in high prevalence areas [2,3] and may occur in up to 90% of mothers who are hepatitis B surface antigen (HBsAg) positive without prophylaxis [4]. This high rate of transmission may be partially due to the high proportion of patients with active replication, hepatitis B e antigen (HBeAg) positivity [5–8], and high maternal viral load during reproductive years [9–12].

Although no anti-CHB therapies are currently approved for use in pregnancy, women in their child-bearing years with CHB liver disease may need antiviral therapy, including during pregnancy, or be actively taking antivirals when they become pregnant. Moreover, pregnant women in the immune tolerant phase of CHB with high HBV DNA levels (>10^8 copies/ml; 2×10^7 IU/ml) may want to be considered for antiviral therapy to reduce the viremia and the risk of MTCT that can occur despite neonatal immunoprophylaxis [9,13]. The use of antiviral therapies in pregnancy is controversial and knowledge of their risks is not widely disseminated among hepatologists. Accordingly, data on the safety of antivirals in pregnancy, and especially their impact on potential teratogenic risk, are of paramount importance when counseling pregnant patients with CHB on risks and benefits to their offspring.

Antiviral therapies for CHB and human immunodeficiency virus (HIV) infections have advanced markedly in the last decade and the benefits of treatment are clear. CHB patients experience low (<1%/year) rates of viral resistance and breakthrough with up to 5 years of antiviral monotherapy with entecavir or

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tenofovir [14,15], and long-term virus suppression is associated with slowing of liver disease progression and reversal of fibrosis and cirrhosis [16–18]. For HIV, the use of combination antiretroviral therapy with a backbone of two nucleos(t)ide analogues plus at least one drug from another class, also reliably produces durable suppression of HIV viremia [19,20], restores immune function [21], reduces HIV- [22,23] and non-HIV- [24–26] related mortality and morbidity, and prevents transmission [27,28]. In HIV infection, the use of antivirals to suppress HIV RNA levels, particularly during late pregnancy, has also dramatically reduced the rate of MTCT [29,30].

The Antiretroviral Pregnancy Registry (APR) is an international, voluntary registry that monitors prenatal exposures to antiviral drugs to detect a possible increased risk of major birth defects in a prospective exposure-registration cohort [31]. Although the primary focus of the Registry has been on women with HIV infection, data collection on CHB monoinfected patients began in 2003, and data on birth outcome are now also available for these women.

The aim of this study is to review the APR safety data for antivirals approved for the treatment of CHB, where sufficient numbers of reported exposures during pregnancy permit conclusions to be drawn concerning risk of major birth defects, i.e., lamivudine (LAM) and tenofovir disoproxil fumarate (TDF). The objective is to compare major birth defect rates to population-based controls for all antivirals and then for these two antiviral agents and classes of antivirals. In addition, we compared major birth defect rates and other birth outcomes (e.g., spontaneous, and induced, abortions and stillbirths) following antiviral exposure commencing in the first versus (*vs.*) remaining trimesters of pregnancy. Though these data exist in summary formats elsewhere, this is the first attempt to quantify and tabulate these risks as they pertain to HBV drugs in a manner useful to practicing hepatologists.

Materials and methods

The APR

The APR is an international, voluntary prospective exposure-registration cohort study established in January 1989 that monitors major birth defects and adverse fetal outcomes (e.g., spontaneous abortions, induced abortions, stillbirths) in pregnancies exposed to antiviral medications to treat maternal HIV and/or CHB infections. Data collection on exposure in CHB monoinfected mothers commenced in January 2003. Maternal safety and efficacy data are not addressed in this cohort. More details about the design of this cohort can be found in the 2011 interim report [31].

The APR begins collecting data on individual drugs after FDA approval. Thus, data on exposure to LAM began in 1989 and to TDF in 2001. We restricted our individual drug analyses to LAM and TDF because only limited data are available for exposure to other CHB drugs including entecavir, telbivudine, and adefovir dipivoxil.

Reporting to the APR is restricted to health care providers and is on a voluntary basis. Data are not verified. To limit reporting bias, pregnancy must be prospectively registered with the APR prior to delivery and then pregnancy outcome must be known and reported to the APR post-delivery. An independent advisory committee of members from the CDC, US Food and Drug Administration (FDA), and National Institutes of Health provide oversight of APR scientific conduct and analyses.

Approximately 1500 new cases (1300 from the US) are added annually to the APR. Interim primary analysis reports are issued twice each year and are publically available on the website (www.APRegistry.com). Data for the current study cover the reporting period from January 1, 1989 through January 31, 2011. Patients excluded from this analysis are those lost to follow-up and those with a pending outcome.

Study design and outcomes

The primary aim of this study is to describe the prevalence of major birth defects per 100 live births in women with HIV alone, HIV/CHB, or CHB alone who are exposed to antiviral therapy. Birth defects in non-live births categorized in the APR as spontaneous abortion, induced abortion, stillbirth and live birth [31] with first trimester exposure to nucleotide reverse transcriptase inhibitor (NtRTI) regimens and all antiviral regimens over the same time period are also reviewed.

APR birth defect rates are calculated for the overall cohort, each antiviral drug class (nucleos(t)ide reverse transcriptase inhibitors (NRTI, NtRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI)), and individually for LAM and TDF since these two antiviral agents have sufficient data for analysis and are relevant to treatment of CHB as well as HIV infection. Birth defect rates are also compared between those with earliest exposure beginning in the first trimester and those with only second/third trimester exposure.

We compared the prevalence of birth defects in the APR to that observed in the Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance system administered by the CDC, as per standard practice [31,32]. The MACDP actively searches for birth defects among all pregnancy outcomes in five counties of the metropolitan Atlanta area with approximately 50,000 annual births in a population of about 2.9 million. The MACDP prevalence of birth defects used for comparison identified births in the years that most closely mirrored the years APR has been in operation (1989–2003). Additional comparison groups used include two large multicenter cohorts of infants with prenatal antiviral exposure: (1) the European Collaborative Study [33], a prospective cohort of HIV-infected pregnant women at 26 centers in nine European countries and (2) the National Study of HIV in Pregnancy and Childhood in the United Kingdom and Ireland [34], a population-based surveillance study of HIV positive women and their children.

The APR defines a birth defect case as a fetus or infant with at least one of any major structural or chromosomal defect diagnosed by 6 years of age or any cluster of two or more conditional abnormalities. In addition, any structural or chromosomal defect detected in the prenatal evaluation of the pregnancy of an aborted fetus or deceased infant is evaluated and is considered a case under the above conditions, unless the prenatal diagnosis is actively ruled out postnatally. The Registry's definition of a birth defect case is modified from the MACDP system, having been designed to be more sensitive than the case definition by the CDC. A defect classification system, derived from the common ICD-9-CM-based surveillance coding system (the British Pediatric Association or ''BPA coding'') is used by the APR.

Statistical analyses and power

Compared to CDC's expected prevalence, with 80% power and a type 1 error rate of 5%, a cohort of 200 newborns exposed to antiviral drugs in the first trimester is sufficient to detect a 2.2-fold increased risk of overall birth defects. Thus, only antivirals with at least 200 cases of exposure are included in the formal analysis. A cohort of 1000 newborns exposed to antiviral drugs in the first trimester is sufficient to detect a 1.5-fold increased risk of overall birth defects.

Descriptive statistics were generated for maternal demographics. Prevalence rates for birth defects in live births by trimester of earliest exposure to TDF- and LAM-containing regimens and all ARV regimens were calculated and reported as point estimates with 95% confidence intervals. The rate of birth defects in non-live births with first trimester exposure to NtRTI regimens and all ARV regimens was also calculated. All data analyses were performed with SAS version 9.1 (Cary, NC, USA).

Results

This APR interim report analysis examined 13,711 cases, prospectively enrolled between January 1, 1989 and January 31, 2011. Patients excluded from this analysis included 1364 (8.7%) cases lost to follow-up and 535 (3.4%) cases pending outcome (Table 1). Patients with HIV infection comprised 93.9% (including 147 or 1% of patients with HIV–HBV co-infection), HBV monoinfection 1.2%, HIV post-exposure prophylaxis 0.3%, unknown 1.3% and missing 3.2%. Since the vast majority of the cohort was composed of HIV-infected pregnant women, the only 2 drugs approved for CHB with sufficient exposure data ($\geqslant$200 enrolled cases) in the

Table 1. Population for analysis: prospective registry cases (enrolled in APR from January 1, 1989 through January 31, 2011).

Pregnancies enrolled	15,610
Pending cases[a]	535 (3.4%)
Cases lost to follow-up[b]	1364 (8.7%)
Reports used in analysis	13,711 (87.8%)

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

APR were TDF and LAM. Numbers of pregnancy exposures were insufficient to draw conclusions on exposure risk for the other approved anti-CHB therapies such as adefovir dipivoxil (n = 42), entecavir (n = 27), and telbivudine (n = 15). We did not analyze data for the fixed dose combination tenofovir/emtricatabine as it is not FDA approved for CHB. Maternal demographics for the final study group are summarized in Table 2.

The overall birth defect prevalence per 100 live births for all antivirals was 2.8% (95% CI 2.6–3.1%) (Table 3). This prevalence rate is statistically similar to that reported in the general population described in the MACDP from 1989 to 2003 (2.72%, 95% CI 2.68–2.76, $p = 0.87$). Compared to two other large prospective cohort studies of newborns with prenatal exposure to antivirals, this birth defect rate is statistically similar to that of the United Kingdom and Ireland study [34] (2.8% (232/8242), 95% CI 2.5–3.2%, $p = 0.90$) and somewhat higher than the European Collaborative Study [33] (1.5% (39/2645), 95% CI 1.1–2.0%, $p < 0.001$).

The prevalence of major birth defects in pregnancies with first trimester exposure to antivirals (3.0%, 95% CI 2.5–3.4%; Table 3) is similar to that with first exposure during the second and third trimesters (2.7%, 95% CI 2.4–3.1%). The relative risk of birth defects for first trimester exposures compared to second and third trimesters is 1.08, 95% CI 0.88–1.32. No specific patterns of major birth defects were observed for any individual antiviral or overall. When the smaller group of CHB monoinfected patients was analyzed (n = 161), no significant differences in rate or pattern of birth defects were seen when compared to the overall cohort (data not shown).

The birth defect prevalence with first trimester exposure to the NRTI class (including LAM) and nucleotide NtRTI class (including TDF) is similar to that for all antiviral regimens (3.0% and 2.3% *vs.* 3.0% respectively; Table 3). The birth defect prevalence with exposure specifically to LAM- and TDF-containing regimens is similar to that for all antiviral regimens; earliest exposure commencing in the first trimester (LAM 3.1%, TDF 2.4%, all ARV regimens 3.0%) and earliest exposure commencing in the second or third trimester (LAM, 2.7%, TDF 2.0%, all antiviral regimens 2.8%, Table 3). The prevalence of birth defects in non-live births with first trimester exposure to NtRTI regimens and all antiviral regimens also shows no obvious imbalance, Table 4.

For TDF as well as most HIV-1-specific medications, sufficient numbers of first trimester exposures have been monitored to detect at least a twofold increase in risk of overall birth defects. No such increases have been detected to date. For LAM and zidovudine, sufficient first trimester exposures ($n \geqslant 1000$) have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases with LAM have been detected to date.

Discussion

This is the first report using Antiretroviral Pregnancy Registry (APR) data to describe the rates of major birth defects in newborns of women with *in utero* exposure to antiviral medications approved for use in CHB. Our analysis evaluates CHB and HIV antivirals overall, and then specifically LAM and TDF and their

Table 2. Maternal demographics at registration.

Pregnancies enrolled	January 1, 1989-January 31, 2011	13,711
Median age (IQR)[a]		28.0 (9.0) yr
Race/ethnicity	Black	7674 (56.0%)
	Hispanic	2633 (19.2%)
	White	2186 (15.9%)
	Asian	219 (1.6%)
	Others	397 (2.9%)
	Missing	602 (4.4%)
CD4+ T-cell count at start of pregnancy	≥500 cells/μl	3876 (28.3%)
	200-499 cells/μl	5843 (42.6%)
	<200 cells/μl	2212 (16.1%)
HIV-infected	A. Asymptomatic, acute (primary) HIV or PGL[b]	9933 (72.4%)
	B. Symptomatic, not (A) or (C)	1088 (7.9%)
	C. AIDS-indicator conditions	1864 (13.6%)
	D. HIV/HBV co-infected	147 (1%)
HIV uninfected	HIV post-exposure prophylaxis	40 (0.3%)
	Hepatitis B monoinfected[c]	161 (1.2%)

[a]IQR, interquartile range.
[b]PGL, persistent generalized adenopathy.
[c]HBV monoinfected data collection commenced January 2003.

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Table 3. Number of birth defects[a] in live births by trimester of earliest exposure to LAM[g]- and TDF[h]-containing regimens and all antiviral regimens in APR: January 1, 1989–January 31, 2011.

		Overall		Trimester of earliest exposure			
				1st trimester		2nd/3rd trimester	
		Number of defects/ live births	Prevalence (%) (95% CI)	Number of defects/ live births	Prevalence (%) (95% CI)	Number of defects/ live births	Prevalence (%) (95% CI)
APR	All antivirals[b]	371/13,040	2.8 (2.6-3.1)	164/5555	3.0 (2.5-3.4)	205/7483	2.7 (2.4-3.1)
	NRTI[c] regimens			161/5364		207/7532	
	NtRTI[d] regimens			26/1134		13/637	
	NNRTI[e] regimens			41/1505		49/1506	
	PI[f] regimens			90/2932		127/4607	
	LAM[g] regimens			118/3864	3.1 (2.5-3.7)	169/6230	2.7 (2.3-3.1)
	TDF[h] regimens			26/1092	2.4 (1.6-3.5)	13/639	2.0 (1.1-3.5)
MACDP[i] [31]	-		2.72 (2.68-2.76)	-	-	-	-
European collaborative study [33]	All antivirals	39/2645	1.5 (1.1-2.0)	18/880	2.0 (1.2-3.2)	21/1765	1.2 (0.7-1.8)
UK and Ireland [34]	All antivirals	297/10,513	2.8 (2.5-3.2)	95/3190	3.0 (2.4-3.6)	202/7323	2.8 (2.4-3.2)

[a]Defects meeting the CDC criteria only. Excludes reported defects in abortions <20 weeks of gestation.
[b]Due to unknown trimester of exposure data for 2 case(s), the specific counts may not sum to the overall total.
[c]NRTI, nucleoside reverse transcriptase inhibitor.
[d]NtRTI, nucleotide reverse transcriptase inhibitor.
[e]NNRTI, non-nucleoside reverse transcriptase inhibitor.
[f]PI, protease inhibitor.
[g]LAM, lamivudine.
[h]TDF, tenofovir disoproxil fumarate.
[i]The MACDP includes infants in a general population who may or may not have been exposed to antivirals *in utero*.

associated drug classes (NRTI and NtRTI, respectively). LAM and TDF are the only two drugs in the APR approved for CHB treatment with sufficient data available to draw reasonable conclusions regarding fetal safety (i.e., risk of major birth defect). Though it would be preferable to have been able to study all HBV drugs, the lack of sufficient case numbers for entecavir, adefovir, and telbivudine in any dataset makes drawing conclusions on these drugs impossible. However, future prospective studies particularly of entecavir and tenofovir are needed. The results of our analysis show no increased risk of major birth defects with antivirals overall or specifically with LAM or TDF compared with population-based controls. Compared to two large prospective cohorts of mothers exposed to antivirals, the rate of major birth defects in the APR is similar to that in the UK and Ireland cohort but somewhat higher than that in the European Collaborative Study cohort. As noted previously, this difference most likely reflects variations in definitions of cases and birth defects, case ascertainment, and rates of prenatal diagnoses [33]. The fact that initial exposure to these medications in the first, versus remaining trimesters was associated with similar birth defect rates supports a lack of teratogenicity. Given the large number of CHB-infected women of child-bearing potential worldwide, safety data are of great interest in relation to fetal drug exposure, especially beginning in the first trimester of pregnancy.

Although LAM and TDF are licensed for CHB and HIV treatment, neither drug is approved for use in pregnancy. LAM and TDF are currently rated pregnancy category C and B, respectively, by the US FDA, based primarily on animal data and a paucity of evidence in humans without clear evidence of harm. Published data regarding use of LAM or TDF for CHB in pregnancy are limited predominantly to commencement in the third trimester in mothers with high HBV DNA levels, to reduce the maternal viremia and, consequently, lower the risk of MTCT of HBV. Concern remains over the propensity to develop viral resistance to LAM [35] if it is used throughout the pregnancy or postpartum, rather than restricted to the third trimester, whereas, no resistance to TDF has been detected to date with up to 3 years of monotherapy for CHB [36].

For women that are or may become pregnant, the decision to use any medical therapy is complex having to balance benefits versus risks to the fetus as well as the mother. For HIV, the need for therapy for the mother and the absence of effective post-exposure prophylaxis for the baby makes antiviral therapy during pregnancy the accepted standard-of-care. The issue of maternal antiviral therapy is more controversial for CHB. Many women of child-bearing age are in the immune tolerant phase of CHB, which lacks traditional indications antiviral therapy, and most women can postpone antiviral treatment until after completion of child-bearing. Additionally, post-delivery neonatal combined immunoprophylaxis is successful at preventing CHB infection in approximately 90% of infants, thus, prevention of MTCT of HBV does not require treatment during pregnancy for most women. However, the current failure rate of post-exposure neonatal immunoprophylaxis against MTCT of HBV may be unacceptably high (~9%) in women with high levels of viremia (serum HBV DNA >10^6 copies/ml; ~2×10^5 IU/ml) [9]. Additionally, knowledge as to which drugs are safe during

Table 4. Number of birth defects in non-live births[a] with first trimester exposure to NRTI[b] and NtRTI[c] regimens and all antiviral regimens: January 1, 1989–January 31, 2011.

	NRTI[b]		NtRTI[c]		All antivirals	
	Birth defects/ non-live birth	Prevalence (%)	Birth defects/ non-live birth	Prevalence (%)	Birth defects/ non-live birth	Prevalence (%)
Spontaneous loss	0/287	0	0/109	0	0/306	0
Stillbirth	3/88	3.4	0/32	0	3/97	3.0
Induced abortions	7/353	2.0	3/98	1.3	7/395	1.8
Overall	10/728	1.4	3/239	1.3	10/798	1.3

[a]Defined as a stillborn infant, or a spontaneous or induced abortion $\geqslant$20 weeks of gestation.
[b]NRTI, nucleoside reverse transcriptase inhibitor.
[c]NtRTI, nucleotide reverse transcriptase inhibitor.

pregnancy can expand potential candidates for treatment among women of child-bearing age.

The purpose of this study is not to advocate off-label use of antiviral therapies in pregnancy. Instead, we wish to draw attention to the utility of the Antiretroviral Pregnancy Registry when counseling pregnant women and those of child-bearing potential with CHB on the fetal safety of antiviral therapies in pregnancy. To our knowledge, the APR represents the largest publically available safety database of its kind with over 13,000 evaluable pregnancy outcomes to date.

The limitations of the APR include its reliance on voluntary reporting with possible underreporting or differential reporting of cases as well as lack of verification of cases or birth defects in non-cases. In addition, most birth defect cases are identified shortly after birth with limited attempts at longer-term follow-up. For example, bone development and fracture risk are a concern due to the potential effects of TDF on bone loss. On this topic, the data are reassuring in that none of the defects reported reflect a problem with bone formation or unexpected fractures. However, "under-reporting" is likely and thus ascertainment of these complications is expected to be limited, since neonatal X-ray is not the standard, so a subtle non-clinical fracture would be missed. However, the Registry also receives and evaluates all retrospective (spontaneous) case reports as well (for signal generation), and has received no signal indicating issues with bone development. This is in keeping with additional data in children born to HIV-infected women that have not shown effects on growth or bone development at 1–5 years of age [37,38], though one study did show slightly lower length for age but not weight for age at 1 year despite equal incidence of low birth weight and size in children born to women taking TDF [39].

The overall impact of these biases could be non-directional or confound the true rate. However, all cases need to be identified and reported during pregnancy (before delivery) to minimize reporting bias, thus only cases that never get reported (pending and lost to follow-up cases) are likely to have systematic bias. The pending cases are a small percentage of the total (3.4%) and patients lost to follow-up (8.7%) are less likely to have directional bias. As a result, these cases are unlikely to influence the overall findings. Additionally, the consistency of the data between drugs within a class strengthens the likelihood that these results are free from major systematic bias. Comparisons of early defects to the MACDP is the standard approach to epidemiologic measurements of drug safety during pregnancy and combined with measurement of differences across trimesters should reduce or eliminate systematic underreporting. Furthermore, the results to date reflect primarily women with HIV infection although reporting is open to women taking antivirals for CHB. The numbers of cases with HBV monoinfection or HBV/HIV co-infection remain small. This is possibly due to limited historic awareness of this database among hepatologists, the belief that other physicians (PCP, OB/GYN) may be responsible for the reporting, a lack of interest/time/incentives, and the use of 'Antiretroviral' in the Registry's title. Thus, most women enrolled are taking multiple antiretroviral agents for HIV monoinfection and outcomes in HBV monoinfection may differ from those with HIV infection. Finally, treatment efficacy, including rates of viral suppression and MTCT transmission, and maternal safety are not assessed in the Registry or in this analysis. Both treatment efficacy and maternal safety should be studied prospectively in further clinical studies.

Currently the APR is the largest publicly available database that reports on exposure to CHB and HIV nucleoside and nucleotide antiviral drugs in all trimesters of pregnancy and provides the most robust safety data to date. In reviewing all reported birth defects from the APR, the defects reported show no apparent increases in frequency with first trimester versus later exposures and no pattern to suggest a common cause. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients. However, potential limitations of registries such as this should be recognized. Reporting of safety outcomes to the Antiretroviral Pregnancy Registry (www.APRegistry.com) for women exposed to all anti-CHB drugs during pregnancy should be encouraged to increase the data available to our patients in the future.

Financial support

Financial support was provided by Gilead Sciences.

Author contributions

Robert S. Brown, Jr. contributed fully to the concepts, design and writing of the manuscript.

Elizabeth C. Verna contributed fully to the concepts, design and writing of the manuscript.

Marcus R. Pereira contributed fully to the concepts, design and writing of the manuscript.

Hugh H. Tilson served as a liaison to the APR where he is involved in collection, analysis, and reporting of the APRs data, and also served as writer, reviewer and commentator.

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Christopher Aguilar, serves as Gilead's sponsor representative to the APR, facilitating the manuscript's progress through the APR publications committee approval process, and also served as writer, reviewer and commentator.

Cheng-Shiun Leu provided biostatistical support and contributed to manuscript preparation.

Maria Buti contributed fully to the concepts, design and writing of the manuscript.

Elizabeth A. Fagan contributed fully to the concepts, design and writing of the manuscript.

Conflict of interest

Robert S. Brown, Jr. receives support from Gilead Sciences Inc. for consulting and research. Christopher Aguilar is an employee of Gilead Sciences Inc. and holds stock. Elizabeth A. Fagan is/was an employee of Gilead Sciences Inc. and holds stock.

The other authors have nothing to disclose.

Addendum

Advisory committee consensus statement

In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds no apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause. The Registry notes modest but statistically significant elevations of overall defect rates with didanosine and nelfinavir compared with its population-based comparator, the MACDP. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Health care providers are encouraged to report eligible patients to the Registry at www.APRegistry.com.

References

[1] Maynard JE. Hepatitis B: global importance and need for control. Vaccine 1990;8 (Suppl.):S18–S20, discussion S21–13.

[2] Beasley RP, Hwang LY, Lin CC, Leu ML, Stevens CE, Szmuness W, et al. Incidence of hepatitis B virus infections in preschool children in Taiwan. J Infect Dis 1982;146:198–204.

[3] Alter MJ, Hadler SC, Margolis HS, Alexander WJ, Hu PY, Judson FN, et al. The changing epidemiology of hepatitis B in the United States. Need for alternative vaccination strategies. JAMA 1990;263:1218–1222.

[4] Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med 1975;292:771–774.

[5] Lok AS, Lai CL, Wu PC, Leung EK, Lam TS. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. Gastroenterology 1987;92:1839–1843.

[6] Lok AS, Lai CL. A longitudinal follow-up of asymptomatic hepatitis B surface antigen-positive Chinese children. Hepatology 1988;8:1130–1133.

[7] Liaw YF, Chu CM, Lin DY, Sheen IS, Yang CY, Huang MJ. Age-specific prevalence and significance of hepatitis B e antigen and antibody in chronic hepatitis B virus infection in Taiwan: a comparison among asymptomatic carriers, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. J Med Virol 1984;13:385–391.

[8] Stevens CE, Toy PT, Tong MJ, Taylor PE, Vyas GN, Nair PV, et al. Perinatal hepatitis B virus transmission in the United States. Prevention by passive–active immunization. JAMA 1985;253:1740–1745.

[9] Wiseman E, Fraser MA, Holden S, Glass A, Kidson BL, Heron LG, et al. Perinatal transmission of hepatitis B virus: an Australian experience. Med J Aust 2009;190:489–492.

[10] Burk RD, Hwang LY, Ho GY, Shafritz DA, Beasley RP. Outcome of perinatal hepatitis B virus exposure is dependent on maternal virus load. J Infect Dis 1994;170:1418–1423.

[11] Li XM, Shi MF, Yang YB, Shi ZJ, Hou HY, Shen HM, et al. Effect of hepatitis B immunoglobulin on interruption of HBV intrauterine infection. World J Gastroenterol 2004;10:3215–3217.

[12] Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive–active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat 2012;19:e18–25.

[13] Shi Z, Yang Y, Ma L, Li X, Schreiber A. Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. Obstet Gynecol 2010;116:147–159.

[14] Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661–662.

[15] Tenney DJ, Rose RE, Baldick CJ, Pokornowski KA, Eggers BJ, Fang J, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. Hepatology 2009;49:1503–1514.

[16] Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology 2006;131:1743–1751.

[17] Chang TT, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 2010;52:886–893.

[18] Schiff ER, Lee SS, Chao YC, Kew Yoon S, Bessone F, Wu SS, et al. Long-term treatment with entecavir induces reversal of advanced fibrosis or cirrhosis in patients with chronic hepatitis B. Clin Gastroenterol Hepatol 2011;9:274–276.

[19] Thompson MA, Aberg JA, Cahn P, Montaner JS, Rizzardini G, Telenti A, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA 2010;304:321–333.

[20] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available from: http://www-aidsinfonihgov/ContentFiles/AdultandAdolescentGLpdf. [Accessed June 27, 2011].

[21] Garcia F, de Lazzari E, Plana M, Castro P, Mestre G, Nomdedeu M, et al. Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. J Acquir Immune Defic Syndr 2004;36:702–713.

[22] Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008;372:293–299.

[23] van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. AIDS 2010;24:1527–1535.

[24] El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006;355:2283–2296.

[25] Baker JV, Peng G, Rapkin J, Abrams DI, Silverberg MJ, MacArthur RD, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. AIDS 2008;22:841–848.

[26] Bruyand M, Thiebaut R, Lawson-Ayayi S, Joly P, Sasco AJ, Mercie P, et al. Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. Clin Infect Dis 2009;49:1109–1116.

[27] Bunnell R, Ekwaru JP, Solberg P, Wamai N, Bikaako-Kajura W, Were W, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. AIDS 2006;20:85–92.

[28] Castilla J, Del Romero J, Hernando V, Marincovich B, Garcia S, Rodriguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. J Acquir Immune Defic Syndr 2005;40:96–101.

[29] Garcia PM, Kalish LA, Pitt J, Minkoff H, Quinn TC, Burchett SK, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. N Engl J Med 1999;341:394–402.

[30] Mofenson L, Taylor AW, Rogers M, Campsmith M, Ruffo NM, Clark J, et al. Achievements in public health. Reduction in perinatal transmission of HIV infection–United States, 1985–2005. MMWR Morb Mortal Wkly Rep 2006;55:592–597.
[31] International APRSCAPR, Interim Report for 1 January 1989 through 31 January 2011. Wilmington NRC, www.APRegistry.com. CAfU.
[32] Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R, et al. Reporting birth defects surveillance data 1968–2003. Birth Defects Res A Clin Mol Teratol 2007;79:65–186.
[33] Patel D, Thorne C, Fiore S, Newell ML. Does highly active antiretroviral therapy increase the risk of congenital abnormalities in HIV-infected women? J Acquir Immune Defic Syndr 2005;40:116–118.
[34] 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;23:519–524.
[35] Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 2003;125:1714–1722.
[36] Heathcote EJ, Marcellin P, Buti M, Gane E, De Man RA, Krastev Z, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. Gastroenterology 2011;140:132–143.
[37] Vigano A, Mora S, Giacomet V, Stucchi S, Manfredini V, Gabiano C, 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;16:1259–1266.
[38] 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;42:1581–1585.
[39] Siberry GK, Williams PL, Mendez H, Seage 3rd GR, Jacobson DL, Hazra R, et al. Safety of tenofovir use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. AIDS 2012;26:1151–1159.