BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.13542
www.bjog.org

Epidemiology

Association between in utero zidovudine exposure and nondefect adverse birth outcomes: analysis of prospectively collected data from the Antiretroviral Pregnancy Registry

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Accepted 24 May 2015. Published Online 12 August 2015.

Objective To examine the association between nondefect adverse birth outcomes and in utero exposure to zidovudine (ZDV)-containing regimens versus non-ZDV antiretroviral (ARV) regimens.

Design Analysis of prospectively-collected data.

Setting Global.

Population HIV-infected pregnant women prenatally exposed to antiretrovirals.

Methods Estimation of prevalence of and risk for nondefect adverse birth outcomes among HIV-infected women.

Main outcome measures Prevalence of and risk for nondefect adverse birth outcomes.

Results Among 12 780 singleton birth outcomes with in utero ZDV exposure, 96.1% were live births; 3.9% were spontaneous abortions, induced abortions or stillbirths. Among live births, 16.4% were low birthweight (LBW); 12.3% were premature. Among 1904 outcomes with in utero exposure to non-ZDV ARV regimens, 85.8% were live births; 14.2% were spontaneous abortions, induced abortions or stillbirths. Among live births, 14.1% were LBW; 12.4% were premature. Relative risk comparing exposure to ZDV-containing ARV regimens to non-ZDV ARV regimens for spontaneous abortions was 0.18 (95% confidence interval [95% CI] 0.14–0.22); induced abortions 0.28 (95% CI 0.22–0.36); stillbirths 0.76 (95% CI 0.51–1.12); premature births 1.00 (95% CI 0.87–1.15) and LBW 1.17 (95% CI 1.02–1.33).

Conclusion Prevalence of nondefect adverse birth outcomes is lower among outcomes with in utero ZDV exposure versus in utero non-ZDV ARV exposure. The risks for spontaneous and induced abortions were no different for ZDV-containing regimens versus non-ZDV ARV regimens. For premature births and stillbirths, there was no significant difference in risk between the two regimens. The risk of LBW was statistically significantly higher among ZDV-containing regimens versus non-ZDV ARV regimens.

Keywords Epidemiology HIV, pregnancy outcomes, zidovudine.

Tweetable abstract ZDV-containing regimens do not increase the risk for nondefect adverse birth outcomes.

Please cite this paper as: Vannappagari V, Koram N, Albano J, Tilson H, Gee C. Association between in utero zidovudine exposure and nondefect adverse birth outcomes: analysis of prospectively collected data from the Antiretroviral Pregnancy Registry. BJOG 2016;123:910–916.

Introduction

Zidovudine (ZDV) was the first antiretroviral (ARV) to be approved for treatment of HIV/AIDS in the USA. WHO guidelines for first-line regimens for HIV-positive pregnant women include ZDV.[1,2]

The Antiretroviral Pregnancy Registry (APR) monitors birth defects in pregnant women exposed to ARVs. Data from the most recent APR interim report published in June 2014 indicate that the overall prevalence of birth defects following first-trimester exposure to any ARV monitored by the registry is 2.8 (95% confidence interval [95% CI]:

2.5–3.3)[3]*. This proportion is not significantly higher than those reported in the APR's two population-based comparators, the Metropolitan Atlanta Congenital Defects Program (the Centers for Disease Control and Prevention's birth defects surveillance system) with 2.72 per 100 live births[4] and the Texas Birth Defects Registry with a reported rate of 4.17 per 100 live births.[5] Among first-trimester ZDV exposures, the APR reports no increase in the risk of overall birth defects, nor in the risk of birth defects in the cardiovascular and genitourinary systems.[6] The prevalence of birth defects among women with first-trimester ZDV exposure is 3.2% (95% CI 2.7–3.8%).[3] The complete APR interim report is available online at http://www.apregistry.com/forms/interim_report.pdf.

The full prescribing information for ZDV in the USA suggests that although no differences in pregnancy-related adverse events between pregnant women with ZDV exposure compared with those with placebo exposure have been observed, animal studies have shown teratogenicity, resulting in a US Food and Drug Administration Pregnancy Category C status. In this analysis, we examine the association between adverse pregnancy outcomes other than birth defects and the use of ZDV-containing regimens during pregnancy, compared with non-ZDV ARV regimens.

Methods

This is a secondary analysis of data from the APR from 1 January 1989 through to 31 July 2013. The APR is described in detail in a previous analysis.[7] Briefly, the APR is a pregnancy registry that monitors for early signal of increased risk for birth defects following prenatal exposure to ARVs. The majority of case reports are from the USA and its territories (77.6%); the remaining reports are from 66 other countries.[3]

Pregnant women prenatally exposed to any ARV are prospectively registered before the birth outcome being known, and are followed through to the end of the pregnancy. Data on maternal risk factors and birth outcomes are also collected. The APR has institutional review board (IRB) approval from Western IRB, and was granted a waiver from obtaining informed consent.

A birth outcome is defined at the time of delivery or fetal loss, or when a defect detected on a prenatal test is reported at enrolment. Although the APR also collects data from clinical trials and retrospective studies, the primary APR cohort is limited to prospectively registered women. Only singleton births are included in the current analysis; multiple births such as twin and triplet births are excluded because of the increased risk of adverse outcomes associated with such pregnancies.[8–10] We also compare in utero ZDV exposure at any time during pregnancy to in utero non-ZDV exposure, because drug exposure at any time during pregnancy may be relevant for birth outcomes.

Gestational weeks are calculated starting from the first day of the last menstrual period. If the date of the last menstrual period is unknown, the estimated delivery date is used. If gestational week is inconsistent with exposure dates and/or the date of outcome (outside ± 1 week for the first trimester, outside ± 2 weeks for the second and third trimesters), a corrected estimated delivery date where ultrasound data are available is used.

The following adverse birth outcomes other than birth defects are included in our analyses: spontaneous and induced abortions, stillbirths, premature births (<37 weeks gestation), very premature births (<32 weeks gestation), low birthweight (LBW; <2500 g) and very low birthweight (VLBW; <1500 g). The APR defines spontaneous abortion as death of a fetus or expulsion of the products of conception before 20 weeks gestation. A stillbirth is defined as the death of a fetus occurring at 20 weeks of gestation or more, or for situations in which the gestational age is unavailable, a fetus weighing at least 500 g.

Statistical analysis

The prevalence of nondefect adverse birth outcomes was estimated, and the relative risks and 95% CI comparing outcomes with prenatal exposure to ZDV-containing regimens versus exposure to non-ZDV ARV regimens were calculated. Depending on whether the data analysed were continuous or categorical, the independent *t*-test or Fisher's exact test was used to calculate *P*-values. Unknown or missing values were excluded from the analysis. For spontaneous losses, induced abortions and stillbirths, prevalence was estimated using the total number of pregnancies as the denominator, with the 95% CI based on the Clopper–Pearson exact binomial method.[11,12] For prematurity and LBW, prevalence was estimated using the total number of live singleton births as the denominator. Outcomes with birth defects, and all outcomes with unknown gestational age or unknown birthweight, were excluded. The 95% CI were calculated using the Clopper–Pearson exact binomial method. Relative risks were calculated comparing

*The APR Advisory Committee Consensus Statement[3]: 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 comparators, the Metropolitan Atlanta Congenital Defects Program and Texas Birth Defects Registry. 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 counselling patients. However, potential limitations of registries such as this should be recognised. The Registry is ongoing. Healthcare providers are encouraged to report eligible patients to the Registry at www.APRegistry.com.

ZDV-containing regimens to non-ZDV ARV regimens. The 95% CI for the relative risks were calculated using the normal asymptotic method. All analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Maternal demographics

Of the 14 950 pregnancies from prospectively registered HIV-infected women for which outcome is known, 14 684 were singleton pregnancies, 262 were pregnancies with twins and four were with triplets. Pregnancies with multiple outcomes were excluded from all subsequent analyses.

Of the 14 684 singleton pregnancy outcomes, 12 780 were prenatally exposed to ZDV in any trimester; 1904 had prenatal non-ZDV ARV exposure. Table 1 describes maternal demographics for these two groups. We found no difference between groups in baseline CD4 counts; however, women exposed to non-ZDV ARV combinations were older. A higher proportion of Hispanic women were on ZDV-containing regimens compared with non-ZDV ARV regimens (Table 1). A listing of ZDV-containing regimens and non-ZDV regimens is presented in Table 2.

Among the 12 780 singleton pregnancies with in utero ZDV exposure, 96.1% were live births, and 3.9% were nondefect adverse outcomes (spontaneous abortions 1.3%; induced abortions 1.4%; stillbirths 1.2%). When restricted to ZDV exposures in the first trimester, the prevalence of spontaneous abortions increased to 3.7% and induced abortions increased to 4.2%. Among live births, 16.4% had LBW <2500 g, 2.1% had VLBW <1500 g, 12.3% were premature <37 weeks gestation, and 2.2% were very premature <32 weeks gestation. Among 1904 outcomes with in utero non-ZDV ARV regimen exposure, 85.8% were live births and 14.2% resulted in nondefect adverse outcomes (spontaneous abortions 7.6%; induced abortions 5.1%; stillbirths 1.5%). When restricted to non-ZDV exposures in the first trimester, the proportion of spontaneous abortions increased to 9.6% and induced abortions increased to 6.4%. Among live births, 14.1% had LBW <2500 g, 1.9% had VLBW <1500 g, 12.4% were premature <37 weeks of gestation, and 2.1% were very premature <32 weeks of

Table 1. Maternal characteristics: singleton prospective pregnancies by ZDV exposure during pregnancy among HIV-infected women reported to the APR through to 31 July 2013 with outcome

Characteristic	Overall	Regimens containing ZDV	Regimens excluding ZDV	*P*-value
Number of pregnancies	14 684	12 780	1904	
Age (years)*				
n	14 608	12 725	1883	<0.0001
Mean (SD)	28.2 (6.04)	27.9 (6.00)	30.0 (6.00)	
Median (interquartile range)	28.0 (9.0)	28.0 (9.0)	30.0 (8.0)	
Minimum – Maximum	13–55	13–55	14–48	
Missing	76 (0.5%)	55 (0.4%)	21 (1.1%)	
Race, *n* (%)**				
White	2272 (15.5)	1969 (15.4)	303 (15.9)	<0.0001
Black	8682 (59.1)	7506 (58.7)	1176 (61.8)	
Hispanic	2915 (19.9)	2623 (20.5)	292 (15.3)	
Asian	128 (0.9)	99 (0.8)	29 (1.5)	
Other	402 (2.7)	333 (2.6)	69 (3.6)	
Missing	285 (1.9)	250 (2.0)	35 (1.8)	
CD4$^+$ T-cell categories at start of pregnancy, *n* (%)**				
≥500 μl	4561 (31.1)	3966 (31.0)	595 (31.3)	0.1071
200–499 μl	6583 (44.8)	5692 (44.5)	891 (46.8)	
<200 μl	2407 (16.4)	2122 (16.6)	285 (15.0)	
Unknown	77 (0.5)	64 (0.5)	13 (0.7)	
N/A	24 (0.2)	13 (0.1)	11 (0.6)	
Missing	1032 (7.0)	923 (7.2)	109 (5.7)	
Country of reported origin, *n* (%)				
USA	11 872 (80.8)	10 684 (83.6)	1188 (62.4)	<0.0001
Other	2808 (19.1)	2093 (16.4)	715 (37.6)	
Missing	4 (0.0)	3 (0.0)	1 (0.1)	

Percentages are based on the number of pregnancies; pregnancies include 266 multiple gestation births (262 twin and four triplet).
**P*-value is based on the independent *t*-test.
***P*-value is based on the Fisher's exact test (chi-square test for Race). Analysis does not include N/A, Unknown, or Missing values.

Table 2. Regimens with and without ZDV by number of exposed pregnancies reported to the APR through to 31 July 2013 with outcome

Regimens containing ZDV	Regimens excluding ZDV
≥1000 exposed pregnancies	**≥1000 exposed pregnancies**
ZDV	n/a
3TC & NFV & ZDV	
3TC & NVP & ZDV	
3TC & LPV & RTV & ZDV	
500–999 exposed pregnancies	**500–999 exposed pregnancies**
3TC & ZDV	ATV & FTC & RTV & TDF
ABC & 3TC & ZDV	
100–499 exposed pregnancies	**100–499 exposed pregnancies**
3TC & TDF & ZDV	TDF
EFV & 3TC & ZDV	FTC & TDF
IDV & 3TC & ZDV	3TC & NFV & d4T
	3TC & NVP & d4T
	EFV & 3TC & d4T
	EFV & FTC & TDF
	DRV & FTC & RTV & TDF
	FTC & LPV & RTV & TDF

Regimens with <100 exposed pregnancies reported are not listed. 3TC, lamivudine; ABC, abacavir; ADV, adefovir dipivoxil; APV, amprenavir; ATV, atazanavir sulphate; d4T, stavudine; ddC, zalcitabine; ddI, didanosine; DLV, delavirdine mesylate; DRV, darunavir; EFV, efavirenz; ETR, etravirine; ETV, entecavir; FOS, fosamprenavir calcium; FTC, emtricitabine; IDV, indinavir; LdT, telbivudine; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NFV, nelfinavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; SQV, saquinavir mesylate or saquinavir; TDF, tenofovir disporoxil fumatrate; TPV, tipranavir; and ZDV, zidovudine. Occurrences of 3TC & ZDV may represent the combination product.

gestation (Table 3). For APR overall, 8.6% of term deliveries (≥37 weeks) were LBW <2500 g. Among pregnant women with exposure to ZDV-containing regimens, 8.8% of term deliveries (≥37 weeks) were LBW <2500 g; among those with non-ZDV ARV exposure, 7.0% of term deliveries were LBW.

The relative risks comparing exposure to ZDV-containing regimens with non-ZDV ARV regimens were 0.18 (95% CI 0.14–0.22; $P < 0.0001$) for spontaneous abortions; 0.28 (95% CI 0.22–0.36; $P < 0.0001$) for induced abortions; 0.76 (95% CI 0.51–1.12; $P = 0.17$) for stillbirths; 1.00 (95% CI 0.87–1.15; $P = 0.97$) for preterm births; and 1.17 (95% CI 1.02–1.33; $P = 0.02$) for LBW (Table 3).

The relative risks for spontaneous abortions and induced abortions were significantly lower in the ZDV-exposed group. The risks for stillbirths and preterm births were similar between the two groups. The risk for LBW was statistically significantly higher among those with prenatal exposure to ZDV.

Discussion

Main findings

A higher proportion of nondefect adverse pregnancy outcomes was observed among infants with prenatal exposure to non-ZDV ARV regimens, compared with those with prenatal exposure to ZDV-containing regimens. For LBW, a higher proportion was observed among infants with prenatal exposure to ZDV-containing regimens. However, similar rates of prematurity were observed among both groups. The risk for spontaneous and induced abortions was significantly lower among those with prenatal ZDV exposure, compared with those with prenatal non-ZDV ARV exposure, although this finding must be interpreted with caution as discussed below. The risk for LBW was significantly higher among infants with in utero exposure to ZDV-containing regimens. No significant difference was observed between the two groups in risk of stillbirths and premature births.

Strength and limitations

An advantage of this study is its large sample size. However, likely confounders such as disease status and severity, which are not completely ascertained by the APR, and unmeasured confounders, particularly non ARV-drug factors like concomitant drugs, illicit drug use, alcohol and tobacco use, are not measured and controlled for in the analyses. Unmeasured confounders may also include health-related behaviours such as poor nutrition, which can influence maternal body mass index. Adverse birth outcomes other than birth defects are not the primary goal of the APR or the reporting provider. This may have resulted in possible underestimation of the birth outcomes analysed in this study. Since LBW and VLBW are also outside the scope of the APR, it was not possible to assess the morbidity associated with these two variables. Very early pregnancy losses are difficult to capture under the voluntary reporting nature of the registry, which leads to underestimation of the losses. Reporting bias due to cultural or legal constraints in countries where induced abortions are illegal is also a possibility in this study and can result in the misclassification of these types of abortions as spontaneous abortions. There is a lack of information regarding the timing of the initiation of antiretroviral therapy, as well as indication for antiretroviral therapy; however, information comparing exposure for the first time during the first trimester versus in the second/third trimesters is available and has been assessed in this analysis. Future research assessing the risk associated with prenatal exposure to ARVs could consider propensity scoring or use of instrumental variables, subject to availability of data, for more accurate estimates.

Table 3. Prevalence and relative risk of non-defect adverse pregnancy outcomes: ZDV versus non-ZDV ARV exposed, reported to the Antiretroviral Pregnancy Registry, prospective data through July 31, 2013

Birth outcomes	Regimens containing ZDV		Regimens excluding ZDV		Relative risk******* (95% CI)	*P*-value*******
	n (%)	Prevalence (%) (95% CI)	*n* (%)	Prevalence (%) (95% CI)		
Live births	12 278 (96.1)	–	1633 (85.8)	–	–	
Spontaneous Abortions*	171 (1.3)	1.34 (1.15, 1.55)	145 (7.6)	7.62 (6.46, 8.90)	0.18 (0.14, 0.22)	<0.0001
Stillbirths*	147 (1.2)	1.15 (0.97, 1.35)	29 (1.5)	1.52 (1.02, 2.18)	0.76 (0.51, 1.12)	0.17
Induced abortions*	184 (1.4)	1.44 (1.24, 1.66)	97 (5.1)	5.09 (4.15, 6.18)	0.28 (0.22, 0.36)	<0.0001
Total adverse birth outcomes**	502 (3.9)	–	271 (14.2)	–	–	–
Birth weight***	*n***** = 11044	–	*n***** = 1508	–	–	–
<2500 g	1811 (16.4)	16.40 (15.71, 17.10)	212 (14.1)	14.06 (12.34, 15.92)	1.17 (1.02, 1.33)	0.02
<1500 g	232 (2.1)	–	28 (1.9)	–	–	–
Unknown	881	–	89	–	–	–
Gestational Age****	*n****** = 11907	–	*n****** = 1587	–	–	–
<37 weeks	1467 (12.3)	12.32 (11.74, 12.92)	196 (12.4)	12.35 (10.77, 14.07)	1.00 (0.87, 1.15)	0.97
<32 weeks	257 (2.2)	–	34 (2.1)	–	–	–
Unknown	18	–	10	–	–	–

Percentages are based on the total outcomes in the respective analysis.
***Prevalence is based on the number of pregnancies. 95% CI is based on the exact binomial (Clopper-Pearson) method.
****Total adverse birth outcomes include still births, spontaneous or induced abortions, and exclude birth defects in live births
*****Prevalence is based on the number of live singleton births – excludes cases with defects and cases with unknown birth weight. 95% CI is based on the exact binomial (Clopper-Pearson) method.
******Prevalence is based on the number of live singleton births – excludes cases with defects and cases with unknown gestational age. 95% CI is based on the exact binomial (Clopper-Pearson) method.
*******Excludes cases with unknown birth weight
********Excludes cases with unknown gestational age.
*********Relative Risk – Regimens Containing ZDV versus Regimens Excluding ZDV. The 95% CI is based on the normal asymptotic method. *P*-value is based on the Fisher's Exact test.

Interpretation

In a review of published literature, studies that have examined the association between ZDV use in pregnancy and adverse outcomes have typically looked at preterm delivery as the outcome of interest.[13–15] These studies also compared the use of highly active antiretroviral therapy (HAART) during pregnancy and ZDV monotherapy. As most studies defined HAART based upon the presence of either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor, and did not specify the components of the nucleoside reverse transcriptase inhibitor backbone of the regimen, it was often not possible to determine the proportion of women receiving ZDV for any particular analysis. In this study, a wider range of adverse birth outcomes other than birth defects are examined, as well as prematurity, and ZDV-containing regimens are compared with non-ZDV ARV regimens to better isolate the influence of ZDV use during pregnancy on birth outcomes, so contributing to the literature.

Data on the influence of ZDV use during pregnancy on birth outcomes in published literature are conflicting. In some studies that have compared HAART use to ZDV monotherapy, an increased risk of preterm delivery among HAART users has been reported.[14,15] However, Tuomala et al.[16] reported on a combined analysis of five prospective cohorts and two randomised controlled trials, and did not find an effect of HAART on preterm delivery, in comparison to ZDV monotherapy (odds ratio 1.08, 95% CI 0.71–1.62). In this study, no significant difference in risk of preterm delivery was observed between ZDV-containing regimens and non-ZDV ARV regimens. Among studies that examined LBW as an outcome, two African studies[14,17] found an increased risk of LBW with HAART exposure (either before pregnancy or antenatal exposure), whereas three others[16,18,19] (two in the USA, one in Latin America and the Caribbean) found no effect. Data from this study indicated an increased risk for LBW among pregnancy outcomes with exposure to ZDV-containing regimens, compared with non-ZDV ARV regimens.

In studies that have examined the relationship between HAART or ZDV monotherapy use during pregnancy, HAART was associated with a higher risk of stillbirth.[14,20,21] Tuomala et al. reported a decreased risk of stillbirth and prematurity associated with use of ZDV-containing antiretroviral therapy in late pregnancy compared with non-ZDV ARV therapy (odds ratio 0.06, 95% CI 0.02–0.18).[21] In contrast, this study observed no significant difference in risk of stillbirths associated with ZDV-containing regimens compared with non-ZDV ARV regimens. We also found that the risks for spontaneous abortions and induced abortions were lower for ZDV-containing regimens compared with non-ZDV ARV regimens. However, non-ZDV regimens in this study were associated with older maternal age, a variable highly correlated with pregnancy loss rates, and this may explain some of the difference noted here. Due to limitations in the data collection process already described, although a statistically significant lower risk for pregnancy loss was observed for ZDV-containing regimens, it cannot be concluded that this regimen is protective, but rather that compared to non-ZDV ARV regimens, ZDV-containing regimens do not increase the risk for spontaneous and induced abortions. Data on these two outcomes in published literature are limited and further research is recommended.

Conclusion

Data from this study show that the prevalence of adverse birth outcomes other than birth defects is similar among pregnant HIV-positive women prenatally exposed to ZDV compared with those prenatally exposed to non-ZDV ARV regimens. The risks for spontaneous abortions and induced abortions were no different for exposure to ZDV-containing regimens compared with non-ZDV ARV regimens. For prematurity and stillbirths, there was no significant difference in risk between the two regimens. However, the risk of LBW was significantly higher among ZDV-containing regimens compared with non-ZDV ARV regimens. Pregnant women must be carefully evaluated, and ZDV-containing therapy prescribed only if the potential benefits to the woman outweigh the potential risks to the fetus.

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Contribution to authorship

VV was involved in the study design, protocol writing, data interpretation and manuscript writing and review; NK was involved in protocol writing, data analysis, data interpretation and manuscript writing; JA and CG were involved in study design, data analysis, data interpretation and manuscript review; HT was involved in study design, data interpretation and manuscript review.

Details of ethics approval

Institutional review board approval was obtained from the Western IRB for the protocol to establish and maintain the APR, and all study procedures were conducted in accordance with the ethical standards of the Western IRB and with the Helsinki Declaration of 1975, as revised in 2000. The APR was granted a waiver from obtaining patient informed consent. To preserve the patient's confidentiality, registration is conducted anonymously through the healthcare provider rather than the patient. Registry data are collected with no patient identifiers, and follow up is managed through the use of APR-assigned identification numbers maintained by the healthcare providers.

Funding

The APR is funded by the 24 manufacturers of the 38 antiretroviral medications monitored by the APR. This study received additional funding from ViiV Healthcare.

Other disclosures: Clinical Trial Registration: ClinicalTrials.gov. NCT01137981. Preliminary analyses of these data were presented in 2013: Vani Vannappagari, Jessica Albano, Hugh Tilson, Conway Gee, Anisha Gandhi, Nana Koram, Catherine Ryan. 'Zidovudine Exposure during Pregnancy and Birth Outcomes: Data from The Antiretroviral Pregnancy Registry' (Poster). 29th ICPE (International Conference on PharmacoEpidemiology); August 25-28, 2013; Montreal, Canada.

Acknowledgements

The authors acknowledge the efforts of all clinicians submitting cases to the APR; the APR Steering Committee in reviewing this manuscript; Taylor Cook, INC Research, LLC Coordinating Center staff; Catherine Ryan, Project Manager at INC Research at the time the work was done; and Anisha Gandhi, research assistant at GlaxoSmithKline at the time the work was done. ■

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