Antiretroviral Safety in Pregnancy: An Updated Analysis of Prospective Reports from the Antiretroviral Pregnancy Registry

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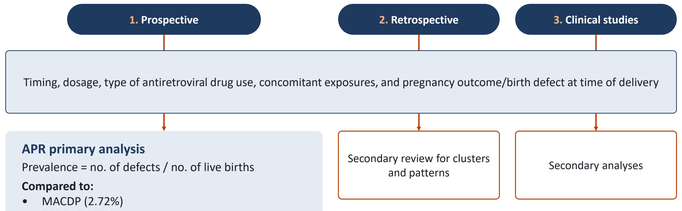
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Introduction

Antiretroviral therapy (ART) has dramatically reduced perinatal HIV transmission, yet ongoing pharmacovigilance remains essential to ensure the safety of *in utero* drug exposure. The Antiretroviral Pregnancy Registry (APR), established in 1989, prospectively monitors prenatal antiretroviral (ARV) exposures to detect early signals of teratogenicity.

Methods

Prospective exposure-registration cohort with data from 73 countries; prospective cases (registered before the outcome is known) analyzed through July 31, 2025.



Results

28,097
prospectively reported pregnancies

24,750
reports with outcomes

73
contributing countries

36 yrs
of surveillance (1989–2025)

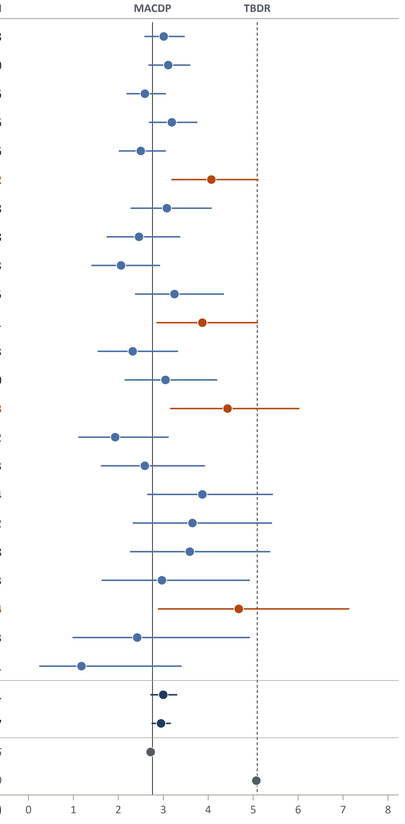
BIRTH DEFECT PREVALENCE BY EXPOSURE

1st trimester	**3.0%** 95% CI 2.7–3.3
2nd/3rd trimester	**2.9%** 95% CI 2.55-3.21
Prevalence ratio, 1st vs. 2nd/3rd	**1.05** 95% CI 0.9–1.22

Figure 1. Prevalence of birth defects, 1st-trimester exposures

APR data, 1 January 1989 – 31 July 2025, compared with population-based surveillance

ARV / comparator	Defects / live births	Prev. %	95% CI
Lamivudine	175/5820	3.01	2.58–3.48
Emtricitabine	174/5597	3.11	2.67–3.60
Tenofovir DF	135/5205	2.59	2.18–3.06
Zidovudine	136/4262	3.19	2.68–3.76
Ritonavir	90/3606	2.50	2.01–3.06
Tenofovir alafenamide	**69/1696**	**4.07**	**3.18–5.12**
Abacavir	47/1525	3.08	2.27–4.08
Atazanavir	37/1502	2.46	1.74–3.38
Lopinavir	30/1454	2.06	1.40–2.93
Dolutegravir	44/1352	3.25	2.37–4.35
Nelfinavir	**47/1216**	**3.87**	**2.85–5.11**
Efavirenz	28/1208	2.32	1.54–3.33
Nevirapine	36/1180	3.05	2.14–4.20
Bictegravir	**38/858**	**4.43**	**3.15–6.03**
Rilpivirine	16/827	1.93	1.11–3.12
Stavudine	21/811	2.59	1.61–3.93
Darunavir	31/802	3.87	2.64–5.44
Cobicistat	23/631	3.65	2.32–5.42
Raltegravir	22/613	3.59	2.26–5.38
Elvitegravir	14/472	2.97	1.63–4.93
Didanosine	**20/427**	**4.68**	**2.88–7.14**
Indinavir	7/289	2.42	0.98–4.93
Telbivudine	3/254	1.18	0.24–3.41
First trimester APR	**393/13093**	**3.00**	**2.71–3.31**
Any trimester APR	**691/23423**	**2.95**	**2.74–3.17**
MACDP		*2.72*	*2.68–2.76*
TBDR		*5.07*	*5.06–5.09*



● Lower 95% CI above MACDP upper limit

Solid line: MACDP upper 95% CI (2.76%) · Dashed line: TBDR upper 95% CI (5.09%) · Clopper–Pearson exact binomial CIs

Table 1. Drug-specific risk assessment

Powered to detect a ≥2-fold increase in overall birth defects
BIC, COBI, DRV, d4T, ddI, EVG, IDV, RAL, RPV
Outcome: no such increases detected

Powered to detect a ≥1.5-fold increase in overall birth defects and a 2-fold increase in cardiovascular and genitourinary defects
3TC, ABC, ATV, EFV, FTC, LPV/r, NFV, NVP, RTV, TDF, ZDV, TAF, DTG
Outcome: no such increases detected

Insufficient exposures reported to assess risk
CAB, DOR, ETR, FTR, LEN, T-20
Outcome: not available

Conclusions

- No significant difference in overall birth defect prevalence versus MACDP (2.72%; 95% CI 2.68–2.76) or TBDR (5.07%; 95% CI 5.06–5.09).
- Four ARVs (ddI, NFV, TAF, BIC) show higher 1st-trimester prevalence than MACDP but not TBDR; all cases continue to be monitored.
- Updated interim data spanning 36 years of surveillance continue to support the safety of ARVs in pregnancy.

"The Registry finds no apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause; however, potential limitations of registries should be recognized."
— APR Advisory Committee

Abbreviations: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FTC = emtricitabine; FTR = fostemsavir; IDV = indinavir; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NVP = nevirapine; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine; MACDP = Metropolitan Atlanta Congenital Defects Program; TBDR = Texas Birth Defects Registry. **References:** [References]