Background

In 2008 DHHS:
• 1st line: AZT, 3TC, LPV/r and NVP (CD4≤200)
• ABC, nelfinavir, saquinavir/r, or indinavir/r listed as alternative agents
• TDF, FTC, ATV/r, DRV/r, RAL listed as "insufficient data to recommend"; EFV not recommended

In 2017 DHHS:
• 1st line: ABC/3TC or TDF/FTC are preferred backbones; ATV/r, DRV/r, or RAL are preferred 3rd agents
• ZDV/3TC, LPV/r, EFV, RPV listed as alternative agents
• DTG, EVG, TAF, COBI listed as "insufficient data"

Perinatal ARV recommendations are generally not informed by clinical trials, but most often from cumulative clinical experience and passive reporting of suspected ARV-related toxicities to mom or infant via:
• ARV pregnancy registries
• Pharmaceutical post-marketing surveillance

The recently published PROMISE trial (Fowler et al, NEJM 2016), a RCT of ABC/3TC vs. 3TC+NVP, included 2,015 eligible women randomized to treatment arms: ABC/3TC or 3TC+NVP. The primary outcome was preterm delivery in women exposed to tenofovir during pregnancy. The null hypothesis was a 1% reduction of preterm delivery in the ABC/3TC group (relative to the 3TC+NVP group). Tenofovir was given as tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) or lamivudine (3TC) + nevirapine (NVP). The null hypothesis was not rejected with p-value of 0.298.

Methods

Data from the CPHSP were reviewed for the period 1997–2015.

Data evaluated included:
• Maternal race/ethnicity and HIV acquisition risk category
• Province of birth
• Antiretroviral choice
• Preterm (<37wks) delivery

Research Question

What is the rate of preterm delivery among women treated with tenofovir-based ART versus other ART combinations in Canada in the CPHSP?

Results

Among 2816 cART-treated mother-infant pairs (MIPs) from 1997-2015
• 1732 used zidovudine (61.5%)
• 575 used abacavir (20.4%)
• 501 used tenofovir (15.1%)

Tenofovir use in pregnancy increased from 0.77% in 2004 to 54.1% in 2015, meanwhile, zidovudine use decreased from 100% in 1997 to 14.7% in 2015

Multivariate analysis

• Overall preterm delivery rate was 16% with a higher rate in tenofovir treated mothers (19.4% vs. 15.2%, p=0.022).
• No differences were found between mothers treated vs not treated with: abacavir, zidovudine, protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) or integrase inhibitors (INSTIs).
• No difference in preterm delivery rate among women exposed to tenofovir with versus without PI, NNRTI, or INSTI.

Discussion

We found an increased rate of preterm delivery (16%) amongst HIV+ women in Canada relative to general population:
• Preterm delivery rate in singleton pregnancies in Canada 2000–2013 = 6.2%.
• IDU and elevated VL were consistently associated with preterm delivery in MV analyses, but TDF (and NVP) was no longer associated when combinations of multiple NRTIs excluded from analysis.
• ARV components may play a role or may be confounded by other unmeasured predictors:
  • Maternal age & comorbidities (DM, infection)
  • Smoking, nutrition, quality of care
  • Combinations of the 3 main NRTIs are suggestive of:
    • 3TC allergy/intolerance (unlikely)
    • ARV resistance (more likely)

The limitations of this study are similar to those of most observational/surveillance studies:
• Unclear role of missing data
• Unmeasured covariates & confounders
• Non-uniformity of care across geography and over time

Conclusions

• CPHSP data re-confirms an increased prevalence of preterm delivery in women living with HIV (2-3x general population in Canada).
• While higher rates of preterm delivery were seen in TDF-treated women, TDF itself does not seem likely to be causally linked.