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HIV, HAART and preterm delivery

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Introduction - PMTCT

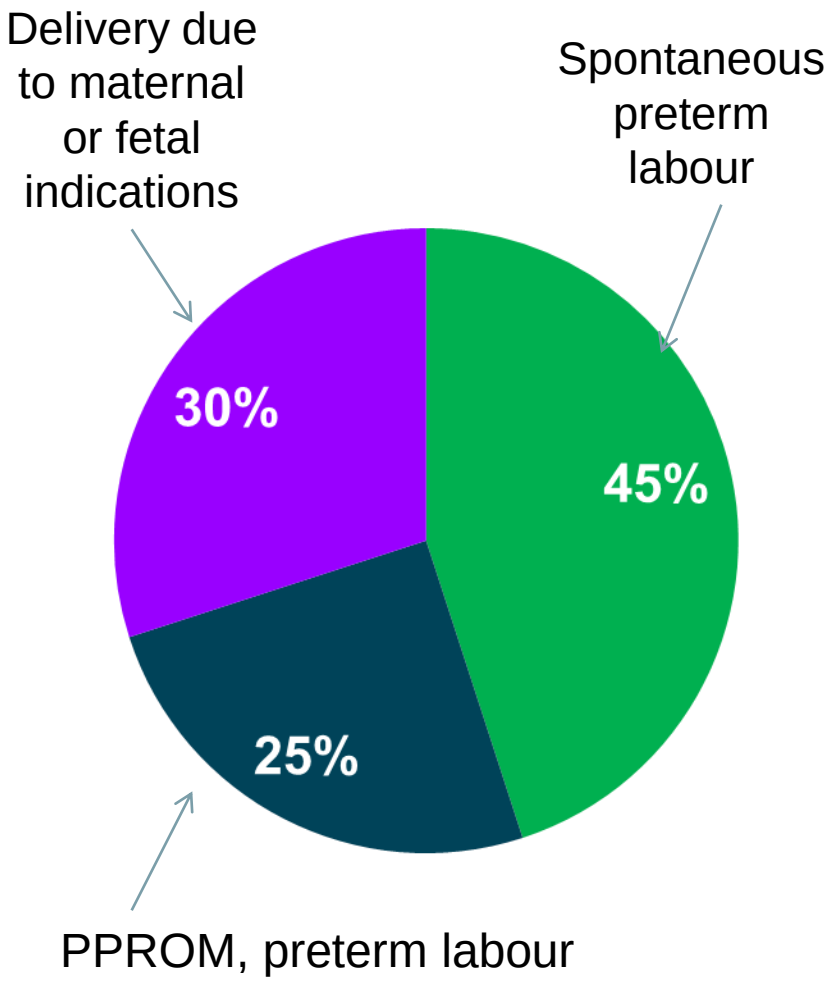
- Tremendous success in PMTCT worldwide
- UNAIDS goal: “elimination” of MTCT
  - Reduction in MTCT rates to below 5% worldwide by 2015
- MTCT rates ~1% in Western Europe
- >95% diagnosed pregnant women in UK receive cART

Introduction – PTD & HIV

- Concerns regarding PTD in women with HIV were first raised more than 20 years ago
  - Influence of HIV and immunosuppression on pregnancy outcomes
- First report to suggest link between PTD and combination ART came from Switzerland in 1998 (case series)

Lorenzi et al AIDS 1998

Preterm birth: causes



From: Goldenberg et al Lancet 2008

- Events leading to preterm birth are incompletely understood
- Multiple pathways include inflammation / infection, maternal / fetal stress, abnormal uterine distension, bleeding, others
- Risk factors include:

  socio-economic factors, maternal smoking, illicit drug use, maternal age, multiple gestations, maternal BMI, previous PTD, intrauterine infection, bacterial vaginosis

Increased risk of PTD associated with cART

- Subsequently, a number of other studies (mainly in Europe, but some from the US and elsewhere) have reported similar findings
  - Associations of between 1.5 to 3.5 fold increased risk (with different ART reference groups)
  - Adjusted for a range of (but not all) confounders
  - Some studies only found association with PI-based HAART

European Collaborative Study (ECS) and Swiss MoCHiV 2000; ECS 2004; Cotter et al, 2006 (USA); Boer et al, 2007 (Netherlands); Schulte et al, 2007 (USA); Townsend et al, 2007 (UK and Ireland); Ravizza et al 2007 (Italy); Grosch-Wörner et al, 2008 (Germany/Austria)

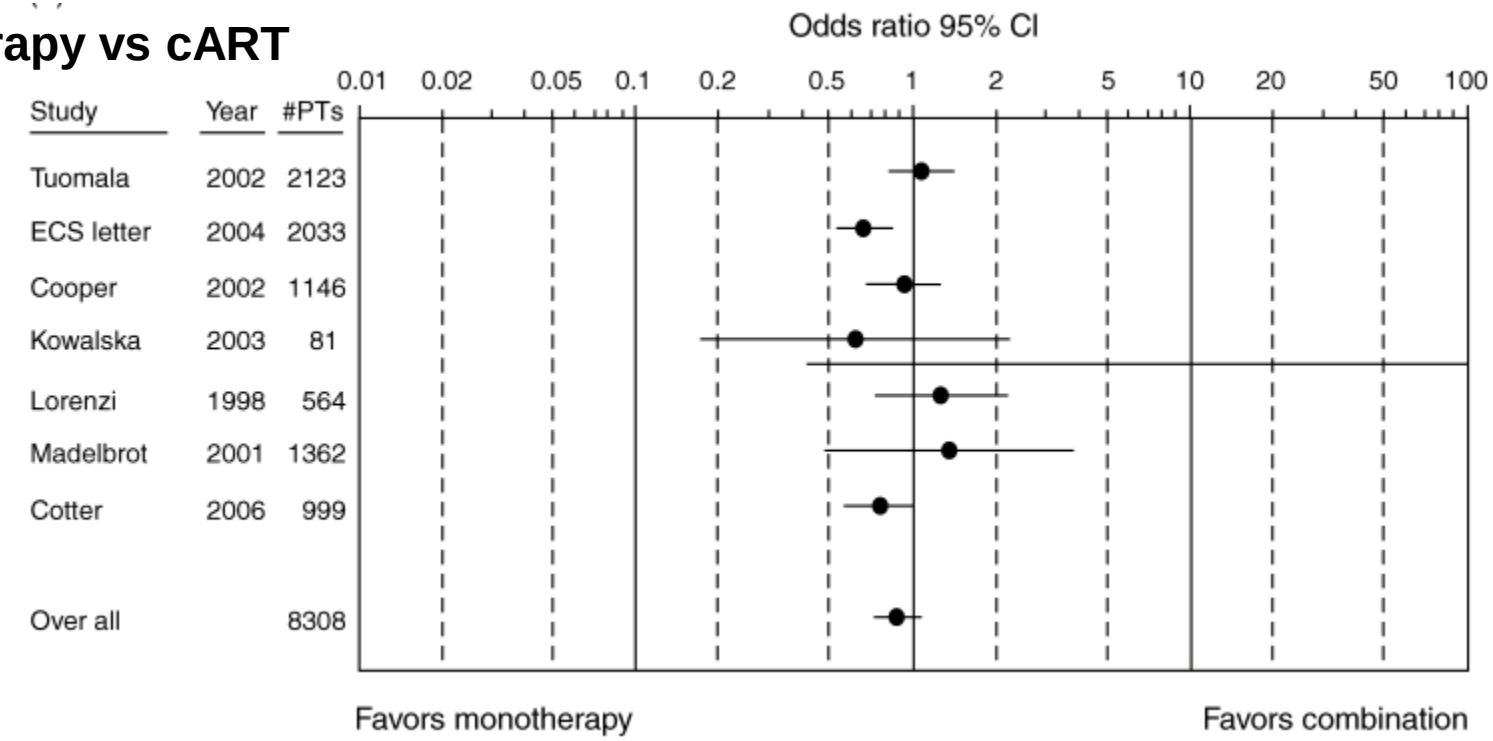
No association between cART and PTD

- Studies not finding an association:
  - Tuomala et al, 2002 (USA)
  - Tuomala et al 2005 (USA)
  - Szyld et al, 2006 (Latin America/Caribbean)
  - Patel et al, 2010 (USA)

Meta-analysis, Kourtis et al AIDS 2007

- Included studies published up to 2006
- ART not associated with increased risk of PTD overall: OR 1.01 (95% CI 0.8, 1.3)

Monotherapy vs cART



Sub-group analyses, Kourtis et al 2007

- Despite the overall finding, sub-group analyses did reveal some significant positive associations
- PI versus non-PI HAART was associated with increased risk of PTD
  - OR 1.35 (95% CI 1.1, 1.7)
- HAART started pre-pregnancy / 1st trimester versus later in pregnancy:
  - OR 1.7 (95% CI 1.1, 2.7)

Why are findings inconsistent?

- Possible explanations include differences in:
  - Case ascertainment / outcome misclassification
  - Choice of ART reference group
  - Unmeasured confounding (prior preterm delivery, smoking, etc)
  - Bias in indication for treatment
  - Underlying population differences
  - Statistical power
- Issues of populations and methods are critical to the interpretation of these diverse findings

ART & PTD: a pooled analysis of data from the US and Europe

Townsend et al 2010 BJOG

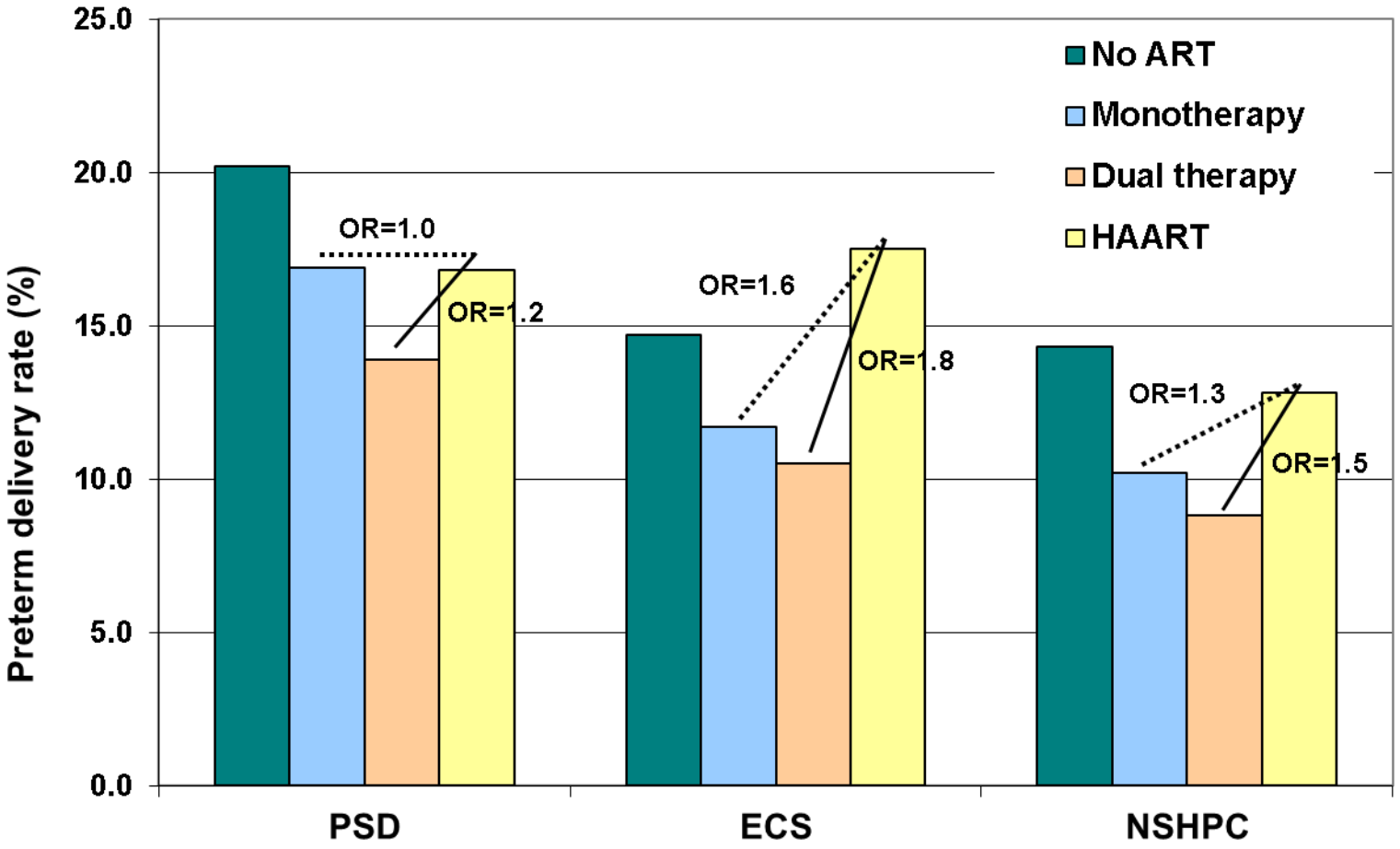
- Using three studies with **different methodologies** and with **variation in baseline population characteristics** to shed light on reasons for the conflicting literature on PTD and cART
- Investigated:
  - Association between cART and PTD within each of the three studies
  - Whether appropriate to pool individual patient data
  - Estimate of association between cART and PTD in pooled dataset

Pooled analysis: participating studies

- Pediatric Spectrum of HIV Disease project (PSD)
  - Medical record-based cohort (1990-2004) in US; 8667 women
- European Collaborative Study (ECS)
  - Consented cohort study (1990-2006); 9 countries; 4253 women
- National Study of HIV in Pregnancy and Childhood (NSHPC)
  - National population-based surveillance study (1990-2006); 6665 women

There were considerable differences between studies in maternal characteristics and use of ART, despite very similar time-scales

Pooled Analysis: PTD rates by ART group and study



Lines indicate comparisons between treatment groups (HAART vs mono or HAART vs dual); OR=odds ratio

Association between ART and PTD, comparing cART with dual therapy

- Significant increase in PTD risk in women on cART vs dual therapy in adjusted analyses*
  - aOR **1.50** (95% CI 1.20-1.82)
- PTD also positively associated with
  - Black versus white ethnicity aOR 1.48 (1.20-1.82)
  - IDU versus non-IDU aOR 1.93 (1.59-2.33)
  - Maternal symptoms/CD4<200 vs asymptomatic / CD4>200 aOR 1.82 (1.54-2.16)

*after adjusting for study, ethnic group, region of birth, IDU, year and clinical status/CD4 count

What is the role of PIs?

- Several studies have shown associations specifically with PI-based cART and PTD
- New findings from a trial in Botswana and a MTCT cohort study in France have added to the evidence base

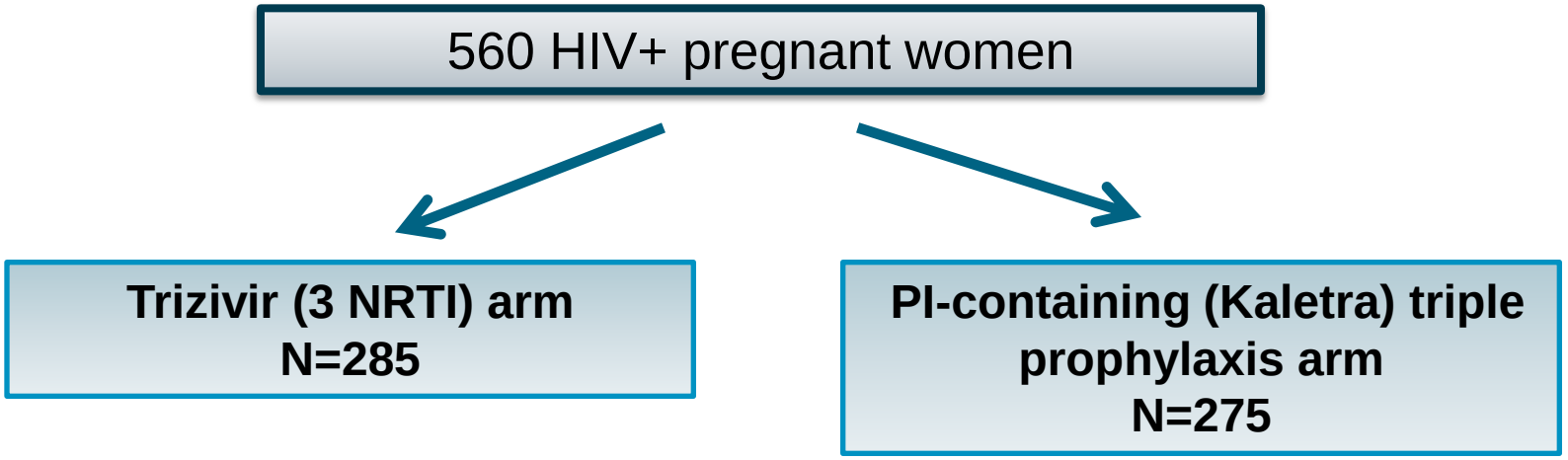
PTD and PI-based cART: Mma Bana study

- Mma Bana randomized clinical trial (Shapiro et al NEJM 2010)
  - Botswana
  - Comparing PI-containing triple antiretroviral prophylaxis with triple NRTI prophylaxis in PMTCT
  - Overall MTCT rate was 1.1%

- Secondary analysis to investigate risk factors for PTD
  - All women had CD4 counts ≥200 cells/mm^3

Powis et al, JID 2011

Mma Bana trial: methods



Secondary analysis: PTD*

N=263

N=267

Exclusions: LTFU before delivery, stillbirth, twins, preterm emergency CS

- ART from 26-34 weeks of pregnancy and continued postpartum whilst breastfeeding (max 6 mths)

Mma Bana analysis: results

- Women in PI-arm had **significantly higher PTD rate** than women in 3 NRTI arm at **21.4%** versus **11.8%**
- Maternal CD4 count, viral load, education, age, gestational age at starting ART were not associated with risk of PTD
- **Type of ART** and **maternal income** were significantly associated with PTD risk in unadjusted analyses:
  - PI-containing regimen associated with **2-fold increased risk** (OR 2.03, 95%CI 1.26-3.27) vs NRTI regimen
  - Women with any income had significantly lower risk vs women with none

Mma Bana: results

- In analysis adjusting for maternal income, **aOR for PI-based ART = 2.02** (95%CI 1.25-3.27)
- Also evaluated median change in BMI one month after ART initiation:
  - 0.5 kg/m^2 in NRTI arm and 0.3 kg/m^2 in PI arm (p<0.001)
- No significant association between BMI change and risk of PTD
  - OR=0.81 (95% CI 0.53-1.24) for each 1kg/m^2 increase
- No significant difference between rate of very PTD (<32 weeks) between arms (3.3% for PI-arm, 1.8% NRTI-arm)
  - NB trial design (enrolment in 3rd trimester) limited ability to evaluate vPTD

Mma Bana findings: interpretation

- First time an association between PI-based ART and PTD reported from Africa
- Randomisation allows investigation of the effect of PI but trial was not designed to answer questions re PTD
- Finding of reduced weight gain associated with PI use is novel, but this was not significantly associated with PTD
- Magnitude of increased risk associated with PI-regimen (2-fold) is unexpected
  - High background rate of PTD in Botswana
  - Limited power of the study
- Should these results be seen more as a reduced risk in the NRTI group rather than an increased risk in the PI group?

See Kourtis, JID 2011 editorial

Role of ritonavir-boosting?

- Analysis from the French Perinatal Cohort (EPF)
- Explored factors associated with PTD in a restricted analysis of pregnant women with HIV
  - Starting PI-based cART antenatally
  - Delivering between 2005 and 2009
  - N=1253; 1066 on boosted-PI (81% on LPV/rtv) and 187 on non-boosted PI (92% on nelfinavir)
- Addressing some of the limitations of earlier studies
  - Reduced the potential for indication bias
  - Adjusted for confounding factors such as maternal smoking and BMI

Sibiude et al *Clin Inf Dis* 2012

Results from French Perinatal Study

- PTD rate was 14.4% in boosted and 9.1% in non-boosted PI groups
- Significantly increased probability of PTD associated with boosted versus non-boosted PI in adjusted analysis
  - adjusted hazard ratio of 2.03 (95% CI 1.06, 3.89)
- Maternal CDC stage C disease was associated with a two-fold increased risk of PTD

Sibiude et al *Clin Inf Dis* 2012

Interpretation of French results

- Some analysis of metabolic, hepatic and vascular complications was attempted (but small Ns) to explore potential mechanisms
- Homogeneity of treatment within groups
- Are the observed differences in PTD influenced by the ritonavir booster, the main PI or the overall effectiveness of the regimen?

Spontaneous and iatrogenic preterm delivery

- 70% PTD are spontaneous and 30% “iatrogenic” (ie for maternal / fetal indications)
- Underlying mechanisms differ
- In a Spanish study (n=517), HAART started from 20 weeks was associated with iatrogenic PTD (aOR 6.2), but not with spontaneous PTD (adjustment included smoking, prior PTD, age, CD4 count, ethnicity, education)
- In French cohort, the positive association between PTD risk and boosted PI-regimens was weaker for spontaneous than for iatrogenic PTD

(Lopez et al AIDS 2012, Sibiude et al CID 2012)

Mechanisms

Ritonavir toxicity?

- Ritonavir is associated with metabolic changes
- It is known to interfere with adrenal enzymes
- French Perinatal Study hypothesized that an effect of ritonavir on the maternal/fetal adrenal system might mediate increased PTD risk by increasing rates of maternal complications

Mechanisms

Immunological?

- Cytokine environment in pregnancy
- Th1 to Th2 switch is a feature of normal pregnancy
- In HIV infection there is a similar Th1 to Th2 switch that is reversed with use of HAART
- Fiore et al (J Reprod Imm 2006)
  - Significant increase in PTD risk associated with increases in IL-2 (a Th1 cytokine)
  - Reduced IL-10 (a Th2 cytokine) concentrations in treated vs untreated women

Immune mechanisms?

- Research at St Mary's
- HIV positive pregnant women had higher mean concentrations of Th1, Th17 and inhibitory IL-10 cytokines at 20 weeks gestation than negative controls
- Among HIV-positive pregnant women
  - Those on cART (with PI or NNRTI) had significantly lower IL-10 concentrations than those on NRTIs only
  - Those having a PTD had significantly lower IL-10 concentrations than women who delivered at term

(Short et al CROI 2012)

- Strong association (aOR 5.03) between starting PI-based cART in pregnancy and PTD (Martin & Taylor, JID 2007)
  - Is Th1 to Th2 shift more dramatic in this situation?

What are the clinical implications?

- Risk of any treatment / intervention must be considered in relation to the corresponding benefits
- These are indisputable regarding use of antenatal cART with respect to PMTCT and treatment of maternal disease
- Based on UK data, it is estimated that for every 100 transmissions prevented through use of cART (vs mono), 63 additional preterm deliveries would occur
  - 63% of these expected to occur at >32 weeks gestation

(Townsend et al 2010 Antivir Ther)

Preterm infants

- Preterm births account for 75% of perinatal mortality
- Preterm infants are at risk of death, LBW, respiratory problems, life-threatening infections and long-term disability
- Most preterm infants (~80%) of women on cART in studies to date have been born at 32-36 weeks gestation
- No study has addressed the issue of long-term sequelae in preterm infants in the context of maternal HIV and cART exposure

Resource-limited settings

- Survival chances of a preterm infant are very much lower
- Implications of an increased risk of PTD with cART is thus more serious in these settings

In Mma Bana study

- 9% of preterm infants had ≥1 severe or life-threatening RTI episode in first 6 months of life vs 2% term infants (p=0.003)
- Preterm infants had 5-fold increased risk of death in first 6 months of life than term infants

Resource-limited settings

- Around 1.5 million HIV-positive women delivered in low/middle income countries in 2010
- WHO 2010 guidelines for antenatal ARVs for PMTCT:
  - Option A - ZDVm (delivery sdNVP, ZDV&3TC postnatal "tail")
  - Option B - **triple ARV prophylaxis**
- In 2011, 61% of eligible mother-infant pairs received effective prophylaxis to prevent infant infections during pregnancy / delivery

Conclusions

- Mechanisms remain elusive
- PTD has multifactorial causes, which remain incompletely understood in general
- Recent studies have addressed some of the limitations of older studies, but remain imperfect
- Observational data need careful interpretation
- We need further research and evaluation, particularly in African settings
  - PTD is one of primary outcomes in PROMISE trial

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