A new piece in the puzzle of antiretroviral therapy in pregnancy and preterm delivery risk

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Mother-to-child transmission (MTCT) is the most significant source of HIV infection in children worldwide and recent years have seen some tremendous successes with respect to its prevention. UNAIDS and partners have called for the "virtual elimination" of MTCT, that is, the reduction of the number of new paediatric HIV infections by 90% between 2009 and 2015 and reduction of MTCT rates to below 5% worldwide [1]. In resource-rich settings, high antenatal coverage, good access to and uptake of interventions for prevention of MTCT (PMTCT) and widespread use of combination antiretroviral therapy (ART) have contributed to the very low MTCT rates now reported (<1-2%) [2-5].

Concerns about preterm delivery in HIV-positive women were first raised more than 20 years ago, with the initial concerns relating to the influence of HIV and its associated immunosuppression on pregnancy outcomes. A positive association between use of combination ART and preterm delivery was first reported in Europe in 2000 [6]. Subsequently, a number of other studies reporting significant associations of 1.5 to 3.5 fold increased risk between antenatal combination ART and preterm delivery have added to the published literature on ART and pregnancy outcomes [7-14]. These studies varied in their approach, for example with different ART reference groups used in the analyses, and in their ability to adjust for confounders; of note, some found the association to be limited to protease inhibitor (PI)-based combination ART. Last year, the first evidence from Africa of an association between preterm delivery and type of combination ART was published: a secondary

analysis from the Mma Bana trial in Botswana demonstrated a higher preterm delivery rate in the group of pregnant women randomized to PI-containing triple antiretroviral regimens compared with those in the triple nucleoside reverse transcriptase inhibitor arm, with an odds ratio (OR) of 2.03 (95% confidence interval (CI) 1.26, 3.27) [15].

However, other studies, predominantly carried out in the US and South America, have not found an association between preterm delivery and combination ART use in pregnancy [16-19]. Kourtis and colleagues performed a meta-analysis of studies carried out up to 2006, reporting no association between ART and increased risk of preterm delivery overall (OR 1.01 (95% CI 0.8, 1.3); however, sub-group analyses showed an OR of 1.35 (95% CI 1.1, 1.7) for PI-containing versus non-PI-containing ART and an OR of 1.7 (95% CI 1.1, 2.7) for ART started pre-pregnancy or in the first trimester versus later in pregnancy [20]. Possible explanations for the conflicting evidence base include differences in case ascertainment, choice of ART reference group, unmeasured confounding, bias in indication for treatment, statistical power and underlying population differences.

Preterm delivery rates vary by world region, Europe having the lowest rate at an estimated 6% and Africa the highest at around 12% [21]. Events leading to preterm birth in the general population remain incompletely understood and multiple pathways have been implicated including inflammation and/or infection, maternal and/or fetal stress, abnormal uterine distension and bleeding. There are a number of different factors associated with preterm delivery risk, including socio-economic factors, ethnicity, maternal smoking, illicit drug use, maternal age, multiple gestation, maternal body mass index (BMI), previous preterm delivery, intrauterine infection and bacterial vaginosis. It is estimated that in the general population 40-45% of preterm births are due to spontaneous preterm labour, 30-35% to maternal or fetal indications and 25-30% to premature preterm rupture of membranes (PPROM) or preterm labour [22].

In this issue of the *Clinical Infectious Diseases*, a study by Jeanne Sibiude and colleagues uses data from the French Perinatal Cohort (EPF) to explore factors associated with preterm delivery in HIV-

positive pregnant women starting PI-based ART antenatally and delivering between 2005 and 2009; they also report on preterm delivery rates in the EPF between 1990 and 2009, with a significant increase over calendar time [23]. This study, from a large and well-characterised national cohort, advances our understanding of the complex relationship between ART use in pregnancy and preterm delivery by addressing some of the limitations of earlier studies. By restricting the analysis to women starting PI-based ART regimens in pregnancy, the authors have reduced the potential for indication bias. Unlike some earlier studies, the analyses adjusted for factors known to be associated with preterm delivery such as maternal smoking and BMI. It is the first time that ritonavir-boosted PIs have been compared with non-boosted PIs with respect to preterm delivery risk, and interestingly the results showed a significantly increased probability of preterm delivery associated with boosted versus non-boosted PI (adjusted hazard ratio of 2.03). The outcomes investigated included all preterm births as well as spontaneous preterm births (i.e. excluding "induced" preterm deliveries resulting from caesarean section due to maternal/fetal complications other than PPROM or induction of labour). The authors point out that the association between preterm delivery and boosted PI-regimens was weaker for spontaneous preterm delivery compared with induced preterm delivery, although the hazard ratio for the latter was not shown.

The authors have tried to shed some light on potential mechanisms by analysing data on metabolic, hepatic and vascular complications, and conclude that the increased rate of maternal complications has led to an increase in induced preterm deliveries in women receiving boosted PIs, although the evidence to support this is limited due to small numbers within groups. They also hypothesize that an effect of ritonavir on the maternal/fetal adrenal system might mediate increased risk of preterm delivery. It was interesting to note that other known risk factors for preterm delivery were not significant in this population (i.e. smoking and BMI) although Centers for Disease Control and Prevention stage C was independently associated with a two-fold increased risk, the latter underscoring the multifactorial aetiology of preterm delivery. Interpretation of observational data, as always, requires caution. Sibiude and colleagues rightly point out several limitations to their

study. In particular, the boosted and non-boosted PI groups were each predominated by a specific PI, respectively lopinavir/ritonavir (81% of the group) and nelfinavir (92%), limiting the potential to explore whether the observed differences in preterm delivery were influenced by the ritonavir booster, the main PI or the overall effectiveness of the regimen.

As with previous studies indicating an association between combination ART and preterm delivery, the question of whether there might be clinical management implications is important, particularly in the context of the indisputable benefits of antenatal combination ART with respect to PMTCT and treatment of maternal disease. It is well established that preterm infants are at increased risk of respiratory problems, life-threatening infections, long-term disability and death compared with those born at term. In the EPF study, the rate of severe preterm delivery (i.e. <32 weeks) was low at 2.7%, with this group representing 16% of all preterm births, although data were not provided on the distribution of gestational ages among the preterm deliveries as a whole, nor on the longer-term sequelae of preterm delivery in the infants. The survival chances of a preterm infant are very much higher in resource-rich countries than in resource-poor settings, where the capacity to care for preterm infants may be limited. The vast majority of pregnant HIV-positive women live in sub-Saharan Africa, and the question of a potential adverse impact of PI-containing ART on pregnancy outcomes needs to be considered in the context of the high background rates of preterm delivery, reflecting factors such as concurrent infections, malnutrition and limited antenatal care. In the 2010 WHO guidelines on use of antiretroviral drugs in pregnancy, one option for PMTCT prophylaxis for women not needing treatment for their own health involves use of a triple antiretroviral prophylaxis regimen, with lopinavir/ritonavir one of the recommended regimens. As use of antenatal triple drug prophylaxis increases in sub-Saharan Africa, it will be essential to monitor and evaluate adverse pregnancy outcomes, which may be more difficult to manage in this setting. Investigation of the relative risks and benefits of different strategies for PMTCT for women not requiring therapy in resource-limited countries should incorporate information on safety, remembering that the overall goal is not only to prevent vertical infections but also to save lives.

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