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Screening for STIs in Antenatal Care is Especially Important Among HIV-Infected Women

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The paper by Adachi et al entitled Chlamydia and Gonorrhea in HIV-infected Pregnant Women and Infant HIV Transmission is in this issue of *Sexually Transmitted Diseases*.¹ Its data are from the HIV Prevention Trials Network (HPTN) 040 protocol, a unique study that provided definitive clinical trials data to document the benefits of post-exposure prophylaxis with antiretroviral (ARV) medications for babies whose HIV-infected mothers had received no antiretroviral therapy (ART) either antenatally or intrapartum.² The HPTN 040 study was supported by the National Institutes of Health and was conducted from 2004-2010 in Brazil (68% of enrolled mothers-infants), South Africa (30%), and Argentina and the U.S. (<2.0%). The investigators wisely recognized the opportunities for discovery within this study and obtained data on sexually transmitted infections (STI) including *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG).¹

The parent HPTN 040 study was designed to see whether combinations of ARVs would work better than zidovudine (ZDV) alone for post-exposure prophylaxis in exposed infants whose HIV seropositive mothers had not received ARVs.² The 1684 infants enrolled were formula fed and were randomized into a ZDV-alone group (the global standard at that time), a 2-drug group (ZDV and nevirapine [NVP]), and a 3-drug group (ZDV, zalcitabine, and lamivudine). Intrapartum transmission occurred in 4.8% (95% confidence interval [CI], 3.2 to 7.1) of infants in the ZDV group vs. 2.2% (95% CI, 1.2 to 3.9; $P=0.046$) in the ZDV/NVP group, and 2.4% (95% CI, 1.4 to 4.3) in the 3-drug group. The total HIV transmission rate (antepartum and intrapartum) was 8.5%, highest in the ZDV only group ($P=0.03$ for the comparisons with the 2 and 3-drug groups). On multivariate analysis, ZDV monotherapy, higher maternal viral load, and maternal illicit drug use were associated significantly with MTCT. Hence, there may have been children in the HPTN 040 who remind us of the initial outcome thought to have been seen in so-called “Mississippi baby”, i.e., children infected with HIV who were prevented or even cured by early use of ARVs.^{3,4}

Syphilis data from HPTN 040 were published previously.⁵ Serological evidence of syphilis without documented treatment was noted in 10.3% (n=171) of 1664 HIV-infected pregnant women. Fully 1.4% of their 1684 infants (n=24) were dually HIV and syphilis infected. Compared with HIV-infected women, syphilis-HIV co-infected women were more likely to be non-white (adjusted odds ratio [AOR] = 2.5, 95% CI: 1.5-4.2), to have consumed alcohol during pregnancy (AOR = 1.5, 95% CI: 1.1-2.1), and to have had maternal to child HIV transmission (MTCT; AOR = 2.1, 95% CI: 1.3-3.4). Compared with HIV-infected or HIV-exposed infants, syphilis-HIV co-infected infants were significantly more likely to be born to mothers with venereal disease research laboratory (VDRL) titers 1:16 (AOR 3, 95% CI: 1.1-8.2) and higher viral loads (AOR 1.5, 95% CI: 1.1-1.9). Of 6 VDRL-positive newborns with symptomatic syphilis, 2 died and 2 more were HIV-infected.⁵ Complementing this analysis, Adachi et al have now provided multivariable assessment of potential contributions of CT and NG bacterial co-infections on the risk of MTCT from the same HPTN 040 study.¹

The rigor and size of the HPTN 040 STI analysis are impressive compared to most prior work published on this subject. Fully 81.5% of the 1684 women enrolled in the parent study had valid urine samples using the Xpert® CT/NG assay on the GeneXpert® platform, for a sample size of HIV-infected women with 1373 valid test results. Clinical conduct and laboratory/data quality control were superb, typical of studies conducted within the NIH HIV/AIDS networks (the HPTN and IMPAACT networks, in this case).^{6,7}

Prevalence was high, 18.1% for CT and 4.6% for NG based on the molecular platform diagnosis.¹ Along with the previously reported syphilis prevalence of 10.3%, one can speculate that over 20% of women in the HPTN 040 study had a treatable bacterial STI (the number of women co-infected with syphilis and either CT or NG or both was not specified).^{1,5} Both CT and NG were detected in 2.5% of women. The overall rate of HIV MTCT was 8.5%. The findings of critical public health importance are that the highest MTCT occurred among infants born to CT and NG infected mothers: mothers infected with only CT (10.7%) and with both CT and NG (14.3%) were more likely to have HIV infected offspring than STI uninfected women (8.1%; $p = 0.04$). Given that infants born to CT-infected mothers had almost a 1.5-fold increased risk for HIV infection ($P < 0.1$), the critical importance of screening and treatment for STIs during pregnancy among HIV-infected women is reinforced.

While the Mwanza study unambiguously illustrated that STI control can help reduce heterosexual transmission of HIV, the Rakai and Masaka and other studies have not demonstrated HIV transmission reduction with STI control. Therefore, the value of STI control for overall HIV prevention has been debated, as its benefits have not proven robust across studies and effectiveness may depend on specific HIV-epidemic conditions.⁸⁻¹² Whether control of reproductive tract infections would reduce MTCT was studied in the HPTN 024 trial, and no impact of prepartum antibiotic therapy was noted beyond the benefit of NVP prophylaxis.¹³⁻¹⁵ Despite the failure of the intervention, the epidemiologic evidence is strong that STI co-infection with maternal HIV is a risk factor for perinatal transmission, just as it is for sexual transmission.^{16,17}

Clinical trials purists might say that failure of an intervention to prevent MTCT (like HPTN 024) suggests that STI control in pregnancy is not important for disease prevention and control. The counterargument is that the epidemiological evidence is overwhelming and the biological rationale is powerful for STIs as a risk factor for HIV acquisition. Perhaps all can agree that STI control should be a part of an HIV program, though it may not be as high a priority as other HIV prevention strategies that have been more consistently successful in clinical trials. In the case of MTCT, the policy issue is even more straightforward. Since it is critically important to prevent congenital syphilis, its screening and treatment during pregnancy applies to all women, making the MTCT issue an academic one. However, the approach to ophthalmia neonatorum due to CT or NG is post-exposure prophylaxis with antibiotic ointment, neither of which will do any good for the mother or for prevention of MTCT and may have other disadvantages.¹⁸

In the case of high background prevalence rates seen in many antenatal venues,^{19,20} the findings of Adachi et al from HPTN 040 will add a component of critical evidence needed for decision analysis in favor of investments for antenatal CT and NG screening and treatment, alongside syphilis and HIV screening.^{1,5} With the need for integrated antenatal HIV and syphilis screening and control, decision analysis models are available focusing on antenatal syphilis control.²¹⁻³⁸ Other screening opportunities exist for group B streptococcus, hepatitis B virus, herpes simplex virus, and other diseases that should be brought within a multiplex-type screening technology, but are beyond the scope of this commentary.³⁹ Cost-effectiveness of chlamydia screening has been studied extensively,⁴⁰⁻⁴² but without the benefit of the HIV-impact data from Adachi et al.¹ New decision analysis models of the cost effectiveness of CT and NG screening in pregnancy are both possible and needed for public health policy planning.

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