The global community has called for the elimination of new HIV infections among children by 2015 and keeping their mothers alive [1]. Though viewed by some as overly optimistic and aspirational, this call to action has generated unprecedented momentum and transformed the global dialogue around prevention of mother-to-child HIV transmission (PMTCT) to emphasize efficiency, effectiveness and measurable impact of efforts to prevent new pediatric HIV infections. The 2013 WHO guidelines for the use of antiretroviral drugs in pregnant and breastfeeding women also represent a major paradigm shift from previous recommendations for PMTCT in low and middle-income settings (Table 1) [2].

For the first time, the ART strategy for pregnant women is fully harmonized with the recommended first-line regimen for nonpregnant adults (once-daily tenofovir + lamivudine/efavirenz + emtricitabine). And, perhaps, more dramatically, the PMTCT regimen will no longer be determined by the woman’s health status. Rather, all women, irrespective of CD4+ T-cell count or clinical stage, will initiate standard first-line ART to reduce the risk of HIV transmission to the child and to her uninfected partners. For programmatic and operational reasons, particularly in generalized HIV epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment (the ‘option B+’ approach), whereas in some countries, for women not eligible for ART for their own health, consideration can be given to stopping the antiretroviral drug regimen after the period of MTCT risk has ceased (‘option B’) [2]. Using pregnancy status as the sole criterion to initiate ART represents a substantial change from previous PMTCT guidance, which traditionally recommended different antiretroviral regimens (prophylaxis vs. treatment) on the basis of maternal health status and vertical transmission risk. This simplified approach – initiation of the tenofovir + lamivudine/efavirenz + emtricitabine for all pregnant and breastfeeding women and, for most, continuation as lifelong treatment – furthers the notion of treatment as prevention, which has been the basic tenet of PMTCT, and should dramatically expand access to ART among pregnant and breastfeeding women.

Over the past decade, there has been a progressive increase in antiretroviral drug use for PMTCT, from single-dose nevirapine, to short-course prophylaxis, to, in 2010 [3], a stratified approach with lifelong ART for eligible pregnant women and, for healthier women, a prophylaxis regimen of either twice-daily zidovudine during pregnancy and daily nevirapine to their infants during breastfeeding (option A), or maternal triple antiretroviral drug through breastfeeding (option B). And although thought to be highly and equally efficacious regimens for preventing transmission, implementation in the field has been fraught with complexity. Few low and middle-income countries have been successful in efforts to scale up these antiretroviral regimens [4], particularly to identify and treat ART-eligible women who are at highest risk for both HIV disease progression and MTCT during pregnancy and breastfeeding [5]. In 2012, among pregnant women who needed ART for their own health, less than 50% received it in 10 priority countries for the elimination of mother-to-child transmission Global Plan [4]. By eliminating the need for CD4+ T-cell count determination to identify treatment eligibility, and with the use of the same once-daily regimen for all pregnant women as in nonpregnant adults, option B+ simplifies program implementation, and as demonstrated in Malawi [6], where the approach was innovated, should substantially improve ART uptake among pregnant and breastfeeding women [7].

Correspondence to Elaine J. Abrams, MD, ICAP, Mailman School of Public Health, 722 W 168th Street, New York, NY 10032, USA.
Tel: +1 212 342 0543; e-mail: eja1@columbia.edu

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Historically, the PMTCT community has been moderately conservative in recommended approaches and regimens, balancing risk of transmission, maternal health concerns, and safety of drugs for mother and fetus. There has been particular reluctance to use emtricitabine during pregnancy, given teratogenic effects observed in primates exposed in utero to emtricitabine, several reports of neural tube and other central nervous system defects in children with first trimester exposure [8], and an US Food and Drug Administration (FDA) pregnancy category D classification [9]. Given other drug options, emtricitabine was generally avoided for pregnant women and women considering pregnancy. However, emtricitabine use has increased over the past years in nonpregnant adult populations in low and middle-income settings and in 2010 WHO-recommended tenofovir + lamivudine/efavirenz + emtricitabine as a fixed-dose combination, (FDC) is recommended option for ART initiation [13]. Harmonizing the available fixed dose combination tenofovir + lamivudine/efavirenz + emtricitabine as first-line treatment for adults and all pregnant women including those with higher CD4 T-cell count was a logical next step. Emtricitabine was further preferred over nevirapine given concerns about the increased risk of maternal hepatotoxicity of nevirapine in this group [14,15].

The following article by Ford et al. provides additional evidence of the safety of emtricitabine in pregnancy for women with HIV [16]. This is the third updated systematic review and meta-analysis, including data from the Antiretroviral Pregnancy Registry. Overall, there were 44 congenital anomalies reported among 1995 live births to women receiving emtricitabine in the first trimester. The authors found no increase in overall birth defects and no elevated signal for emtricitabine compared with other antiretroviral drug exposures in pregnancy [relative risk 0.78; 95% confidence interval (CI) 0.56–1.09]. With one identified neural tube defect, the estimated prevalence from the systematic review continues to be approximately 7 per 10,000 population (0.07%), which is comparable to the estimates of 0.1% in the general population. Although a much larger sample size is needed to definitively rule out a two-fold increase in low-incidence birth defects, these findings are reassuring.

Similarly, concerns linger around tenofovir use during pregnancy. In adult and pediatric populations, tenofovir

### Table 1. Summary of recommendations for use of antiretroviral drugs for pregnant and breastfeeding women and HIV-exposed infants in the 2013 WHO guidelines [2].

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation/ Quality of evidence</th>
</tr>
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<tbody>
<tr>
<td>All pregnant and breastfeeding women with HIV should initiate triple ARVs, which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART. For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women infected with HIV should initiate ART as lifelong treatment. In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased.</td>
<td>Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) tenofovir + lamivudine/efavirenz + emtricitabine as a fixed-dose combination, (FDC) is recommended option for ART initiation.</td>
<td>Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>Viral load is recommended as the preferred approach to diagnose and confirm ARV treatment failure. If viral load is not available, CD4 and clinical monitoring should be used to diagnose treatment failure.</td>
<td>Strong recommendation, low-quality evidence</td>
</tr>
<tr>
<td>Infants of mothers who are receiving ART and breast feeding should receive 6 weeks of infant prophylaxis with daily nevirapine; infants receiving replacement feeding should receive 4–6 weeks of infant prophylaxis with daily nevirapine (or twice daily AZT). Prophylaxis should begin at birth or when the exposure is recognized postpartum.</td>
<td>Strong recommendation, low to moderate-quality evidence for breastfeeding infants; low quality of evidence for infants receiving only replacement feeding.</td>
</tr>
</tbody>
</table>
Antiretroviral therapy (ART) has been associated with renal dysfunction and bone density loss. Findings from several studies of infants with in-utero tenofovir exposure suggest no increase in poor pregnancy outcomes or congenital defects [12,17,18]. Studies are currently underway to formally evaluate tenofovir exposure on a variety of infant outcomes including growth and bone mineral content.

Any antiretroviral drug use during pregnancy is not without risk to the fetus, but when balanced against the benefits of preventing infant infection and treating maternal HIV disease, ART use appears to be highly favorable. Operational and programmatic imperatives further support the choice of once-daily tenofovir + lamivudine/efavirenz + emtricitabine as the first-line regimen for pregnant and breastfeeding women. It will be, however, critical to continue to monitor outcomes and confirm the findings of Ford et al., as these drugs are more widely used in pregnant and breastfeeding populations.

Over the past decade, the ART scale-up in low and middle-income countries has met with unprecedented success. More than 9.7 million people have initiated ART and an estimated 5.5 million AIDS-related deaths have been averted in low and middle-income countries [4]. Unfortunately, pregnant women have been somewhat marginalized and under-represented among those on ART [19]. Option B/B+ offers a unique opportunity to achieve equity for this population, but it will require thoughtful investment – investments in the health systems in which women and children receive PMTCT and other health services, as well as investments to transform PMTCT services into ART programs prepared to engage in lifetime ART care for this population [20]. The WHO 2013 guidelines for the use of antiretroviral drugs for treating and preventing HIV infection provides a platform and a catalyst to effectively prevent new pediatric HIV infections and keep mothers alive, but it remains up to the global community to ensure that these aspirations are realized.

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Conflicts of interest
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References


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