Time for ''Test and Treat'' in Prevention of Mother-to-Child Transmission Programs in Low- and Middle-Income Countries

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Abstract: Significant progress has been made in the prevention of mother-to-child transmission (PMTCT) of HIV. In 2008, an estimated 1.4 million pregnant women living with HIV in low- and middle-income countries (LMIC) gave birth and almost half of these accessed antiretroviral drugs to prevent HIV transmission to their infants, which ranged from single-dose nevirapine to full combination antiretroviral therapy (ART). Although this represents a significant increase in ART coverage, much more remains to be done in terms of HIV testing and counseling, establishment of ART eligibility, and postnatal treatment and care. In November 2009, the World Health Organization issued new PMTCT guidelines for LMIC, stressing the benefits of earlier initiation of ART during pregnancy and its continuation throughout the delivery and the breastfeeding periods. A key recommendation of these guidelines is to start ART for all HIV-positive pregnant women with a CD4 count below 350 cells/mm^3, irrespective of clinical stage. This makes access to CD4 testing more crucial than ever for the successful implementation of PMTCT programs, since clinical staging performs poorly in identifying pregnant women eligible for ART. However, there are still many barriers to accessing CD4 testing in remote health structures implementing antenatal care services, particularly in countries with a high HIV prevalence. In these settings, universal ART initiation among HIV-positive pregnant women, irrespective of CD4 cell count or clinical staging, is a potentially superior strategy for the prevention of vertical transmission and the improvement of mothers' health.

Key Words: antiretroviral therapy, breastfeeding, CD4 count, HIV, low- and middle-income countries, PMTCT

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In many countries, the vertical transmission of HIV has been virtually eliminated thanks to routine opt-out antenatal HIV testing, maternal and infant use of antiretroviral therapy (ART), elective cesarean section and complete avoidance of breastfeeding.[1] Unfortunately, this is not the case for many low- and middle-income countries (LMIC) with a high burden of HIV.[2] Although progress has been made, in 2008 only 21% of pregnant women in LMIC were tested for HIV during their pregnancy, only 24% of HIV-positive pregnant women were assessed with a CD4 cell count for ART eligibility for their own health, only 45% of HIV-positive pregnant women received antiretroviral (ARV) drugs, and only 32% of infants born to HIV-positive mothers received postnatal prophylaxis. There is still a long way to go to reach the United Nations General Assembly Special Session target of 80% coverage for prevention of mother-to-child-transmission (PMTCT) and a 50% reduction in the proportion of infants infected with HIV by 2010 in LMIC (Fig. 1).

The reasons for this are multiple. Historically, antenatal care (ANC) services have not been equipped to provide HIV testing and counseling or combination ART (cART). Most women in LMIC access ANC in the most peripheral level of health services. Ensuring that staff at this level is trained and available to provide HIV testing and counseling on a large scale is a challenge, as is the problem of providing a reliable uninterrupted supply of HIV tests.

However, 6 of the 10 countries estimated to have the largest numbers of pregnant women living with HIV (Kenya, Malawi, Mozambique, South Africa, United Republic of Tanzania and Zambia) have reached testing coverage of around 60%–80% among pregnant women,[2] showing that the provider-initiated HIV testing strategy has been successful and that the vast majority of women accept PMTCT services once they are available.

Due to accumulating evidence of the benefits of early initiation of cART and of continued ARV prophylaxis during breastfeeding, the World Health Organization (WHO) issued new PMTCT guidelines at the end of 2009.[3,4] Besides clinical stage 3 and 4, all pregnant women with a CD4 cell count ≤350 cells per cubic millimeter should receive cART for their own health, which is expected to be of substantial benefit to the prevention of maternal deaths and infant infections.[5,6] For pregnant women who do not need ART for their own health, recommended prophylaxis with zidovudine monotherapy or with cART now starts earlier in pregnancy, continues until delivery, and is followed by different options for extended maternal and infant prophylaxis during breastfeeding.

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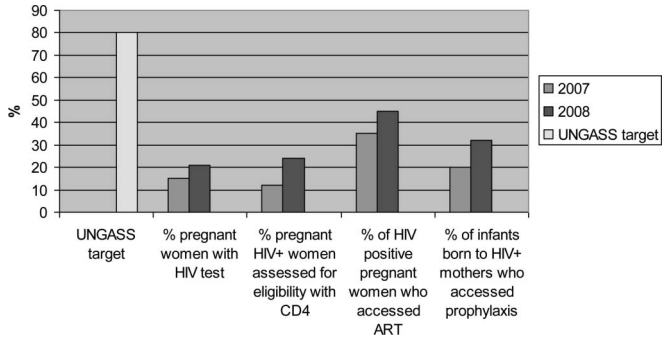

FIGURE 1. Recent evolution of PMTCT coverage in LMIC and remaining gaps to reach the UNGASS target of 80%*. *Adapted from WHO/UNAIDS/Unicef. Progress report 2009;(2). LMIC, low- and middle-income countries; PMTC, prevention of mother-to-child transmission; UNGASS, United Nations General Assembly Special Session on HIV/AIDS.

The study by Carter et al[7] in this issue of *J Acquir Immune Defic Syndr*. compares the performance of immunological and clinical criteria to identify pregnant and postpartum women eligible for ART according to the latest WHO ART initiation guidelines for adults, including pregnant women.[3] Clinical (WHO staging) and immunological (CD4 cell count) baseline data from 6036 women, enrolled in a multicountry MTCT-Plus Initiative, were assessed in light of the new ART initiation criteria (CD4 cell count $\leq$350 cells/mm^3 or WHO clinical stage 3 or 4, irrespective of CD4 cell count). They found that clinical staging alone could identify only 23% of all women eligible for ART, whereas 94% met the CD4 cell count criterion. They conclude that access to CD4 cell counts is, more than ever, pivotal for the establishment of successful PMTCT programs when aiming for maximal impact on maternal health and vertical transmission of HIV.

Although the efforts of the WHO and the international scientific community to provide evidence-based guidance for improved PMTCT interventions should be commended, the feasibility and applicability of these new guidelines is likely to be limited in resource-limited settings because they critically depend on the availability of CD4 cell counts. Successful PMTCT interventions are best offered as an integral part of mother and child health services,[8] down to the most peripheral level of care. However, poor ability to assess clinical stage and limited or no access to CD4 cell counts, particularly in the periphery of under-resourced health structures, continue to represent major hurdles in moving beyond current achievements (results from a mid-2009 survey among alumni from the Institute of Tropical Medicine-Antwerp on access and quality of PMTCT interventions in national or nongovernmental organization–supported programs in 24 sub-Saharan African countries; A. De Weggheleire, personal communication, March 15, 2010).

Acknowledging these resource limitations at the lower care levels and the generally challenging contexts in which the interventions need to be implemented, waiting (or pushing) for the wider availability of CD4 technology may delay access to an effective and safe intervention to prevent the death of mothers and/or their infant. In some high burden countries, a low-tech "test and treat" intervention for all HIV-positive pregnant women not yet on ART—regardless of the CD4 cell count and clinical stage—will be a more feasible option to reach larger numbers of women. Such a simplified public health approach has proven to work for the general ART roll-out in high-burden countries.[9] Universal start of cART during pregnancy is the standard of care in resource-rich settings; why not implement it in countries where HIV/AIDS is the leading cause of mortality among women in reproductive age and an important contributor to infant mortality?[10–12]

The "test and treat" strategy should include continued emphasis on early provider-initiated testing and counseling in all ANC settings, with repeated HIV testing later in pregnancy and at delivery and postpartum for those women in whom an initial HIV test is negative; starting cART in all women identified as HIV positive as soon as possible after 14th week of pregnancy, and continue throughout the delivery and breastfeeding period. Moreover, unless we opt for life-long treatment of all HIV-positive pregnant women, we would still need a CD4 cell count to decide who can stop ART when the risk of vertical transmission is over.[5] Therefore, life-long continuation of cART beyond the breastfeeding period would certainly facilitate implementation and avoid seemingly contradictory messages around ART "ART is life long" and PMTCT "ART may be stopped."

Based on current evidence,[6,7] we estimate that 50% of the target group is eligible for ART for its own health (CD4 cell count $\leq$350 cells/mm^3). An additional 25% would initiate treatment with a CD4 cell count between 350 and 500 cells/mm^3, which is completely in line with new trends in resource-rich settings.[13] The situation is more controversial for the last group of pregnant HIV-infected women, representing an estimated proportion of 25%, who would initiate treatment with a CD4 cell count $>$500 cells per cubic millimeter. Evidence from observational cohort studies suggests that patients who started treatment at CD4 cell counts $>$500 cells per cubic millimeter have better outcomes when compared with the patients who deferred treatment till a CD4 cell count $<$500 cells per cubic millimeter.[14]

Potential safety issues associated with the use of ARVs in pregnancy and breastfeeding for the exposed infants are incompletely quantified, but reported as minimal,[15,16] and the benefits of ART use in a breast feeding population outweigh the risk of potential adverse effects in LMIC, where breastfeeding is responsible for 30%–60% of all HIV infections in children and where children who do not breastfeed are more likely to die from malnutrition and diarrhea.[17]

Questions related to the negative impact of stopping or continuing ART after delivery or breastfeeding period for those women that do not need ART for their own health remain for the most part unanswered. The SMART study showed that nonpregnant adults interrupting therapy with a CD4 cell count $>$350 cells per cubic millimeter and resuming it when the CD4 cell count fell to 250 cells per cubic millimeter had a higher rate of AIDS-related opportunistic disease and death.[18]

Other studies using a threshold of 350 cells per cubic millimeter for reinitiating ART tended to show fewer

differences in outcomes between continuous versus interrupted therapy.[19–21] Although recent studies[22,23] among women stopping ART after pregnancy have been generally reassuring in the sense that this strategy does not increase the short-term risk of HIV disease progression, the continued vigilance and monitoring needed to highlight a possible CD4 cell count decline and the need to reinitiate ART would be hardly feasible in LMIC. Lack of availability of CD4 cell counts would, therefore, increase the risk of unnoticed disease progression in the group of women in whom treatment interruption has been carried out.

Another drawback of interrupting ARV treatment after breastfeeding has stopped is that women are at risk of becoming pregnant again although having a high rebound viral load. There are also concerns about the risk of development of HIV drug resistance in repeated stop and restart ART scenarios. On the other hand questions remain on how to sustain long-term adherence and retention in LMIC,[24] and this may be particularly challenging in healthy women who do not yet need ART for their own health.

More solid answers on these questions can be expected from the IMPAACT-PROMISE study but at earliest in 2014.[25] In the meanwhile, we have to deal with the unacceptable evidence of more than 1000 new infant HIV infections each day. Therefore, innovative simplified approaches to PMTCT are needed and knowing that effective preventive treatment is available, and that low-tech simplified approaches have worked in the past in low-resource settings for other critical health problems, we advocate for a rapid implementation of a universal "test and treat" strategy in all HIV-positive pregnant women in high-burden HIV countries.

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