# Optimal Versus Suboptimal Treatment for HIV-Infected Pregnant Women and HIV-Exposed Infants in Clinical Research Studies

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Lehman et al[1] study in this issue of *J Acquir Immune Defic Syndr* uses a randomized trial design to compare the emergence of viral resistance in women receiving highly active antiretroviral therapy (HAART) compared with zidovudine (ZDV) plus single-dose nevirapine (sdNVP) on the emergence of viral resistance. Treatment was initiated at 34 weeks gestation and continued through 6 months of breastfeeding. Women whose CD4 counts were greater than 500 cells per cubic millimeter or less than 200 cells per cubic millimeter were referred elsewhere for additional evaluation. Allele-specific polymerase chain reaction assays identifying K103N and Y181C mutations showed low levels of resistant virus in 75% of women treated with ZDV/sdNVP and only 8% of women treated with HAART. This study, along with other recently published studies, a Cochran Review of prevention of mother-to-child transmission of HIV (PMTCT) clinical trials and additional reports at the 2009 Conference on Retroviruses and Opportunistic Infections, offer an opportunity to comment on the progress of clinical research studies for (PMTCT) especially in relation to how well clinical research studies integrate what is now known about optimal prevention and prophylaxis and what should currently be considered optimal treatment in resource-limited countries to maximize efficacy and reduce the emergence of HIV resistance.[2–5]

Historically, 1994 marked the year of one of the most important advances in HIV prevention efforts. The National Institutes of Health–sponsored clinical research study (ACTG 076) conclusively demonstrated that ZDV, administered to HIV-infected pregnant women beginning at 14 to 34 weeks of gestation and given to formula-fed infants for 6 weeks after birth, reduced HIV transmission by 66%.[6] Criticism of the study after its publication was based on ethical concerns regarding the use of a placebo-controlled clinical trial design for research studies in infants.[7,8] The criticism was eventually superseded by the realization that the study results could profoundly impact millions of lives of HIV-infected pregnant women and their noninfected infants and could accelerate interventions for PMTCT in resource-limited countries.[9] Despite optimism, specific obstacles had to be overcome—ZDV was expensive, monotherapy was associated with viral resistance, health care infrastructure and prenatal care were inadequate, antiretroviral (ARV) drugs were in short supply, and the need for breastfeeding resulted in continued infant exposure to HIV. Additional solutions were required, especially in populations where formula feeding could not be safely substituted for breastfeeding. In response, numerous clinical research studies were planned and executed to address the unique obstacles to prevent mother to child HIV transmission worldwide.[3,5,10]

In 1999, a second breakthrough clinical research study for PMTCT brought encouraging results suggesting that an abbreviated course of antiretroviral therapy (ART) could be used in resource-limited countries. The National Institutes of Health–sponsored study, HIVNET 012, demonstrated that sdNVP, given to HIV-infected pregnant women during labor and delivery, and a single dose to their infants shortly after delivery, could reduce HIV transmission by 50% even when breastfeeding was continued.[11] Nevirapine was inexpensive, stable without refrigeration, and could be easily administered by midlevel

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health care workers, birth attendants, or HIV-infected mothers.[12,13] The study results were not without controversy, however, as it was shown subsequently that sdNVP was associated with a high rate of drug resistance.[14,15]

Since 1994, more than 45 clinical trials have been conducted to evaluate maternal HIV treatment and prevention for PMTCT in resource-limited countries. Due to the economic and infrastructure constraints of resource-limited settings, many trials sought to identify the minimum short-course ARV administration necessary for PMTCT before efficacy was lost, a curious twist in the history of clinical research considering the magnitude and urgency of the HIV epidemic. One such study included an ultrashort ZDV regimen despite placing infants at high risk for HIV infection. Predictably, the ultrashort arm was found to be inferior to longer treatment and resulted in a higher rate of perinatal HIV transmission.[16] Basically, a spectrum of studies included the evaluation of various short-course combinations of ARVs for PMTCT, when to initiate treatment during pregnancy, the preferred duration for treatment during pregnancy, and duration of ARVs for women and their infants after delivery while breastfeeding continued.

Retrospectively, as clinical studies identify the advantages of early uninterrupted treatment, ethical questions arise regarding the necessity for extensive clinical trials of various permutations of PMTCT regimen approaches, especially those using reduced treatment in resource-limited settings. The failure to apply the lessons learned from other clinical studies for treatment and prophylaxis for PMTCT and the overly cautious approaches of leaders in global health placed too many HIV-infected mothers and their HIV-exposed infants at risk for disease progression including, reduced efficacy of some ARVs due to viral resistance, continued high rates of viral resistance that may be transmitted to others, mother to child transmission rates that did not match those in developed countries, and unnecessarily high mortality rates in infants.

Current international HIV treatment and prophylaxis guidelines recommend the use of HAART to maximize efficacy and prevent the emergence of drug-resistant HIV.[17,18] Guidelines and publications also recommend early initiation of HAART at higher CD4 counts which has been shown in pediatric and adult studies to significantly reduce morbidity and mortality. Marked decreases in the cost and greater availability of ARVs along with persuasive clinical data shifted the criteria for initiating optimal ART in resource-limited countries toward earlier treatment at higher CD4 counts.

The change in recommendations was noted by those who perform mathematical modeling to predict what might happen if early diagnosis of HIV infection and more aggressive implementation of ART were to be initiated simultaneously.[19] This model suggested that HIV transmission could be dramatically decreased and HIV seroprevalence reduced to $<1\%$ if HIV testing were coupled with immediate initiation of treatment regardless of CD4 count.[19,20]

Recent publication of guidelines by international organizations such as WHO have slowly shifted away from recommendations to initiate treatment in only the most advanced cases of HIV infection to recommendations that are more consistent with current clinical data demonstrating the compelling advantages of early treatment approaches. Other international organizations have been more aggressive, recommending initiation of HAART in asymptomatic individuals at higher CD4 counts.[21] Current recommendations for optimal prophylaxis are well defined and consist of HAART administered for at least 4 weeks after exposure to HIV.[22,23]

At this point in the epidemic, there is consensus on the principles that define optimal treatment and prophylaxis of HIV infection, and it seems appropriate to ask whether participants in clinical trials for PMTCT in resource-limited countries are being offered the best available treatment.

1. HAART is the standard of care for the treatment of HIV infection for children and adults.[21,24,25]
2. HAART is the standard of care for post exposure prophylaxis of HIV infection.[22,23]
3. Suboptimal treatment (the use of fewer than 3 drugs) does not control HIV infection and increases viral resistance.[21,26–28]
4. Interrupted treatment increases the potential for drug resistance, viral rebound, opportunistic infection, mortality, and subsequent response to treatment.[27–31]
5. Delayed treatment, either by initiating treatment at low CD4 counts or waiting until the patient is symptomatic, is associated with increased morbidity and mortality which may persist for years.[32]
6. Early treatment with HAART and control of HIV infection decreases HIV transmission to sexual partners, lowers death rates, prevents opportunistic infections, and decreases HIV transmission at the population level.[20,32–36]
7. HAART reduces viral load, which is the major factor in HIV transmission.[37]
8. Continued use of ART while breastfeeding reduces HIV transmission and emergence of viral resistance.[1,20,38,39]

Clinical research studies for PMTCT have not aggressively incorporated these principles into their study design in resource-limited countries. Initially, implementation of PMTCT in resource-limited countries was hindered by the availability and expense of ARVs and inadequate infrastructure. As a result, clinical studies for PMTCT in breast-feeding populations continued to use suboptimal treatment and prophylaxis including the use of fewer than 3 drugs, interrupted treatment of mothers, shortened duration of treatment, shortened duration of prophylaxis, and initiation of treatment at more advanced stages of HIV infection.[40–44] Results of these studies were predictable and confirmed what had been previously demonstrated—HIV transmission rates to infants increase with the use of suboptimal treatment for PMTCT and mono or dual prophylaxis results in a higher risk of HIV transmission and drug resistance.[16,45–49]

The consequences of the use of a suboptimal treatment in clinical trials for the treatment of HIV-infected children was highlighted when a recent clinical trial was halted because the mortality in the deferred (suboptimal) treatment arm significantly exceeded that of the early treatment arm.[50] The study is an example of a clinical trial design for treatment of HIV-infected children, which failed to acknowledge published evidence that delayed treatment was not the optimal means for controlling HIV disease progression.[51] Studies of HIV-infected

infants had demonstrated that HIV progressed more rapidly in children than adults; the mortality in untreated HIV-infected infants was 50% by 1 year old age; immune recovery after treatment was better in young infants; bacterial infections occurred at higher CD4 counts and are reduced by HAART; and growth and development, including neurologic development, are significantly greater when treatment is initiated early.[51]

Now that ARV treatment is more accessible in countries where research studies for PMTCT and treatment of children are performed, optimal treatment for PMTCT in clinical research studies should include early initiation of HAART for all HIV-infected pregnant women, and continuation of HAART during and after breastfeeding has ceased. Short courses of HAART, use of 1 or 2 ARVs, and premature discontinuation of HAART after exposure to HIV should be considered suboptimal treatment and prophylaxis. There is ample evidence at this time to conclude that single drug treatment and prophylaxis consistently results in drug resistance; delayed initiation of treatment and short duration of treatment consistently results in increased HIV transmission; and premature cessation of prophylaxis although HIV exposure continues results in increased HIV infection.[3,16,52–55] Clinical research trials, conducted within countries supported by international programs that provide HAART for the general population or where optimal treatment of HIV infection is available, should be obligated to provide the best available treatment within clinical research studies. The transition from an economically based to an optimal efficacy-based rationale for PMTCT and treatment of children has not occurred quickly enough in clinical research trials, placing too many HIV-infected women and HIV-exposed infants at risk.[56]

At this juncture in the HIV epidemic, clinical research studies for PMTCT should conform to high ethical standards defined as the best available care and high efficacy standards defined as providing optimal treatment and prophylaxis as the minimal intervention.[56] To do less, provides an unintentional signal to international organizations and National Ministries of Health that HIV-infected pregnant women and their infants need not receive the same level of treatment and prophylaxis as other HIV-infected or HIV-exposed individuals. Comparison interventions should consist of treatment and prevention arms that seek to enhance efficacy beyond current optimal treatment regimens although focusing on short-term and long-term safety evaluation of exposure to ARVs.[39] Likewise, international research efforts should focus on improving the science of implementation and identify ways to improve diagnosis, access, adherence, and retention of women and infants while using the best available treatment and prophylactic regimens to reduce the continued unacceptably high numbers of perinatal HIV-infected infants in resource-poor settings.

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