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Use of antiretrovirals during pregnancy and breastfeeding in low-income and middle-income countries

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Abstract

Purpose of review—The purpose of the study was to review recent evidence on the use of antiretrovirals during pregnancy and breastfeeding in low-income and middle-income settings.

Recent findings—Access to antiretroviral prophylaxis strategies for HIV-infected pregnant women has increased globally, but two-thirds of women in need still do not receive even the simplest regimen for the prevention of mother-to-child transmission of HIV, and most pregnant women in need of antiretroviral treatment do not receive it. The use of combination antiretroviral treatment in pregnancy in low-resource settings is safe and effective, and increasing evidence supports starting ongoing antiretroviral treatment at a CD4 cell count below 350/μl in pregnant women. The use of appropriate short-course antiretroviral prophylactic regimens is effective for prevention of mother-to-child transmission of HIV in women with higher CD4 cell counts. New data on the use of antiretroviral prophylaxis to prevent transmission through breastfeeding demonstrate that both maternal antiretroviral treatment and extended infant prophylaxis are effective.

Summary—Antiretroviral use in pregnancy can benefit mothers in need of treatment and reduce the risk of mother-to-child transmission. Emerging evidence of the effectiveness of antiretroviral prophylaxis in preventing transmission through breastfeeding is encouraging and likely to influence practice in the future.

Keywords

antiretroviral drugs; breastfeeding; HIV; pregnancy; prevention of mother-to-child transmission

Introduction

Mother-to-child transmission of HIV (MTCT) has become a rare event in well resourced settings, with the widespread access to effective antiretroviral treatment, but around 370 000 children were newly infected with HIV in 2008, with 90% of these in sub-Saharan Africa [1••]. This represents a decrease from previous estimates [2], which may reflect the growing impact of prevention of mother-to-child transmission (PMTCT) programs. The complications of HIV infection are also major causal factors for maternal mortality in high prevalence HIV areas, especially in sub-Saharan Africa [3,4•,5,6], and it appears that increased antiretroviral treatment access has yet to result in an improvement in maternal mortality figures in high prevalence settings [7•].

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Antiretroviral access

Access to antiretroviral therapy has expanded dramatically in low-resource settings in the past 3 years, rising by 42% in 2007 alone, providing treatment to more than 3 million people, but still not reaching the other two-thirds of the estimated 9.7 million people in need of treatment [1••,8••,9]. This increased access to treatment has resulted in more widespread use in pregnant women, but coverage of antiretrovirals, either as treatment or for prophylaxis remains low, despite some very successful initiatives [10•,11,12•,13]. The global coverage of PMTCT services remains suboptimal with only 18% of all pregnant women in low-income and middle-income countries (20.6 million of 115 million pregnant women) estimated to have received an HIV test in 2007, though this had increased from estimates of 16% in 2006 and 10% in 2005 [8••]. Only 33% of HIV-infected women are estimated to have received some PMTCT intervention in 2008, up from 10% previously. HIV testing is essential to identify HIV-infected women in need of antiretroviral interventions, and provider-initiated testing has been shown to dramatically increase uptake rates and facilitate access to care [14–16]. In this review, recent data on aspects of the use of antiretrovirals in pregnant women and during the breastfeeding period for maternal health and for PMTCT are discussed.

Antiretroviral use during pregnancy

The role of the use of combination highly active antiretroviral therapy (HAART) both to benefit maternal health and to reduce the risk of transmission to infants is well established and acknowledged in all major international guidelines [17,18••,19••]. The availability of HAART has driven the transmission rates of HIV to below 1–2% in well resourced settings and has dramatically reduced the numbers of new cases of HIV infection in children to an estimate of less than 500 annually across the whole of the United States and Europe combined [1••]. As an example of this success, in the United Kingdom and Ireland between 2000 and 2006, the overall MTCT rate was 1.2%, and it was 0.8% for women who received at least 14 days of antiretroviral therapy [20]. Similarly, low transmission rates are reported in most well resourced countries [21–24], but progress in low-resource settings has not been as dramatic.

Combination antiretroviral treatment

The WHO reports that only around 12% of HIV-infected pregnant women were assessed for their eligibility to receive antiretroviral therapy in 2007, either clinically or immunologically by CD4 cell count, demonstrating the need for urgent action to improve these services [8••]. Where HAART is available in low-resource settings, the use in pregnancy, either for ongoing treatment or as prophylaxis, has been reported to be safe and effective, in line with experience in well resourced countries, though reports of increased rates of prematurity suggest the need for further investigation of this aspect [12•,25–27,28•,29•,30,31•].

Short-course antiretroviral prophylaxis for prevention of mother-to-child transmission

The use of even the most simple, single-dose nevirapine (NVP)-based PMTCT regimens has been estimated to have averted over 30 000 infections in infants in 2004 and 2005, and this figure is likely to be considerably higher with the increased access to antiretrovirals over the past 5 years [32]. The WHO guidelines for PMTCT, issued in 2006, provide a consensus approach to antiretroviral use in pregnancy for low-resource settings, which includes the provision of HAART for pregnant women who require ongoing treatment, provision of an appropriate antiretroviral prophylactic regimen for those who do not yet need treatment and

appropriate adaptation of infant feeding practices [17]. Substantial data from low-resource countries have shown the efficacy of short-course antiretroviral regimens in these settings [33,34••,35,36•,37•,38]. The use of HAART regimens for prophylaxis is likely to increase in these settings as general access to antiretroviral treatment improves. Concerns remain around the development of NVP resistance in mothers and infants following the use of NVP in PMTCT short-course regimens, or as extended prophylaxis to infants, and the potential impact of this on maternal and infant treatment options [39–43,44••,45].

Antiretroviral prophylaxis during breastfeeding

In well resourced settings, the complete avoidance of breastfeeding has been a major factor in reducing transmission, and breastfeeding is not recommended for HIV-infected women (including those receiving HAART) [18••,19••]. Although the use of replacement feeding has been documented to be safe and feasible in some less resourced settings, such as in Thailand, Brazil and some African urban areas, it is not a feasible option in many low-resource settings [37•,46,47•,48]. The use of exclusive breastfeeding rather than 'mixed' feeding has been shown to provide some protection against infection, but this does not prevent all infections, with transmission rates in exclusively breastfed infants of up to 14% at 6 weeks and 20% at 6 months even in the best managed research settings [49]. Exclusive breastfeeding is not easy to achieve, and its successful promotion relies also on providing supportive health services and in having willing mothers [47•,50••,51,52]. The WHO infant feeding guidance from 2006 reinforced the recommendation that avoidance of breastfeeding should only be recommended for HIV-infected women if affordable, feasible, acceptable, safe and sustainable (AFASS) and recommended weaning as soon as possible to reduce the ongoing risk of infections [53]. An increasing body of evidence since then from very low-resource settings has demonstrated that early weaning may reduce HIV transmission risk but is balanced by a much higher rate of morbidity and mortality in the infants [54••,55–57], and that inappropriate replacement feeding use may have similar consequences [58]. These effects appear to be more severe in infants born to mothers with more advanced disease and lower CD4 cell counts, adding to the urgency to provide appropriate antiretroviral treatment for these mothers [59,60]. The need to find alternative strategies that could maintain the benefits of breastfeeding while reducing the risks of HIV transmission has led to research in two areas of antiretroviral prophylaxis through the period of breastfeeding: either the provision of HAART to mothers or extended prophylaxis to breastfed infants.

Maternal highly active antiretroviral therapy through breastfeeding

Several observational trials have reported success in reducing breast milk transmission in women receiving HAART through the period of breastfeeding [61•,62]. In the Mitra plus study, a transmission rate of 0.9% at 6 months was achieved in infants of women given a HAART regimen of zidovudine (AZT), lamivudine (3TC) and NVP, rising to 1.7% at 12 months and 1.9% at 18 months [62,63]. The Allaitement MAternal sous Tritherapie Antiretrovirale (AMATA) study, conducted in Rwanda, has also reported success of this strategy, with no transmission in women on HAART at 7 months of follow-up [64]. In Mozambique, the Drug Resource Enhancement against AIDS and Malnutrition (DREAM) program has reported a 12-month transmission rate of 1.3% through breastfeeding in infants of mothers on HAART [26] and a positive effect on infant HIV-free survival of infants at 1 year of age as a result of HAART to mothers [25]. In Kenya, the Kisumu Breastfeeding study (KIBS) [65] gave HAART (AZT and 3TC with either NVP or nelfinavir, depending on maternal CD4 cell count) and showed transmission rates of 1.5% at 6 weeks, 2.6% at 6 months and 3.5% at 12 months.

Data from two randomized trials were presented at the 5th IAS Conference, Cape Town, South Africa, 19–22 July 2009, which add important information for this field.

The Kesho Bora study [66], conducted at sites in Burkina Faso, Kenya and South Africa, randomized pregnant women with CD4 cell counts between 200 and 500 cells/μl, between 28 and 36 weeks of pregnancy, to receive either short-course AZT and single-dose NVP in labor or to maternal HAART [AZT, 3TC and lopinavir/ritonavir (LPV/r)]. Treatment was continued in the HAART group to approximately 6.5 months after delivery (or until breastfeeding cessation if this occurred earlier). All infants received single-dose NVP postpartum, and 1-week maternal 'tail' coverage was added to the short-course regimen and 1-week AZT for all infants, as guidelines changed during the study. The cumulative infection rate for infants whose mothers had a baseline CD4 cell count 200–350 cells/μl was significantly reduced at 5.5 vs. 10.5% at 6 months and 6.1 vs. 11.1% at 12 months in the HAART and short-course arms. However, for infants of mothers with baseline CD4 cell counts between 350 and 500 cells/μl, the rates were 4.1 vs. 5.9% at 6 months and 4.9 vs. 7.4% at 12 months, which were not significantly different (P= 0.33). The largest effects were seen between 6 weeks and 6 months [66]. These results add further weight to recommendations to start ongoing antiretroviral therapy at a CD4 cell level of 350 cells/μl or less, and as in the observational studies, provide more evidence of an effect of maternal HAART in reducing breast milk transmission compared with the current standard antepartum and intrapartum short-course regimen.

The Mma Bana study [67] is the first randomized controlled trial to compare two antiretroviral regimens in pregnancy and during breastfeeding. It was a randomized controlled trial in Botswana comparing two HAART regimens given to pregnant and breastfeeding mothers, starting between 26 and 34 weeks of pregnancy and continued until breastfeeding cessation at 6 months postpartum. Women in the trial had CD4 cell counts above 200 cells/μl and would otherwise not eligible for antiretroviral treatment according to the local guidelines. The two regimens compared were abacavir (ABC), AZT and 3TC coformulated as Trizivir, or LPV/r, AZT and 3TC given as Kaletra and Combivir. The study demonstrated excellent adherence to the treatment regimens (over 90%), with a median of 11-week antepartum treatment, high adherence to exclusive breastfeeding (93%) and to cessation of breastfeeding at 6 months, with very low loss to follow-up. The overall transmission rate in this study at 6 months was 1% [95% confidence interval (CI) 0.5–2.0] with only 0.3% of infections occurring during the 6-month period of breastfeeding. Maternal virologic suppression rates at delivery and during breastfeeding did not differ by HAART regimen. This study demonstrates excellent effectiveness of a HAART strategy through pregnancy and breastfeeding in achieving a major reduction in transmission rates.

Extended infant antiretroviral prophylaxis

Two published reports have demonstrated the effect of extended NVP prophylaxis to breastfed infants. In the Six-Week Extended Nevirapine (SWEN) study [68••], a set of comparable trials conducted in Ethiopia, India and Uganda, there was a significant difference in HIV transmission rates at 6weeks between HIV-exposed infants who received a single postpartum dose of NVP and those who received an extended regimen of daily NVP for 6 weeks, with a relative risk of 0.54 (95% CI 0.34–0.85). However, at 6 months, the difference was not significant. An extended 14-week course of NVP, with or without added AZT, commenced at birth in HIV-exposed infants decreased the risk of HIV transmission by as much as 50% at 9 months compared with the standard regimen of single-dose NVP and 1 week of AZT in the Post-Exposure Prophylaxis of Infant (PEPI) study in Malawi [69••]. There appeared to be no added protection afforded by the addition of extended AZT in addition to the NVP. This benefit was lost by 12 months when breastfeeding was prolonged.

The results of these two trials suggest that transmission is not reduced after the extended NVP is stopped, and that more prolonged administration, at least to 6 months, to cover the period of exclusive breastfeeding could be needed.

Other studies on infant prophylaxis, including the Mitra and Stopping Infection from Mother-to-child via Breast-feeding in Africa (SIMBA) studies, have also shown efficacy of extended antiretroviral regimens in decreasing the risk of breast milk transmission, but the duration of breastfeeding was short and the rate of exclusive breast-feeding high in both studies [70,71]. The Mitra study was an open-label, nonrandomized, prospective cohort study in Tanzania, in which infants were treated with AZT and 3TC from birth to 1 week of age and then with 3TC alone during breastfeeding, for a maximum of 6 months. The Kaplan–Meier estimated risk of HIV-1 infection at 6 months in infants who were HIV-negative at 6 weeks was 1.2% (95% CI 0.0–2.4). The cumulative HIV-1 infection or death rate at 6 months was 8.5% (95% CI 5.7–11.4). The HIV-1 transmission rate during breast-feeding in the Mitra study up to 6 months after delivery was more than 50% lower than that in the breastfeeding population of Petra arm A (relative hazard = 2.61; $P = 0.001$; adjusted values) [71].

Comparing maternal highly active antiretroviral therapy and infant prophylaxis

Direct comparison of the results of these studies to date is not possible in most cases, as duration and type of maternal treatment and antiretroviral drugs used for infant prophylaxis, duration of breastfeeding and extent of exclusive breastfeeding are different, but the data suggest that these strategies may have a place in the future [61•].

One trial, reported at the IAS 2009 conference, has compared the two strategies against a standard NVP regimen. The Breastfeeding Antiretroviral and Nutrition (BAN) study [72], in Malawi, is a randomized controlled trial of mother–infant pairs, evaluating two antiretroviral interventions over 24 weeks of exclusive breastfeeding followed by a 4-week period of weaning, among women with CD4 cell counts more than 250 cells/μl with infants uninfected at birth and weighing over 2000 g. All mothers and infants received single-dose NVP and 1-week AZT/3TC ‘tail’ coverage, and also nutritional supplementation. Mother and infants were randomized to receive either maternal HAART (AZT along with 3TC and either NVP, nelfinavir or LPV/r as guidelines for higher CD4 cell count pregnant women changed over the time of the study), or NVP infant prophylaxis or postpartum nutritional supplementation alone, as the control. In contrast to the other reported studies, maternal HAART was started after birth. Among 2637 mother–infant pairs, in-utero transmission was 4.9% (measured as HIV-1 infection at 1 week). The control arm, with no additional postpartum treatment after the standard regimen, was stopped by the Data Safety Monitoring Board (DSMB) study. The results presented show that both the infant NVP and maternal HAART regimens significantly reduced HIV transmission to the infants at 28 weeks compared with the enhanced control arm. Transmission in the infant NVP arm was 1.8 vs. 6.4% in the control arm, ($P<0.0001$), and in the maternal HAART arm, the transmission rate was 3.0 vs. 6.4% in the control arm ($P= 0.0032$). The estimated risk of HIV-1 transmission or death by 28 weeks was 7.6% in the control arm compared with 4.7% in the maternal HAART arm ($P = 0.03$) and 2.9% in the infant NVP arm ($P<0.0001$). This study was not powered for comparisons between the two intervention arms, but has shown a trend toward the infant extended prophylaxis being more effective for HIV-free survival of infants.

As with the other studies above, these data do not extend out past 6 months and longer follow-up results would be helpful for policy development. A large, multinational study is commencing in late 2009 within the International Maternal, Pediatric Adolescent AIDS

Clinical trials (IMPAACT) network [the P1077 PROmoting Maternal and Infant Survival Everywhere (PROMISE) trial], which will compare maternal HAART vs. antenatal AZT and intrapartum NVP, and also maternal HAART vs. extended NVP prophylaxis to infants, with these interventions continued through the full duration of breastfeeding.

Conclusion

There have been several recent research advances in the use of antiretrovirals in pregnancy and to prevent breast milk transmission. These are likely to be reflected in new international guidelines, with revised advice to start antiretrovirals at a CD4 cell count of 350 cells/μl or less and to use some form of antiretroviral prophylaxis through breastfeeding. Ongoing research in the IMPAACT P1077 PROMISE trial will provide further information in the future as to the best of these approaches to reduce transmission through breastfeeding, and whether stopping prophylactic HAART has any long-term adverse impact on maternal health. Translation of these research findings into real impact depends on the improvement of services to reach and care for HIV-infected mothers and their children [48,73–77]. Without significant efforts to improve the coverage and quality of PMTCT services and better use of these to provide access to ongoing treatment for women, we will not achieve the maximum benefit from antiretroviral use in pregnancy in low-resource settings.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 105–106).

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