Prophylactic antiretroviral regimens for prevention of mother-to-child transmission of HIV in resource-limited settings.

Elise Arrivé, François Dabis

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Arrive Elise [*] **, Dabis Francois**

Epidemiologie, sante publique et developpement INSERM : U593, IFR99, Universite Victor Segalen - Bordeaux II, ISPED, FR

* Correspondence should be adressed to: Elise Arrive <Elise.arrive@isped.u-bordeaux2.fr>

Abstract

Purpose of review

With the large international mobilization against HIV/AIDS, more HIV-infected people in resource-limited settings have access to antiretroviral therapy (ART), including pregnant women. The relevance of simplified prophylactic antiretroviral (ARV) regimens for the prevention of mother-to-child transmission (PMTCT) of HIV may become questionable due to their lower efficacy and their higher risk of inducing viral resistance than fully suppressive ART.

Recent findings

Field implementation of current recommendations, impact of prophylactic regimens on subsequent ART response and possible new indications of ART in pregnant women will be reviewed in this paper.

Summary

Prophylactic ARV PMTCT regimens reached only 10 % of the HIV-infected pregnant women in 2006, who were usually offered single-dose nevirapine only. The operational links between antenatal care and ART programmes can now be documented and demonstrate good results in terms of safety and efficacy. The negative impact of single-dose nevirapine exposure on subsequent first-line ART appears worse for mothers with advanced HIV disease at the time of delivery and short interval before ART initiation. Strengthening the links between antenatal care and ART programmes is critical for ART-eligible HIV-infected pregnant women in terms of PMTCT and subsequent ART response. The breastfeeding period could be a new indication for ART in this population.

Author Keywords Prevention of mother-to-child transmission of HIV-1 ; Resource-limited settings ; Prophylactic antiretroviral regimens ; Single-dose nevirapine ; Breastfeeding

Introduction

In industrialized settings, antiretroviral therapy (ART), with at least three potent antiretroviral (ARV) drugs is recommended to prevent mother-to-child transmission (PMTCT) of HIV, even in women with no indication for themselves, and ART should be initiated, in this case, as soon as possible after the first trimester and stopped soon after delivery [1–3]. However, in the United States, short-course regimens of one or two ARVs are still an option for women with plasma viral load <1000 copies/mL, or for those who are screened for HIV late in pregnancy or during labour [1]. In resource-limited settings, ART is recommended only in pregnant women with indication of treatment for themselves, while those who do not meet clinical and immunologic eligibility criteria for ART accordingly to the World Health Organization (WHO) guideline should receive short-course ARV regimens [4]. With the large international mobilization against HIV/AIDS and the great improvement of ARV drug access within the last five years in resource-limited countries, more HIV-infected people have access to ART, including pregnant women [5]. In this context, should indications of ART in pregnant women in resource-limited settings be enlarged? We review here the recent reported evidence on the implementation and effectiveness of the current recommendations for PMTCT in resource-limited countries and on the impact of such regimens on subsequent use of ARVs for treatment or prophylaxis, as well as the potential new indication of ART in pregnant women, the breastfeeding period.

Coverage and effectiveness of PMTCT programmes

The WHO currently recommends the administration of zidovudine (ZDV) initiated as soon as possible from the 28th week of gestation, together with single-dose nevirapine (sdNVP) during labor and seven days of ZDV+lamivudine (3TC) postpartum [6]. The neonate should receive sdNVP and one week of ZDV syrup. Alternatives are possible, according to the local programme implementation capacities and the timing of the maternal screening for HIV infection, the minimum ARV regimen recommended being the administration of sdNVP to the mother and the neonate. However, in many settings reporting their experience in implementing PMTCT programmes, this minimum regimen is the one mainly used, despite the fact that antenatal short-course ZDV has been recommended since 2000 and proved to be safe [5,7–9].

Altogether, the worldwide coverage of PMTCT interventions remains low, with about 10% of HIV infected pregnant women receiving any ARV prophylaxis [5,7]. In addition, difficulties in evaluating PMTCT programmes were recently highlighted, including the inadequacy of current indicators used to monitor and evaluate operational programmes (mainly the cumulative pediatric HIV infection rate, while effective prevention relies on a cascade of steps, whose coverage should be monitored and evaluated at each stage), weak health information systems and poor quality of interventions beside ARV prophylaxis, making difficult the interpretation of the impact of programmes [7,10–12]. Thus, compliance to WHO recommendations is not well documented, particularly the link between PMTCT and ART programmes, a crucial element for programme effectiveness [4]. A recent study, conducted in Abidjan, Côte d'Ivoire, within the MTCT-Plus initiative, in 2003–2006, demonstrated, for instance, that the use of ART as recommended in the WHO guidelines resulted in good outcomes in terms of safety and short and long-term efficacy [13**]. Among 261 HIV-1 infected pregnant women enrolled, 96% received ART or short-course ARV regimens according to their immunological and clinical status. No difference was found between the two groups in terms of pediatric HIV infection rate at one month: 1.0% (95% Confidence Interval [CI]: 0.0–3.1) in children born to women receiving ART vs. 3.1% (CI: 0.1–6.1) in women receiving short-course ARVs (72% short-course ZDV+3TC+sdNVP, 18%, short-course ZDV+sdNVP and 10% sdNVP alone). At 12 months, the probabilities of pediatric HIV infection or death were similar, about 11–12% in the two groups. In the ART group, 7.5% of women developed adverse events related to NVP (administered daily) which resolved with drug changes but none in the short-course ARV group. This example illustrates well the feasibility and the effectiveness of WHO recommendations where PMTCT and care are well established and linked, but very few settings have reported so far such successful outcomes.

Van der Merwe et al. reported their experience from South Africa, in 2004–2005, in implementing interventions to strengthen linkage and integration of ART within antenatal care (ANC) (measuring CD4 cell counts at the first antenatal visit, inclusion of health workers from the ARV treatment services within antenatal clinics, baseline laboratory investigations and adherence counselling at the second antenatal visit, enhanced monitoring system) [14*]. The authors observed a reduced delay between HIV diagnosis and ART initiation over time. However, women with no indication of treatment for themselves received sdNVP only as PMTCT intervention in this setting, without any antepartum ZDV prophylaxis. This may explain the higher MTCT rate at six weeks in children born to women receiving this regimen (10.7%) compared to those receiving ART (4.3%).

In Luzaka, Zambia, Chi et al. reported a high rate of attrition at each step of a PMTCT/ART programme: 56% of the patients with newly diagnosed HIV in an ANC clinic did not undergo initial ART screening because they were not identified by the program staff or they did not come for ART screening [15*]; 54% of ART eligible women did not receive ART because they did not return for their test results or they declined the treatment offer; 34% of not eligible women did not received counselling regarding PMTCT options either because they did not returned for their test results or they refused additional counselling. Among women counselled regarding PMTCT options, 99% of them choose ZDV+NVP rather than NVP alone or ZDV alone.

Altogether, when links between PMTCT and ART programmes are effective and close to the WHO recommendations, good and efficacy can be obtained as reported in well organized programmes with adequate monitoring. However, difficulties to implement such link as well as more complex interventions (adding antepartum ZDV, for instance) remain with the negative consequences on the overall effectiveness and coverage of the programmes. These are the primary reasons while sdNVP remains the most commonly adopted PMTCT regimen, despite its disadvantages including viral resistance.

Nevirapine viral resistance

The concern of Non Nucleosid Reverse Transcriptase Inhibitor (NNRTI) viral resistance induced by sdNVP is of high importance today as it has been for the past three to five years. A recent meta-analysis has estimated the prevalence of NVP resistant mutants at 4–8 weeks postpartum in women who had received sdNVP+/− other anterpartum ARVs at 35.7%, compared to 4.5% among the women who had received additional postpartum ZDV+3TC [16]. In 4–6 week old infants contaminated despite the PMTCT ARV intervention, the prevalence of NVP resistant mutants was higher, 52.6% when only sdNVP was administered compared to 16.5% when other ARVs had been given beside sdNVP to the mother and/or to the child. These findings highlight the important burden of viral resistance induced by NVP exposure and the benefit of providing postpartum ARVs, as recommended in the current WHO guidelines.

In early 2007, Lockman et al. confirmed data reported three years ago by Jourdain et al. from Thailand [17] on the negative impact of previous sdNVP on virologic response to NNRTI-containing ART regimen, in women, particularly if it was initiated less than six months after delivery; the conclusion was quite comparable in children [18**]. In this study, conducted in Botswana, where women were randomized to receive either sdNVP or placebo for PMTCT, the authors observed that, in women initiating ART within six months after delivery, virologic failure rate at six months was higher in women previously exposed than among those not exposed (41.7% vs. 0%, respectively). This negative impact was not observed in women initiating therapy more than six months after delivery, and was not observed either for immunologic

response irrespective of the sub-group. Another study, conducted in Zambia, from routine data collected in public ART facilities did not show any difference in terms of immunologic and clinical response to NNRTI-containing treatment at 12 months [19] whatever sdNVP previous exposure, recent or remote. In Côte d'Ivoire, no negative impact of previous sdNVP was observed on virologic or immunologic response at 12 months of women starting NNRTI-based regimen, but the median delay between delivery and ART initiation was long: 28 months [20]. However, it is worth noting that 3TC viral resistance at 4 weeks postpartum was associated with virologic failure at 12 months, despite a median delay of 15 months between delivery and ART initiation, confirming that this drug should not be recommended antenatally as a part of short-course PMTCT regimen (in this context: short-course ZDV/3TC+sdNVP). Recent findings from South Africa and Côte d'Ivoire also demonstrated that previous exposure to sdNVP did not lower the efficacy of this regimen in a subsequent pregnancy [21].

A study conducted in South Africa confirmed the high prevalence of NNRTI resistance mutations in children exposed to sdNVP, with 45% of HIV-infected infants harbouring resistant virus by 12 weeks of age [22*]. The authors noticed that the 18-month mortality rate they found (454 deaths per 1000 child-years) was higher than those reported for HIV-infected children in sub-Saharan Africa. This findings could be related to the negative impact of sdNVP exposure observed in the Botswana study for both immunological and virologic response of NNRTI-based ART in infants at six months, possibly as a result of selection of resistant virus [18]. Furthermore, Martinson et al. observed that infant detectable viral resistance was associated with higher maternal plasma HIV viral load during pregnancy suggesting that ART provided to pregnant women with advanced HIV disease may reduce selection of resistance in infants, when infected [22]. In another study conducted in South Africa, where only sdNVP was available for PMTCT, most children (69%) who had been infected despite sdNVP administration were infected in utero from mothers with lower CD4 and higher plasma viral load than mothers of uninfected children [23**]. It has also been observed that transmission after six months of life accounted for >85% of late postnatal infant HIV infections in this breastfeeding population and was also associated with higher baseline maternal viral load [24*]. The authors speculated that this pattern could have been influenced by the disappearance of NVP resistance virus six months after delivery and the emergence of wild-type virus, with probable better fitness to replicate in the breastmilk compartment.

Altogether, these studies demonstrate that advanced maternal ARV disease during pregnancy have negative consequences, not only on the MTCT rate, but also on disease progression and development of viral resistance in children infected despite sdNVP, clearly an inappropriate intervention for this population.

To summarize, these recent data confirm the safety of sdNVP use in the context of WHO recommendations but highlight the urgent need to implement PMTCT programmes allowing for effective ART in women who have the indication and for minimizing the overall risk of resistance by offering postpartum short-course ZDV+3TC [4].

Antiretroviral regimens for PMTCT via breastfeeding

There are currently two approaches for the use of ARV regimens to prevent MTCT during breastfeeding: providing ART to pregnant women and prolonged during lactation or providing post-exposure prophylaxis to the infant.

Some experiences of the first approach were reported during the 2007 IAS conference. In the AMATA study (Rwanda), all women received NNRTI-based ART starting after the second trimester of pregnancy and were given the choice between formula feeding (FF) and breastfeeding (BF) with weaning at 6 months [25]. About 57% of the women opted for FF. At 7 months of age, 1.6% of children were diagnosed with HIV infection, including six infections at birth and only one through breastfeeding. No significant difference in morbidity or in mortality was observed. In the MITRA PLUS study (Tanzania), an open-label non-randomized prospective cohort, women were treated with ZDV/3TC/NVP during late pregnancy and BF [26], from 34 weeks of gestation or earlier if the woman had indication. The infants received ZDV/3TC for one week after birth. Mothers were counselled on exclusive BF and encouraged to stop at six months. The cumulative proportion of HIV-1 infected infants was 5.0% (95% CI 3.2–7.0%) at 6 months. Thus, this strategy appeared in line with the findings from the DREAM cohort (Mozambique): HIV RNA levels in breastmilk were significantly lower in women on ART than in untreated women (median of 2.3 vs. 3.4 log at delivery and 1.9 vs. 3.6 log at day 7) [27].

Thus, these two cohort studies showed a low HIV-1 transmission rate in breastfeeding populations receiving ART, with the advantage that mothers eligible for ART benefited from treatment for their own health as well. However, using ART as a prophylactic regimen in women who are not eligible for a treatment for themselves raises the issue of its subsequent cessation. A Thailand study [28] proposed to assess the impact of stopping ART postpartum, comparing two historical cohorts of women not eligible for ART for themselves and followed-up for 15 months after delivery. The first one received ZDV from 32 weeks and sdNVP and the second one ZDV/3TC/NVP from 28 weeks +1 week ZDV/3TC. They did not observe any difference in terms of death/clinical progression between the two groups.

However, women with a CD4 count<350 cells/mm3 were at higher risk for ART need shortly after delivery suggesting that ART should not be stopped in this population.

Providing post-exposure prophylaxis to the infant, the second approach of use of ARV regimens to prevent MTCT during breastfeeding was reported in a recent publication from the Mashi Study [29**]. In this study, mothers received short-course ZDV antenatally and during labor. Mothers and infants were randomized to receive sdNVP or placebo. Infants were randomized to 6 months of BF and ZDV or formula feeding and ZDV for one month. The 7-month HIV infection rates were 9.0% in the first group and 5.6% in the second (p=0.04), but the cumulative mortality was higher in the second group. Finally both strategies had comparable HIV-free survival at 18 months.

Conclusion

The use of fully suppressive ART initiated during pregnancy and the breasfeeding period, even in women with no indication of treatment, is a potentially highly effective PMTCT strategy and this may constitute a very relevant alternative when formula feeding is not judged to be safe or well accepted. However, potential risks for women's health of interrupting ART after delivery and for infants' health of in utero continuous ART exposure are not fully ascertained. The increasing but still limited access to ARV may limit the implementation of such strategy and the risk of toxicity of NVP use in women with higher CD4 counts may require alternative drugs which are not widely available and closer monitoring. Antenatal care facilities should thus be strengthened to provide at least the preferred WHO recommended short-course PMTCT regimen for women with no treatment indication and effective referral to ART programmes for those women at high risk of HIV disease and mother-to-child transmission. It is thus likely that short-course have still a role to play in resource-limited settings for PMTCT, especially if the risk of NVP-induced resistance is controlled. Notwithstanding their role to be confirmed as a neonatal prophylaxis during breastfeeding.

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