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Abstract

Evaluation of: Giuliano M et al. Triple antiretroviral prophylaxis administered during pregnancy and after delivery significantly reduces breast milk viral load: a study within the drug resource enhancement against AIDS and malnutrition program. J Acquir Immune Defic Syndr, 44(3), 286-291 (2007).

Maternal highly active antiretroviral therapy (HAART) starting during the late prenatal period and prolonged during lactation is a potentially interesting strategy to prevent mother-to-child transmission of HIV through breastfeeding in Africa. In this report, Giuliano et al. showed that HIV-infected women treated with HAART from before delivery had lower cell-free HIV RNA load in breastmilk, and were less likely to have a detectable viral load in this compartment one week after delivery, when compared to untreated women. Antiretroviral therapy among HIV-infected breastfeeding mothers could thus be a promising strategy to prevent HIV transmission through breastmilk in Africa if further larger studies confirm its safety. This strategy could also provide a link between prevention and care, since maternal HAART provided in pregnancy and during the breastfeeding period can be thereafter continued among women who meet the criteria for their own health.

Introduction

In this article, the recent publication by Giuliano et al. will be reviewed [1]. The efficacy of short-course peri-partum antiretroviral regimens in preventing mother-to-child transmission of HIV around delivery has been demonstrated in Africa [2]. But the subsequent risk of postnatal HIV transmission remains responsible for a great number of pediatric HIV infections in these settings, where breastfeeding is widely practiced for long durations [3,4]. Modifications of infant feeding practices in terms of breastfeeding duration (complete avoidance of breastfeeding or early weaning) and pattern (promotion of exclusive breastfeeding) aim to reduce this risk [5]. Given appropriate nutritional counseling and care, access to clean water, and a supply of breastmilk substitutes, these alternatives to prolonged breast-feeding can be safe interventions to prevent mother-to-child transmission of HIV in urban African settings [6]. However formula feeding can be associated with higher mortality, morbidity, and stigma in less supported field settings [7,8]. There is therefore an urgent need for interventions that could allow safe breastfeeding, especially when water safety and provision of breastmilk substitutes is not assured.

Maternal highly active antiretroviral therapy (HAART) starting during the late prenatal period and prolonged during lactation constitutes one of these interventions and deserves consideration [9]. The presence of detectable HIV viral load in breastmilk is associated with an increased risk of postnatal HIV transmission [10,11]. By lowering viral load in breastmilk, maternal HAART could therefore reduce substantially reduce the risk of HIV transmission, but to date, the effectiveness of HAART in reducing breastmilk viral load is unknown. The study conducted by Giuliano et al. assessed the potential role of maternal HAART in reducing the risk of breastfeeding-associated HIV transmission.

Results from the article

The study was conducted in Mozambique among HIV-infected pregnant women recruited antenatally in two different sites. Women recruited in the first site (n=40), where HAART was available, received a combination of zidovudine, lamivudine and nevirapine from 28 weeks of gestational age until one month post-partum, and constituted the treated group. Women recruited in the second site (n=40), where HAART was not available, were diagnosed as HIV-infected during delivery and constituted the untreated group. These later women were thereafter included in the program of access to antiretroviral therapy available in the first site, and received HAART when they met the criteria for treatment.

Women from both groups were recommended not to breastfeed and were provided with breastmilk substitutes. For research purposes, they were asked to express milk with breast pumps within three days after delivery, and one week after delivery. The Amplicor assay was used to measure maternal plasma HIV RNA levels, and to quantify cell-free HIV RNA loads in whole breastmilk and its different fractions (lipid layer and skim milk). After extraction of the DNA, the cell-associated HIV DNA load in breastmilk was assessed by real-time PCR technology. The concentration of each antiretroviral drug was measured in plasma and breastmilk of treated women.

The median CD4 count at delivery was 347 cells/ml among untreated women, and 551 among the treated ones ($p<0.001$). The median duration on HAART in this later group was 85 days, ranging from 4 to 165 days. Cell-free HIV RNA levels in plasma and all breastmilk fractions were consistently lower in treated than untreated women (for instance 1.9 vs. 3.6 log in whole milk one week after delivery, $p<0.001$). These levels were at least 1 log lower in the breastmilk than in the plasma of untreated women, but similar in the treated ones. At one week after delivery, 72% and 43% of treated women had HIV RNA levels below 400 and 50 copies/ml respectively, whereas these proportion were 18% and 13% among untreated women (differences statistically significant). After adjustment on CD4 count at delivery, treated women were 4 times more likely to have HIV RNA levels below 50 cells/ml in breastmilk one week after delivery than untreated women (95% confidence interval: 1.2-13.0). Fewer women tended to have detectable cell-associated DNA in breastmilk in the treated compared to the untreated group (32% vs. 55%, $p=0.07$), and the mean DNA loads tended to be lower in treated women with detectable viral load than in the untreated ones. Concerning the drug concentrations seven days after delivery, they were less elevated in breastmilk than plasma for nevirapine, more elevated for lamivudine, and similar for zidovudine. Moreover, a non-negligible proportion of women had measurable drug concentrations in breastmilk, whereas these concentrations were undetectable in plasma at the same time (around 10% for nevirapine, and 20% for lamivudine and zidovudine).

Significance of the results

Although approved by the National Ethical Committee of Mozambique, this study raises some ethical concerns that need to be addressed. First, untreated women were recruited into this research study at a site where no antiretroviral prophylaxis was administrated to pregnant women, and were only later given the opportunity to enter a programme of access to care providing HAART, if meeting the criteria for treatment. More should have been done to

prevent the risk of mother-to-child transmission of HIV among these women. Second, breastmilk was expressed during one week postpartum, but women were instructed not to breastfeed their infants, and they were provided free formula. The authors do not mention for how long the breastmilk substitutes were provided, nor if these women had chosen not to breastfeed, or if they had access to a specific nutritional counseling to safely prepare the formula feeding. These women were producing milk while not breastfeeding and were thus at high risk of suffering from breast engorgement, unless they had been provided with a drug inhibiting lactation at the end of the study, which is not mentioned in the article. There is ample evidence that such practices favors mixed feeding, e.g. giving at the same time both breastmilk and infant formula to the child, which substantially increases the risk of postnatal HIV transmission [12].

Despite these concerns, this study showed that HIV-infected women treated with HAART had lower cell-free HIV RNA load in breastmilk, and were less likely to have a detectable viral load in this compartment, when compared to untreated women. HAART had been initiated in the third trimester of pregnancy and continued for a median duration of three months, irrespective of maternal CD4 count value at delivery, e.g. among both women eligible and non-eligible for antiretroviral treatment. These results are in line with those previously reported on a smaller sample sized study conducted in Botswana among women with baseline CD4 count below 200 cells/ml and treated with HAART before and/or after delivery, with breastmilk samples collected a median 3 months after HAART initiation [13]. In this later study, HAART had no apparent effect on cell-associated HIV DNA load in breastmilk. However, in Giuliano et al. study, although non-significant statistically, cell-associated viral load tended to be less often detected in breastmilk of women treated with HAART than in untreated women. This lack of effect could be explained by the fact that the duration of HAART treatment may have been too short to have reduced the cell-associated viral load in breastmilk [14]. The effect of HAART on reducing cell-free HIV RNA viral load in breastmilk provides encouraging results suggesting that HAART may reduce substantially reduce HIV transmission through breastfeeding. But more than half of the women treated with HAART still had detectable cell-free viral load in their whole milk, which implies the risk of postnatal mother-to-child transmission of HIV may persist among these women. The fact that the effect of HAART was less apparent on HIV DNA load is also of concern, since this cell-associated viral load has been reported to be more often associated with HIV transmission through breastmilk than cell-free viral load [11,15].

Nevirapine, lamivudine and zidovudine were all present in breastmilk of HAART treated women. Detectable concentrations of these drugs in breastmilk were found in the majority of women one week after delivery, despite some of them having undetectable plasma levels at the same time. According to Giuliano et al., this result suggests a possible lag in elimination of drugs in breastmilk. It would have been interesting to understand the pharmacokinetics of these antiretrovirals in the plasma of breastfed infants; this information has been provided in only one study so far [16]. The antiretrovirals contained in breastmilk and ingested by the infants could indeed provide a prophylaxis against the risk of HIV postnatal transmission. But it could also be detrimental for the therapy options of infected children.

Future perspective

This study adds to the growing body of knowledge that antiretroviral therapy among HIV-infected breastfeeding mothers is a promising strategy to prevent HIV transmission through breastmilk in Africa. This strategy could also provide a link between prevention and care, since maternal HAART provided in pregnancy and during the breastfeeding period can be thereafter continued among women who meet the criteria for their own health.

But there are many questions that remain concerning the safety and efficacy of this intervention (Box 1). Larger sample sized longitudinal studies are needed to address these issues. The question of the safety of maternal HAART for the infants is crucial as the development of resistance to antiretrovirals is possible since these infants will be receiving suboptimal levels of drugs for relatively long periods [17]. The issue of the drug toxicity in infants exposed to antiretrovirals through breastfeeding remains also unsolved, as well as the impact of this exposure on infant growth, morbidity and mortality. The effect of HAART exposure on haematological and immunological markers in breastfed infants also needs further investigation [18,19]. The evolution of HIV cell-free and cell associated viral loads in breastmilk needs to be assessed throughout the breastfeeding period to better understand the pathogenesis of postnatal HIV transmission and its potential prevention using antiretroviral drugs. These evaluations need to be completed by reliable estimations of the risk of HIV transmission through breastmilk among women treated with HAART.

Several cohort studies using a variety of antiretroviral regimens are now in development or being conducted in Africa. The implications of these studies will be particularly useful in the current context of the HIV epidemic to tailor appropriate interventions to prevent mother-to-child transmission of HIV through breastmilk in settings with high HIV prevalence.

Box 1. Relevant questions that need to be addressed before considering HAART among breastfeeding mothers as a solution to the problem of HIV transmission through breastmilk in Africa.

- Will HAART lower HIV cell-free and cell associated viral loads in breastmilk, or even make them undetectable?
- Will cell-free and cell associated viral loads be lowered in breastmilk to the same extent as in the blood compartment?
- Which antiretroviral drugs will diffuse in the breastmilk compartment and then in the plasma of breastfed infants? In what quantity?
- Can the risk of postnatal HIV transmission be eliminated if women are treated with HAART?
- Does maternal HAART need to be completed with interventions promoting safer breastfeeding practices, such as exclusive breastfeeding or avoidance of breastfeeding beyond 6 months of age?
- What will be the consequences of maternal HAART in terms of infant drug toxicities and selection of resistance mutations in infants?
- What will be the effect of maternal HAART on haematological and immunological markers in breastfed infants?
- What will be the impact of antiretroviral exposure through breastfeeding on infant growth, morbidity and mortality?

Executive summary

Background

- There is an urgent need for interventions that could allow safe breastfeeding in Africa, especially when water safety and furniture of breastmilk substitutes is not assured.
- By lowering viral load in breastmilk, maternal HAART could reduce substantially reduce the risk of HIV transmission and constitute one of these interventions, but to date, the effectiveness of HAART in reducing breastmilk viral load is unknown.

Methods

- Study conducted in Mozambique among HIV-infected pregnant women: 40 received HAART from 28 weeks of gestational age until one month post-partum, while 40 were not treated with HAART.
- Cell free HIV RNA and cell-associated HIV DNA loads were measured in breastmilk 3 days and 7 days after delivery.
- The concentration of each antiretroviral drug was measured in plasma and breastmilk of treated women.

Main findings

- Women treated with HAART had lower cell-free viral load in breastmilk, and were 4 times more likely to have undetectable HIV RNA levels in breastmilk one week after delivery.
- Detectable concentrations of antiretroviral drugs in breastmilk were found in the majority of women, despite some of them having undetectable plasma levels at the same time.

Conclusion and future perspective

- Antiretroviral therapy among HIV-infected breastfeeding mothers is a promising strategy to prevent HIV transmission through breastmilk in Africa.
- But there are many questions concerning the safety and efficacy of this intervention that need to addressed before considering HAART among breastfeeding mothers as a solution to the problem of HIV transmission through breastmilk in Africa.

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