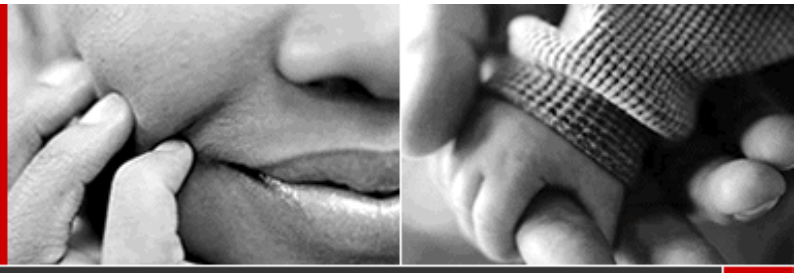

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Healthcare Professional Newsletter

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The conundrum of infant feeding for HIV infected women continues

Breastfeeding is an important intervention in the reduction of infant mortality.
Breastfeeding can potentially prevent up to 13% of child deaths. (1, 2) In an effort to improve the uptake and support for breastfeeding UNICEF launched the "Baby Friendly Hospital" initiative in 1991. This program encourages breastfeeding and actively discourages replacement feeding, bottles and artificial teats.
(http://www.unicef.org/programme/breastfeeding/baby.htm).

What we have learned about breastfeeding associated HIV transmission
The first case of postnatal transmission of HIV through breastfeeding was published in 1985. (3) This initiated a heated debate on the risks and benefits of breast and replacement (formula) feeding for the HIV-exposed infants and also the effect of replacement feeding on breastfeeding in the general population. It was clear from the start that mothers, especially those with little access to resources and support, faced a difficult choice.

Subsequent lessons:(4)(5)(6)

1. The risk of transmission relates to the levels of HIV in breast milk. Higher maternal plasma viral load, lower CD4 count, lower maternal vitamin A, infrequent emptying and mastitis are also risk factors.
2. Although the majority of transmission occurs early in breastfeeding, the risk is cumulative.
3. Where breastfeeding infants are exposed to mixed feeding within the first 2 months of life the risk of transmission increases. Mixed feeding with solids has a 2.9 fold increase in the transmission risk in the first 6 months of life.
4. The viral load in breast milk increases during weaning with a potential increase in the risk of transmission in this time, especially when the weaning is accelerated.
5. Several studies of low resource settings showed that replacement fed infants and infants where breastfeeding discontinued early were at high risk of malnutrition and non-HIV related infectious morbidity and mortality.

Can breastfeeding be made safe?
There are ongoing efforts to facilitate safer breastfeeding. Giving either the mother combination antiretroviral therapy (cART) or individual antiretroviral drugs (ARVs) to the infant successfully reduces the risk of HIV transmission. Infant nevirapine (NVP) emerged as a safe and cost effective public health intervention in multicenter studies from Asia and Africa. This strategy, now also used in the South African public sector advises once daily NVP for the first 6 weeks of life in all infants. Where the mothers do not requiring cART for their own health, NVP is continued in the infant for the duration of breastfeeding. If mothers are on cART, NVP is discontinued at 6 weeks. Initial NVP dosing is based on birth weight and subsequent dosing on age. (6) Dosages for preterm and low birth weight infants have not been established.

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Early diagnostic testing is still recommended. Where the 6-week PCR is negative, breastfeeding is encouraged for the first year of life followed by weaning and retesting 6 weeks after the last exposure. Health care providers must also test children earlier if there is a clinical suspicion. In HIV infected infants, breastfeeding should be continued for as long as possible. Breastfeeding should be exclusive until 6 months of age, after which supplemental feeding, including solids should be commenced. This normal transition does not constitute mixed feeding. It is important to remember that cotrimoxazole should be continued for the duration of breastfeeding regardless of the results of the early HIV PCR and this can only be discontinued once the infant has weaned and follow-up testing is negative.

Although this strategy is attractive in low resource settings where the morbidity and mortality associated with replacement feeding is very high, it is important to note that there will still be HIV transmission, although fewer cases. With extended NVP and maternal cART breastfeeding-associated transmission between 6 weeks and 6 months was 2.6% and 1.1% respectively in 1 large study. (7). Also of note, these strategies do not consider maternal viral suppression or prior failure of maternal therapy.

In addition children, who convert while breast feeding and taking extended nevirapine will not only have the expected NVP and efavirenz resistance, but may also develop mutations to second generation NNRTI such as etravirine. (8) For mothers on cART, babies are exposed to low levels of ARV secreted in the milk, possibly contributing to resistance in infants becoming HIV-infected. This resistance will limit therapeutic options for the infants. Also, the long-term implications of prolonged ARV exposure over months through breast milk are unknown.

In the Public sector in South Africa access to free formula is currently phasing out and all HIV-infected women will be supported to breastfeed.

Should breastfeeding with ARV protection be encouraged in the private sector?
In mothers with reliable access to formula milk, the necessary means to support safe replacement feeds and the support from family, it will be prudent to advise against breastfeeding to absolutely reduce the risk of postnatal HIV transmission. Where the very early PCR (24-48 hours of life) is positive, one can still establish breastfeeding. Achieving Baby Friendly status is a goal for many public and private institutions, possibly harming mothers needing to formula feed for medical indications. HIV infected women should be carefully counseled on formula preparation and cleaning of bottles and teats. The substantial risk of mixed feeding should be made very clear by obstetric and paediatric staff. Issues around disclosure in the home are of particular importance and should be addressed.

Formula-fed HIV exposed infants are still at high risk for gastrointestinal and respiratory infections. This situation will be aggravated because of the lack of protection usually provided by breastfeeding. Therefore it is extremely important to ensure access to all vaccinations, especially rotavirus.

Soya-based feeds should not be given without a specific indication. Weaning and introduction of solids should also be conducted as for HIV unexposed infants.

Conclusion
Despite the reduced risk, breastfeeding remains a potential (but diminishing) source of postnatal HIV infection. Mothers with secure access to formula should be advised to use infant formula. Mothers with excellent virological control and viral load below the limit of detection on an ultra-sensitive assay may elect to breastfeed and in all likelihood, will do so safely.

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Tenofovir and aminoglycosides

Tenofovir causes renal failure or tubular wasting syndrome in a minority of patients taking the drug. A risk factor for this nephrotoxicity is simultaneous use of other nephrotoxic agents. The package insert for tenofovir advise that it 'should be avoided with concurrent or recent use of a nephrotoxic agent'.

Aminoglycosides are used in the treatment of TB: in regimen 2 for retreatment cases (2 months of streptomycin) and in the intensive phase of MDR TB treatment (typically 4-6 months of kanamycin or amikacin). Aminoglycosides are potentially nephrotoxic particularly when taken for long periods and their toxicity occurs at the same site in the kidney as tenofovir (cells of the proximal tubules). We advise against the combination of tenofovir and aminoglycosides. Aminoglycosides are a critical part of the MDR TB regimen and cannot be omitted thus an alternative NRTI to tenofovir (eg. AZT, abacavir or d4T) should be used for the period that the patient is on kanamycin or amikacin. In contrast, in patients requiring regimen 2 TB treatment who are on tenofovir, consideration should be given to omitting streptomycin as there is little evidence that it improves outcomes in retreatment TB treatment regimens. In situations where the combination of tenofovir and aminoglycosides cannot be avoided then creatinine should be monitored closely (we suggest every 2 weeks).

For a more detailed discussion of this issue clinicians are referred to an article in the Southern African Journal of HIV Medicine 2011:12(1) entitled "The risks of concurrent treatment with tenofovir and aminoglycosides in patients with HIV-associated tuberculosis" that can be accessed via the following url:
http://www.sajhivmed.org.za/index.php/sajhivmed/article/view/713/540

Similarly, clinicians should prescribe long-term NSAIDs with caution in patients on tenofovir. Short term NSAID use is unlikely to be problematic, but if NSAIDs need to be used long-term creatinine should be monitored more frequently, for example every 3 months.

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What if my patient's CD4 count does not rise on ART?

After starting ART, providing there is optimal adherence, the majority of patients will have a reduction in plasma HIV viral load to below the limits of detection by 6 months. This is accompanied by a rise in CD4 count that is biphasic: an initial rapid rise in the first month due to recirculation of memory CD4 cells from sites of immune activation into blood (average rise of around 75 cells/µl in the first month) followed by a more gradual rise thereafter which reflects regeneration of naïve CD4 cells (average rise of around 80 cells/µl per year). However, CD4 responses are highly variable. Amongst patients who achieve and sustain virological suppression a substantial minority (10-20%) will experience no rise in CD4 count or a very delayed or a suboptimal rise in CD4 count. This phenomenon has been termed "immunologic discordance".

The reason why certain patients do not reconstitute their CD4 cell count despite viral suppression appears to be related to several factors, including the damage that has been done to the thymus during chronic HIV infection depleting its ability to regenerate naïve T-cells and immune activation on ART driving CD4 T-cell apoptosis. A major risk factor for this immunologic discordance is older age when starting ART.

Various approaches to managing such patients have been proposed or studied. These include intensifying or switching ART to a protease inhibitor-based regimen (PIs have anti-apoptotic effects that could theoretically reduce T-cell loss) and adjunctive interleukin-2 therapy. However, none of these approaches have been demonstrated in clinical studies to have a durable effect on CD4 count in these patients. Patients with immunologic discordance have a better prognosis compared to untreated patients with the same CD4 count, but their risk for mortality or AIDS progression is 2 to 3-fold higher than patients who have an adequate CD4 response on ART. Despite this we do not advise switching or intensifying ART because there is no evidence of benefit. We advise continuing the current ART regimen and cotrimoxazole prophylaxis if the CD4 count remains <200.

In these patients (and patients whose CD4 count drops despite viral suppression on ART), if they are clinically unwell it is also important to consider an opportunistic infection (especially TB) or lymphoma that may cause lymphopaenia. A very rare explanation for poor CD4 response is that the viral load assay being used is not detecting virological failure because of primer mismatch. If there is clinical disease progression despite virological suppression in patients with poor CD4 responses repeating the viral load using a different assay can be considered in consultation with AfA.

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Isoniazid preventive therapy

Tuberculosis is the commonest cause of morbidity and mortality among HIV-infected people in Southern Africa. Many clinical trials in HIV-infected adults have shown that isoniazid preventive therapy (IPT) effectively prevents tuberculosis[1]. Despite this evidence, global coverage of IPT among people living with HIV was estimated to be <1% by the end of 2010[2].

Several major barriers to widespread implementation of IPT have been identified. First, IPT is only effective in patients with positive tuberculin skin tests (TSTs)[1] – in the context of HIV infection a Mantoux of ≥5 mm induration is considered positive. TSTs are difficult to perform in resource-poor settings. Therefore WHO have recommended that TSTs are not required in populations with high tuberculosis prevalence as there is a net population benefit[3]. However, in the Southern African private sector tuberculosis prevalence is probably not as high as in the public sector. Furthermore, TST can easily be performed by private pathology laboratories or by trained health care workers. Therefore AfA recommends IPT only in patients with positive TSTs.

Second, patients with active tuberculosis could inadvertently be exposed to isoniazid monotherapy, which would result in resistance. It is difficult to diagnose tuberculosis in sick HIV-infected adults, but ruling out tuberculosis in ambulant populations turns out to be much simpler. If all of the following four symptoms are absent then tuberculosis is effectively ruled out: active cough (any duration), night sweats, fever, and weight loss[4]. It is not necessary to do a chest x-ray or sputum tests (PCR, smear or culture) if these four symptoms are absent.

Third, a major limitation of IPT is that the duration of benefit with the standard 6 month regimen is lost after 1-2 years[5,6,7]. A large Botswana study comparing the efficacy of 6 months with 36 months IPT has recently been reported[7]. Overall 36 months use of IPT was more effective at preventing TB. All of the benefit was seen in TST positive participants, which is in keeping with all prior IPT studies. The magnitude of the reduction in tuberculosis in the 36 month IPT group was 92% among TST positives, which is a dramatic effect. The prolonged IPT regimen was well tolerated, except in patients with negative TSTs, which is difficult to explain. AfA strongly recommends 36 months IPT, but this must only be given to TST positive patients.

The use of IPT in patients on ART is controversial. Several retrospective cohorts have been published showing additive benefit of IPT and ART in preventing tuberculosis, but in some of the studies the IPT was completed prior to ART. There is potential for more harm than good if IPT is started in patients on ART as the number needed to harm (about 1 in 100 will develop hepatitis from IPT) may exceed the number needed to treat to prevent a case of tuberculosis. A South African randomised controlled trial evaluating the effect of IPT in patients on ART has just been completed and results should be available in 6 months. Until then we do not recommend starting IPT in patients on ART, but patients started on IPT should complete the course if ART needs to be started before the IPT course is complete.

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