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Infant feeding policy debated at the Conference on Retroviruses and Opportunistic Infections

The key reports and related studies

The key findings of the studies have been described recently on www.aidsmap.com. However, there were a number of smaller trials, mathematical models and sub-studies presented at the conference that may help bring the picture a little more into focus.

While the WHO guidelines recommend that HIV-infected mothers avoid breastfeeding whenever replacement-feeding options are "AFASS" (accessible, feasible, affordable, sustainable and safe), (see

<http://www.aidsmap.com/en/news/1C6972FE-B40B-42BC-BC71-2BA36589535E.asp>) the recent outbreak of diarrhoea and increase in infant mortality in formula fed babies in Botswana demonstrated how difficult it is to for even middle-income developing countries to consistently meet AFASS criteria through their public health programmes. However, several speakers noted that there have been other studies in Africa that reported very good results with formula feeding, most notably the Ditrane Plus studies in the Ivory Coast (see <http://www.aidsmap.com/en/news/4B3A0A9D-2500-48E2-8A5E-4C490E212AED.asp>).

Furthermore, the rainy season in Botswana was particularly heavy that year, and may indicate a singular event. However, Dr Charles van der Horst, of the University of North Carolina Chapel Hill, and the primary investigator of the BAN study in Malawi, said that mortality increases after every rainy season in that setting. "Even if I didn't have a calendar, I know when the rainy season starts in Lilongwe because all of a sudden I start seeing dead babies in my study. HIV-negative dead babies. And it's because the rainy season is starting. They are crawling around getting mixed foods which are contaminated and outbreaks," he said.

The other studies presented at the conference were performed in settings where formula feeding from birth was, for one reason or another, deemed impractical or inherently unsafe. The emphasis of these reports was when or how mothers should discontinue breastfeeding their infants.

The Zambia Exclusive Breastfeeding Study (ZEBS) concluded that early abrupt weaning (at four months) does not improve HIV-free survival among HIV-exposed infants — and is harmful to children who are already HIV-infected (full report here:

<http://www.aidsmap.com/en/news/4ACFB8CE-DF88-4385-9C18-33BBFD9FF24B.asp>).

This conclusion differed somewhat from what had been predicted by mathematical models, one of which was presented in a poster session (Atashili). The model calculated HIV transmission, mortality and HIV-free survival rates for several different modes of infant feeding: exclusive formula feeding, exclusive breastfeeding for four months and exclusive breastfeeding for six months — based on perfect and imperfect adherence to each feeding model

Even though it derived its formulae on mortality risk at month 24 from studies that had been conducted in Kenya, Uganda and South Africa, this model could have under-estimated the risk of mortality

associated with breastfeeding avoidance in most settings, given the findings of ZEBS and other reports of higher mortality in infants weaned before six months in areas where HIV was not a major public health problem. In fact, the model calculated roughly equivalent numbers of deaths would occur for each mode of infant feeding.

However, the model predicted that weaning at four months should have improved HIV-free survival at 24 months in comparison with prolonged breastfeeding — and this was plainly not the case in ZEBS. But this was not solely because survival in the abrupt weaning arm was so low, but because early weaning did not reduce HIV transmission as much as had been anticipated.

In fact, some experts suggested that abrupt weaning itself might directly increase the risk of transmission.

"Since breastfeeding is going to continue in the context of HIV, understanding the viral dynamics of HIV in breastmilk, and understanding the risk factors of MTCT of HIV is important," said Katherine Semrau of Boston University, who presented an analysis of some of the factors associated with breastfeeding and MTCT in the first 138 mother/infant pairs in ZEBS.

32 out of the first 138 infants became HIV-infected (as measured by HIV-DNA PCR) over the course of the study). Several factors that have been previously noted in other studies were significantly associated with a higher risk of transmission, such as low haemoglobin levels (<10 g/dl), lower CD4 cell counts and higher plasma viral loads. Levels of HIV RNA (consistently above 50 copies per ml) in breastmilk were also highly associated with transmission (39% of women had consistently detectable viral load and a significantly higher risk of MTCT than women who were either inconsistent or non-shedders (OR = 4.3, 95%CI 2.04 to 9.44).

The breast is typically a conserved compartment to protect breastmilk, and viral load levels there do not always directly correlate with plasma viral load (although higher plasma viral load does tend to be associated with detectable virus in breastmilk). Approximately a third of the women in the study did not have detectable breastmilk viral load indicating that the breastmilk epithelium was effectively preventing HIV from entering the milk. None of the women without detectable viral load in their breastmilk transmitted HIV.

However, a relationship between levels of breast milk HIV RNA and breastmilk sodium (Na) levels was also observed. Na is a marker for epithelial permeability in breast tissue, and although it is typically elevated at the start of lactation, it later declines, typically until weaning. But in this study, when Na was elevated (≥ 13 mM/L) at four months (in 7% of the women), it was associated both with higher levels of viral load in breastmilk viral load and predicted transmission ($p = 0.005$).

Given that half of the women would have been randomised to abrupt weaning, the increased Na at this point could have been the result of abrupt weaning. If abrupt weaning reduces breast membrane integrity, then it could lead to increased viral load and the significantly increase the risk of transmission to an infant who is not yet entirely weaned.

According to another of the investigators of the ZEBS study, Dr Donald Thea of Boston University, "One of the observations that we had, when we looked at viral load in the breastmilk two weeks after weaning had occurred, we saw that there was a one log increase in the amount of virus in breastmilk, implying that there really are factors associated with the mode of weaning that we really need to look into further."

The four other studies, demonstrated that rapid weaning could put HIV-negative infants at greater risk of life-threatening events

than was seen in historical controls where mothers weaned infants normally. (full report here: <http://www.aidsmap.com/en/news/5C963569-20A5-4077-94FF-AE4BE0911886.asp>).

In one of these studies, conducted in Uganda, weaning occurred quite early (at a median of three months) – often just after the mother learned that her infant was HIV-negative. (Although in light of the high rate of transmission around the time of weaning in the ZEBS study, these infants should perhaps be retested). Dr Carolyn Onyango, who presented the findings from Uganda, noted that mothers were being advised to wean upon learning the infant's status – or were often trying to devise other ways to prevent transmission. For example, one woman said that she was going to give her infant black tea to try to keep the baby from becoming infected.

Finally, the three studies demonstrated similarly increased rates of life-threatening diarrhoea even in infants stopped breastfeeding at or shortly before six months – the period of time exclusive breastfeeding is now recommended for women who can't use alternatives. While underscoring the dangers of weaning, it is unclear exactly what safer alternative there might be at this point in a child's life. Furthermore, because these studies were not randomised or controlled, it is impossible to say whether such outcomes as HIV-free survival would have been better in children if exposed to long-term mixed feeding.

Rather, these studies underscore how crucial it is to provide HIV-positive mothers with adequate support. The investigators of these studies tended to stress the need to do more to improve hygiene, and access to safe, clean water. According to Dr Michael Thigden of the US Centre for Disease Control: "Counselling strategies to assist mothers in safe preparation of nutritional weaning foods in resource-limited settings are urgently needed."

Meanwhile, Dr van der Horst stressed the necessity of providing infants extra sources of nutrition. "We asked the women before we started BAN about weaning at six months, and we also did a nutritional study about what they were giving the babies in terms of complementary feeds, and what they would give if they weaned, and it was clear that these babies would die if they didn't get something in addition at six months," he said.

WHO emphasises the mother's individual circumstances

But many of the experts present continued to have differences of opinion about how best to counsel mothers with HIV to feed their children.

The WHO revised guidance recommends tailoring guidance to the mother's individual situation. Dr. Peggy Henderson of the WHO explained the new recommendations at the conference.

"We know that breast feeding is generally the perfect food, providing all the nutrients a baby needs for the first six months of life. It's always ready and it's perfectly hygienic.

However, it does sometimes transmit HIV to the baby. On the other hand, not breast feeding exposes the child to all sorts of risks, including increased risk of mortality from diarrhea and other diseases and malnutrition, especially if breast feeding is not done safely or hygienically," said Dr Henderson. "To help an HIV positive woman make the decision on infant feeding, she needs help from someone trained, doing assessment on her situation."

Dr Henderson offered some clarification on the AFASS criteria that could help counselors perform such an assessment. "For

replacement feeding to be better for an HIV-exposed infant than breast feeding, it needs to be what we call AFASS which means:

- "Acceptable to the mother and it needs to be culturally acceptable for her not to breastfeed.
- Feasible - in other words, the mother has to be able to keep water to feed in the middle of the night.
- Affordable, which means either the government provides it for free or at a subsidised price, or the mother and her family can afford to purchase it without jeopardising the family's finances.
- Sustainable - as you saw in Botswana, there wasn't always formula available at the clinics. Or if the mother buys it, it means that it has to always be in the shops and always close to her, and
- Safe. Which means the water has to be safe or she has to be able to make that water safe. There have to be generally good hygienic conditions." Safety may also need to be reassessed regularly.

In addition to the mother's personal circumstances, the assessment should take into consideration the existing local healthcare capacity as well.

"What is new here is that there is greater consideration about the health services," said Professor Taha Taha of the Bloomberg School of Medicine at John's Hopkins University during another session. "What really exists, are the health services available? Will she be able to get to the clinic if the baby gets sick?"

"We also need to look at what counselling and support is available to the mother to help her replacement feed safely and answer her questions," said Dr Henderson. "Of course, this is not to say that a woman that chooses to exclusively breastfeed, doesn't also need a lot of counselling and support also."

However, some are concerned that these assessments could prove difficult in practice.

"I personally believe the assessment of the AFASS criteria is a bit problematic," said Prof Taha. "Is it left to the woman, left to the counsellor, left to the nurse? Who should decide this?"

Another problem with such assessments is that at present the fear of HIV tends to be out of proportion to the actual risk of morbidity and mortality from unsafe and inadequate feeding. If left up to most mothers, counsellors and even nationally programmes, there could be a bias towards avoidance of breastfeeding before it is truly AFASS, an unrealistic assessment of a programme's ability to provide replacement feeding consistently or the mothers ability to keep the baby's surroundings hygienic enough, particularly during rainy seasons.

Making exclusive breastfeeding AFASS

Of course, countries could put greater efforts into strengthening the capacity to make replacement feeding AFASS. But experts such as Dr Hoosen Coovadia of the University of KwaZulu Natal questioned the wisdom of this approach as a policy choice.

"So you might ask, well, why not choose formula? The problem with choosing formula is that it doesn't come free," said Dr Coovadia. "It costs a lot of money. In my part of the world, it accounts for 30% of our budget for PMTCT. And there are problems with supply and there's a whole host of problems about formula feeding. And if there's no difference, why should we spend more money on things that might cause us more problems?"

Dr Coovadia asserted that, in most African countries, the risk of mortality clearly outweighs the risk of HIV transmission. "If you absolutely had to choose, what would be the outcome? Here are two estimates. If you choose breastfeeding, you would of course have HIV infection. You would have about 300,000 per year in the world.

But if you avoided breastfeeding, the mortality would be about 1.5 million per year. So on the balance of probabilities for poor women in the developing world, there is no other choice than to breastfeed their infants. You shouldn't devise policies for the rich few. There are some but the majority of HIV-infected women are poor."

However, with improving socioeconomic conditions, some developing countries could be approaching health system infrastructures similar to what exists in the industrialised world. Could these countries be ready to recommend formula feeding?

Dr Coovadia suggested one way of gauging this would be to refer to the local infant mortality rate (IMR).

"If your IMR is high, more than 25 per 1000 live births, then you should choose exclusively breastfeeding for six months. And if your IMR is below 25 per 1000 live births, you should choose replacement feeding from birth. Now if you look at South Africa, there is not a single province in the country which has an IMR of less than 25. And yet we provide free formula for all our HIV-exposed babies," he said.

Dr Coovadia believes that efforts should instead focus on reducing transmission from breastfeeding and to make exclusive breastfeeding AFASS.

But first, he stressed "any woman who comes to you clinic with a low CD4 cell count deserves ART for herself. So we can solve that problem. I'm not quite sure what will happen in terms of HIV transmission but it is the right of anyone with a low CD4 cell count. So antenatal clinics should have ART available."

Many believe that ART will reduce HIV transmission in breastfeeding women — although experts are waiting for prospectively designed studies to demonstrate this conclusively. However, even if ART does prevent transmission in breastfeeding women, this poses a whole other set of problems.

Women with CD4 cell counts as high as 350 cells have been shown to transmit HIV by breastfeeding. While moves may be afoot to raise the CD4 threshold for treatment, most resource limited settings still use a threshold of 200 or at most 250 cells — which would leave a large pool of women not on treatment still at risk of transmitting HIV (again, if ART protects against breastmilk transmission). And even if the threshold for treatment is raised to 350 cells, what antiretrovirals would the women use? While women with CD4 cell counts below 250 cells could use nevirapine-based therapy, in women with higher CD4 cells there could be serious risk of hypersensitivity reactions. There are concerns regarding safety with efavirenz-based regimens (even if they have been safely used after the first trimester of pregnancy, use of the drug has not been well studied in young children — who could be exposed to biologically active drug concentrations through breastmilk).

Second line PI-based treatments such as *Kaletra* could be used as first-line therapy in breastfeeding women with higher CD4 cell counts, but this could be cost-prohibitive for many programmes. And little is known about how well protease inhibitors will penetrate breastmilk or whether biologically significant concentrations could be transferred to the breastfeeding infant.

Even the breastmilk pharmacokinetic data on more commonly used drugs, such as nevirapine, AZT and 3TC, are not so encouraging (Mirochnick). In an analysis of antiretroviral concentrations in the breastmilk and in exposed infants in the Kisumu Breastfeeding Study (KiBS) presented at the conference, breastmilk concentrations of nevirapine were about 70% of normal plasma levels. In most infants, the concentrations were above nevirapine's IC₅₀ but below therapeutic targets. Thus children who become infected could be at risk of nevirapine resistance. On the other hand, some infants were found to have NVP plasma

concentrations in excess of adult target concentrations — which could put them at serious risk of toxicity.

3TC concentrations on the other hand were extremely high in the breastmilk — though below optimal plasma concentrations in the infant. Finally, AZT concentrations were extremely low in the breastmilk and infant concentrations were almost always below the limit of quantification.

Similar findings for nevirapine and 3TC levels in breast milk (but not for AZT) were reported from a Mozambique study of 40 women published in the *Journal of Acquired Immune Deficiency Syndromes* in March (Giuliano).

Thus, antiretroviral drugs could be transmitted in biologically significant concentrations via breastmilk to nursing infants but the pharmacokinetics of transfer via breastmilk will vary with individual drugs. What impact they might have on viral load in the breastmilk and transmission has yet to be seen — and may depend on the regimen being used.

Another approach to reducing HIV transmission through breastfeeding would be, in Dr Coovadia's words "to change the type of breastfeeding. There are many types but exclusive breastfeeding — which means, for heaven's sake, don't give water.... Studies show time and again, that exclusive breastfeeding reduces the risk of transmission. Those who exclusive breastfed for 6 months have a lower transmission rate than those who mix feed.

"We have to find ways to make exclusive breastfeeding socially acceptable— because there is stigma and discrimination," he said (and after years of telling HIV-positive women not to breastfeed, it could be difficult to now tell these same women that they should rather breastfeed); Financially affordable — and not to rely on handouts all the time, culturally Appropriate — because mixed feeding is a cultural practice that goes back hundreds if not thousands of years. We have to make it sustainable and we have to make it safe."

And after six months

Questions remain about what to do after six months of exclusive breastfeeding, how should the baby then be weaned and how should the child be fed?

Exclusively breastfeeding for a longer period of time isn't really an option. But there really is no such thing as exclusive breastfeeding beyond six months. According to Dr Coovadia, "no child is engineered by nature to survive only on breastmilk after six months."

Further operational research in each setting will have to be performed to help protect infants at this critical stage. "Must we give them chorine? Must we give them stoves? Money? The next series of studies must somehow address the improvement of broad social economic factors," said Dr Coovadia.

"I think it's very complex, I don't think we have the answers," said Dr Lynne Mofenson of the NIH who co-chaired the discussion session on early breastfeeding cessation. "Part of this discussion was to get people to question some of the things that have been going on. And I think we may have to wait until some of these studies are completed. But even then I think some of the focus of studies right now will be how to make breastfeeding safer during the period from 6 to 12 months."

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about HATiP

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The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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