

# HATiP

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# HIV treatment for mothers and children in Botswana: lessons from a dynamic programme

## The PMTCT protocol

For women who do not yet qualify for ART for their own health, AZT currently forms the cornerstone of Botswana's PMTCT programme, and is now given from week 28 of pregnancy onwards to HIV-positive women with CD4 cells over 200. Single-dose nevirapine (sd-NVP) is also currently given to women during labour, but because of concerns about the development of nevirapine-resistance (which could make the mother less likely to benefit from first-line treatment when she needs it for her own health), this component of the protocol is under review.

One option would be to add seven days of Combivir (AZT/3TC) after labour to reduce the development of nevirapine-resistance, but Botswana is instead leaning towards dropping sd-NVP from the regimen altogether, unless the mother did not have adequate AZT prophylaxis before labour.

According to Prof. Anabwani, during a consultation held in Botswana in April, a consensus was reached that "while theoretically possible, adding Combivir into the programme would present a lot of logistical difficulties," he said. In the meantime, data from Botswana's own Mashi study had demonstrated that maternal sd-NVP offered no significant reduction in HIV transmission to formula fed infants who are given sd-NVP at birth and one month of AZT.

"For those who had had adequate prophylaxis before labour, there was no need to give nevirapine because in that population, nevirapine would compromise the care of the receiving mothers without any added benefit, either for them or the babies," said Prof. Anabwani.

## Increasing the CD4 threshold for ART for pregnant women

Botswana is considering another major change in the PMTCT programme to improve both the outcomes for the mother and the child — increasing the CD4 threshold (currently at 200) for starting ART in pregnant mothers.

"Should we have triple therapy [ART] for all pregnant women?" Dr Gaolathe said during the conference. "Or if not, at least triple therapy for pregnant women up to CD4's of less than 350?"

ART is the norm for all HIV-infected pregnant women in most of Europe and the US, and has resulted in an HIV transmission rate of less than 2%. But adopting this as a norm in resource-limited settings would be expensive and difficult. Furthermore, data suggest that women with higher CD4 cell counts are unlikely to transmit HIV anyway (particularly on PMTCT).

"Those with lower CD4 cell counts [form the majority of transmitters] and one could justify giving them ART for their own sake while improving the efficacy of prevention," said Prof. Anabwani.

According to Professor Sheila Thlou, Botswana's Minister of Health, Botswana is definitely moving in the direction of raising the

CD4 threshold for ART for pregnant women with HIV — to at least 250 and perhaps higher.

## But which ART regimen to use?

However, some of the particulars still must be worked out such as the precise CD4 cut-off and regimen to use. Using the current first-line ART regimen, which is nevirapine-based, in women with CD4 cell counts above 250 has been associated with a ten-fold increase the risk of adverse events such as hepatotoxicity or life-threatening hypersensitivity reactions (Boehringer Ingelheim, 2004) (see

<http://www.aidsmap.com/en/news/C1316A81-32F9-4AA9-A94F-93E3EB4E0D0E.asp>). This could be particularly worrisome in resource-limited settings where it may be difficult to monitor liver function tests in a timely manner.

For example, at the World AIDS Conference in Toronto, researchers working in Malawi reported a number of serious adverse events among mothers with CD4 cells over 200 who were taking nevirapine-based ART. Within only 102.7 months of follow-up for 39 women on nevirapine with AZT/3TC, there were three cases of serious rash (including one near-fatal Stevens-Johnson Syndrome) and one case of clinical hepatitis. However, there were no such adverse events in women taking nelfinavir-based ART or only PMTCT ( $p < 0.0001$ ;  $p = 0.0134$ , respectively). Grade 3-4 neutropenia was significantly more common in the nevirapine cohort than in the other cohorts ( $p = 0.0051$ ;  $p < 0.0001$ , respectively) (Bramson).

Efavirenz-based regimens, on the other hand, are not recommended during pregnancy, particularly in the first trimester, because of significant central nervous birth defects observed in studies with monkeys (FDA 1998). Subsequently, birth defects have also been observed in efavirenz-exposed infants in the US antiretroviral pregnancy registry, though at roughly the same prevalence as seen in the American population (Koren). But there have been a few retrospective case reports of neural tube defects observed in human infants with exposure to efavirenz in the first trimester (Fundaro; De Santis).

However, after the period of organogenesis during the first trimester, the risk of birth defects is significantly lower — and most pregnant women in resource limited settings only present to the antenatal clinic after the first trimester. At the Botswana meeting, Dr Brian Gazzard of Chelsea Westminster said: "I think it's important to bear in mind that in the prospective studies, so far [excess teratogenicity] has not been seen. Now it doesn't prove that it's not going to be there, but it does show that it's not going to be an extremely common problem."

Another, somewhat more expensive option would be to use a protease inhibitor (PI)-based regimen, such as *Kaletra*. In general, PIs have not been used in PMTCT because they do not cross the placenta and theoretically might not provide protection to the infant — however, the relative importance to transmission of transplacental penetration of a drug versus the reduction in maternal viral load is unknown. And anyway, as part of an ART regimen the PI would be given in combination with AZT/3TC, which do cross the placenta (and are associated with less toxicity than ddI or d4T).

Other concerns that PI-based ART might increase insulin resistance, pre-eclampsia and pre-term births have not been consistently born out by recent data. According to data presented at the Botswana Conference by Dr Steven Miller from the Inovir Institute in Johannesburg there were only a few adverse events on

Kaletra-based ART (one incident of PROM with amnionitis, eclampsia and appendicitis with peritonitis) in a study he conducted with 54 pregnant women with HIV. None of these women transmitted HIV to their infants (though all but 5% were delivered by Caesarean section which also reduces the risk transmission).

## Operational challenges of getting pregnant women on ART

"The first priority should be to get women with low CD4 counts onto [ART] – starting in pregnancy and continuing on," said Dr James McIntyre of the Perinatal HIV Research Unit of the University of the Witwatersrand, who also spoke at the Botswana conference. But programmes considering offering ART to women on the basis of CD4 cell counts first need to have a reality check, Dr McIntyre said, because that means that "CD4 counts need to be available for HIV-positive pregnant women in order to decide on appropriate treatment options but few PMTCT services have moved to include CD4 counts at all health service levels."

The Botswana programme recognised some time ago that it would have to decentralise access to CD4 cell testing, and has begun distributing CD4 cell machines in district-level hospitals.

For example, in the past Maun General Hospital, one of the first four pilot ART sites, used to conduct CD4 tests not only for all the health facilities in its own district but for neighbouring parts of the country as well. For example, there are three primary level hospitals (with about 40 beds) neighbouring Maun General Hospital: Gweta, Gumare and Ghanzi Primary Hospitals which are around 200 km, 250 km and 300 km away from Maun respectively.

Now, according to Dr Philip Wangia, who is the Chief Medical Officer at Maun General Hospital, "Gumare and Ghanzi Primary Hospitals have got their own machines for doing CD4 tests. [However], Maun General Hospital does CD4 tests for Gweta Primary Hospital," he said.

And in each setting as CD4 cell counts become more widely available, nurses have to be trained how to interpret them, according to Prof. Anabwani, in order to understand that there is no significant difference between, for example, a CD4 cell count of 220 and a CD4 cell count of 200.

But after women who qualify for ART are identified, perhaps a greater challenge is to fast track the movement of HIV-positive women with low CD4 cell counts from antenatal clinics into the ARV programmes and onto treatment.

"If they are just sent with a letter to the ARV site, then they go to the bottom of the queue; and by the time they get to be seen, they may have already delivered," said Prof. Anabwani.

When women present late in the third trimester, processes such as screening for liver function and adherence counselling have to be abbreviated as well. "You are eating into very critical time. So fast-tracking here means fast-tracking everything. It means probably starting ARVs before doing liver function tests. It means doing your adherence counselling in one day rather than two weeks or three weeks [to ensure] that they start ART as early as possible before they go into labour," said Prof. Anabwani.

Other countries have tackled this issue by beginning to prescribe ART directly at the antenatal clinic. But in Botswana, ARVs can only be given through the ART sites and potentially their satellite clinics – and presently there are 32 such sites, each with two to four satellite clinics, scattered throughout the country.

"The best thing would have been, of course, where you could conduct the antenatal clinic right beside the ART site," said Dr Jibril.

"In the hospitals where they conduct an antenatal clinic, the contiguity is there, so she doesn't have to travel very far."

## Improving infant follow-up

The PMTCT programme has achieved some noticeable improvements in the health of infants in the wards, according to Dr Jibril.

"We used to see very ill children under the age of one year with severe chest infections and most of them died. We don't see that anymore," he said.

However, he noted that it has been extremely difficult to monitor the outcomes of children who go through the programme.

"What we are currently seeing is a child presenting between 9 to 15 months, who has gone through the PMTCT programme. What happens when you ask them to come in for the child to be tested at six weeks? Many of them don't come. The next time they come in very ill and we screen them and they are infected. It's one way that we are losing the gains of PMTCT. Whether they feed correctly or not, nobody follows that up and the next thing they come in infected. So there has been this investment in them through the programme, but there they are."

Mr Ramothwa believes there needs to be "a paradigm shift" among the PMTCT staff. "The biggest challenge is that so far PMTCT programme has been putting too much emphasis on getting the mother to be tested, but not enough on following the baby."

In an effort to improve infant follow-up, Botswana has developed new "Under-5 Cards" for infants, in which information about participation in the PMTCT programme will be transferred from the mother's antenatal card to the infant's Under-5 card. So when the children go to child health clinics, they can be identified as needing cotrimoxazole prophylaxis and needing early diagnosis.

Furthermore, their parents will be monitored for care as needed.

The cards have been successfully tested in the field, but, as is the case in many settings, progress is being held up by a simple thing: a very long wait to get the cards printed.

## Safer infant feeding

Botswana's PMTCT programme has put a great deal of emphasis on safer infant feeding, offering free formula to HIV exposed infants for a year. But as discussed in HATIP #74 (see <http://www.aidsmap.com/cms1177384.asp>), formula feeding in Africa is an example of an idea that is only as good as its implementation, and in the case of infant feeding, implementation has to be almost perfect.

One of the problems has been providing a consistent supply of formula. Some doctors at the Botswana conference told this reporter that they frequently ran out. This was such a problem, according to an article in the September 15<sup>th</sup> edition of Gaborone's The Reporter, that the Ministry of Health sued to cancel its contract with its supplier for failure to supply over 90,000 cans of infant formula. According to the article, the Public Procurement and Asset Disposal Board approved the request from the Ministry of Health, which has now signed a contract with a new supplier.

However, this still may not be the end of the supply problems. "Sometimes it's not an absolute shortage. On many occasions, it's actually logistics, or distribution, which is actually the major cause of shortages," said Dr Jibril.

"The challenge is that even when you want to take it to bigger settlements or health facilities, there is limited storage space; so they can only take so much at a time. Therefore, if you have limited storage space, the frequency of the shipments has to go up, and the

higher the frequency, the more likely you are to encounter logistical problems,” said Mr Ramotlhwa.

According to Dr Jibril and Mr Ramotlhwa, the government has decided to build a warehouse in Francistown to stock both drugs and formula.

“With respect to the infant formula, there are a few warehouses with limited storage capacity in some of the strategic areas to supply health facilities within their defined catchment areas. But it’s always an issue of how much storage capacity is available locally, and what type of storage capacity; for instance, if it is bigger and air conditioned then you can keep more stock there for a longer period,” Dr Ramotlhwa.

“One solution might have been just to let mothers get it from supermarkets,” suggested Prof. Anabwani. “Give them vouchers and get out of the business of distributing it yourself because this formula is available everywhere [at groceries]. Or you could have a fail safe situation, where mothers would be given vouchers to go to any shop to get the milk.”

“The problem is that if the mothers run out of it, then they may do anything because of course they have to feed the children,” said Dr Jibril. As a result, the mothers often use age-inappropriate products that are harmful to the child. “They use whatever is available especially this long-life milk in the box. Then, of course, they end up with problems of diarrhoea.”

As noted in HATIP issue #74, (see <http://www.aidsmap.com/cms1177384.asp>) there was a diarrhoea epidemic in Botswana after unusually heavy rains at the beginning of the year. A US CDC analysis concluded that the water, which is normally safe, was contaminated — and there was an extremely high risk of diarrhoea and death among infants who were not breastfed.

But according to Prof. Anabwani, there are other local factors that need to be considered — such as the fact that most of the microbes identified in that study are ubiquitous in Botswana during the rainy season.

“Cryptosporidia are normal micro-organisms in cattle,” he said. “This is cattle country, and some studies done in South Africa showed that about 100% of all cattle carry it and they excrete it in the urine and the cow dung. So you have a lot of rain. You have flooding everywhere. You have kids playing all over the place. So you have kids playing, literally, in microsporidia. I think that maybe the contamination of water sources also may have played a role but I think that it was much more widespread. I think it was much more likely the way that it happened. Because of cattle and urine and cow dung.

I mean, children playing in the village, just imagine, water ponds, their huts are contaminated...”

“If you don’t take into consideration the cultural situation, you can completely miss the point,” said Mr Ramotlhwa. “What happens is that during the rainy season, people in Botswana want to drink rain water. Outside the rainy season, because there is not much rain water around, they normally use tap water. But during the rainy season, even some of the people coming from the towns, they just drink that rain water. So there is that element — that the water that people may normally use may be safe but during the rainy season people use rain water.”

Travelling across Botswana at the very start of the rainy season, it was easy to see that this is indeed the case. In many of the villages I visited while in Botswana, people said that they indeed preferred to drink rain water, or even water collected from ponds and running streams.

Of course, one of the virtues of breast milk is that it protects infants from common pathogens in the environment — while formula

feeding doesn’t. But at present, the focus in Botswana is how to tackle the cultural factors associated with improper infant feeding.

“Malnutrition in infancy is related to bottle feeding in this country,” said Prof. Anabwani. “For me, it is a question of education and educating the right people. In Botswana, if the mother is not breastfeeding, there is this cultural period of confinement, when she is actually regarded as unclean. She has her own cups— they are not even shared by the rest of the family. She may not even prepare a feed for her own baby, some other people do it. So you need to include the ones who assist the women in that education plan.”

In response to the diarrhoea outbreak, the government redoubled its efforts to get mothers to boil water first, and women were also encouraged to feed their cups infants with cups, which are easier to sterilise. Prof. Anabwani thinks this is too impractical.

“Try to put that into practice,” he said. “You have to think about what that mother lives through every day. I have talked to hundreds of mothers, and I have said to them, ‘why don’t you use the cup?’ They look at me as though I am totally mad. You have to imagine: summer in Botswana, a woman in the massimo (a massimo is like a cattle post or the village, or the lands) surrounded by animals and so on, with a cup, in an atmosphere that has huge numbers of flies? You take the cup, and the child begins and ‘now how am I going to ward off the flies with an open cup?’ It’s not possible to use it! Secondly, at night. A child wakes up in the middle of the night and wants to feed. What is the mother likely to do? Feed the child with a cup in the dark, or is she going to use a bottle that she’s prepared?”

But many sites and healthcare personnel are telling mothers not to use bottles. “Most of [the messages] are opposing,” Prof. Anabwani said. “ ‘Don’t use the bottle, it is bad. Use the cup.’ At Baylor, the nurses used to be so harsh, so the mothers would hide their bottles each time they came to the hospital and as soon as they leave the hospitals, they would begin to use them.”

“But the same people who are telling the mothers to use the cup don’t use the cup. The role models don’t use the cup. The nurses don’t use the cup. The women who are working in high offices, don’t use the cup. Nobody uses the cup. Nobody has ever used the cup at the population level! And yet, that is seen as theoretically being safer and therefore what people should do.”

“Mothers want to use bottles. So instead of insisting that they use something that is so impractical that no one would use it, work with them to how to improve the way they use the bottle. And that is something that is totally lacking. Nobody is teaching mothers how to use the bottles safely in these clinics and I think that is part of the problem.”

## Dried blood spot HIV tests

Finally, one of the most ambitious projects that the PMTCT programme plans to undertake is testing infants for HIV at six weeks, using the dry blood spot HIV PCR test. Dried blood spots are easier to collect (with just a prick to the heel or toe), store and transport than liquid blood samples, and the HIV PCR test results are just as reliable. The programme was piloted quite successfully at eleven clinics and one referral hospital in Gaborone and Francistown — and extension of the programme countrywide should help show how successful the programme is at each site.

“A lot of nurses had been trained and shown that it could work,” said Prof. Anabwani. “So now it is a question of how it can be implemented out there [in more outlying areas].”



"I think the logistics of getting the children there, getting the blood taken, transporting it, getting it tested and sending the feedback back to the place [are] not sorted out yet," said Dr Jibril.

Mr Ramotlhwa doesn't think that getting the children into the clinics should be such a challenge. "According to reports from the EPI programme, more than 80% of children complete their EPI Programme, clearly showing that mothers do bring their babies to the clinics. So if indeed that is the situation then healthcare workers can test them," he said.

But one unexpected hurdle was that the nurses in Botswana refused to draw the blood — not just from infants but any patient.

"An average nurse at the site wanted to do the testing," said Mr Ramotlhwa. "But then the professional leadership was saying, 'well, if you are doing it, you are doing it at your own risk. You are not covered if anything goes wrong.'"

Meetings between the Ministry of Health and the Nursing Association to resolve the issue had led to a stalemate. "But when I was at the ARV programme, we initiated that process again with the relevant stakeholders," said Mr Ramotlhwa.

He said that he "humbled himself" and went to great lengths to make the nursing association feel that its concerns were being adequately addressed. "We walked them through until we had reached our agreement, which had been adopted by the time that I left the government. So I think that they will now do it."

How quickly the testing programme will now be scaled up remains to be seen, as implementation of such plans appears fraught with many such major and minor problems, but both Dr Jibril

and Mr Ramotlhwa feel it is critical for monitoring the programme's effectiveness.

"It's going to tell us a lot about how successful the programme really is. Right now, we don't know," said Dr Jibril.

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## about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

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

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