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AIDS vaccines and HIV transmission via breastfeeding

Is there a role for vaccines in protecting infants against HIV in breast milk?

by Emily Bass

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In 1997, the antenatal clinic at Mulago Hospital in Kampala was the site of a clinical trial that launched a thousand hopes for the battle against AIDS in children. HIVNET 012 showed that a simple, cheap regimen of the antiretroviral drug nevirapine (NVP)--one dose to the mother in labor, one to the infant within 72 hours of birth--reduced rates of HIV transmission at delivery by nearly 50%. In sub-Saharan Africa, that could potentially translate into preventing as many as 300,000 infections per year. But this remains a distant goal: even with a drug donation offer from NVP's manufacturer (Boehringer Ingelheim), the treatment has been very slow to move beyond clinical research settings into local health systems.

And even after birth, most of these children are not out of the woods. Within a year, 10-15% of them will acquire HIV via breastfeeding, whittling away at the successes of early interventions like NVP or AZT (the established but more expensive anti-retroviral that blocks mother-to-child transmission [MTCT]). "700,000 babies get infected in the world each year, up to half through breastfeeding," says Laura Guay of Johns Hopkins University (Baltimore) and Makerere University (Kampala), a pediatrician who has spent more than a decade in Uganda. "Right now, we are desperately in need of something."

The need is so great because, in Uganda and much of the developing world, breastfeeding is still practiced by most HIV-positive women. That's partly due to social stigma: formula feeding can be tantamount to a public declaration of HIV infection. But many women cannot afford formula, or they lack access to clean water or fuel. There are also compelling health reasons, since formula feeding places infants at a higher risk for life-threatening childhood afflictions such as diarrheal diseases, dehydration and malnutrition. Under these circumstances, safeguarding breastfeeding could save more lives than trying to follow the lead of industrialized countries and switch to formula feeding.

That's why Guay and her colleagues at Makerere University are part of the small group of researchers pursuing HIV vaccines as a potential strategy for protecting breastfeeding infants against infection. At press time, Guay and Francis Mmiro, an elder statesman of AIDS research in Uganda, were preparing to submit a trial protocol to both the Johns Hopkins and Ugandan Institutional Review Boards (IRB's)--a first step in the approval process for a Phase I vaccine

trial of Aventis Pasteur's canarypox-based vaccine, ALVAC vCP1452, in newborns. If approved, it will be the first neonatal HIV vaccine trial outside North America.

High hopes and a lowered bar

The notion of a neonatal HIV vaccine may sound like a long shot, since there is still no effective adult vaccine. But the bar for protection in infants may be lower: rather than long-term immunity, a neonatal vaccine need only protect for as long as babies are breastfed. While that can last up to two years, work by leading MTCT researcher Ruth Nduati (University of Nairobi), and a large study in Malawi suggest that the greatest risk of transmission is in the first six months. So even a less effective vaccine might have a major impact. Another ground for optimism: while about 15% of breastfed babies become infected, that leaves 85% who do not--an intriguing, apparently innate protection that is still poorly understood (see article, "Holding HIV at Bay").

The first clinical studies of HIV vaccines in neonates date back to 1993, when a trial led by William Borkowsky (New York University Medical School) tested two different gp120 subunit vaccines and found them to be safe and immunogenic. A few years later, infectious diseases researcher Jack Lambert (then at Johns Hopkins University) launched an NIH-funded neonatal trial of ALVAC vCP205 through the Pediatric AIDS Clinical Trials Group (PACTG 326). This vaccine, based on a canarypox viral vector, was known from Phase I testing in adults to induce cellular immune responses in up to half of all vaccinees. It was also safe in adults, which was key to its selection despite somewhat weak immunogenicity. (Both vCP205 and the related vCP1452 are likely to enter Phase III efficacy trials in adults within the next 1-2 years)

The PACTG 326 trial, conducted at sites throughout the US, followed 27 mother-infant pairs, all of whom received antiretroviral treatment to prevent HIV transmission before and during birth; babies were delivered vaginally or by caesarian section depending on clinical indications. Newborns were immunized with vCP205 within 72 hours of birth and then again at 4, 8 and 12 weeks. While up to 50% of the babies showed cellular immune responses to the vaccine (in proliferation and CTL assays), says Lambert, the responses often hovered near the lower threshold of detection. All babies were exclusively formula-fed and none became infected during the trial.

Aiming to improve on these results, Lambert (now at the Institute of Human Virology, University of Maryland) is overseeing the next phase of PACTG 326, which uses a newer canarypox-based vaccine (ALVAC vCP1452) in a prime-boost regimen with VaxGen's gp120. To date, over 50% of a planned 24 children have been enrolled at PACTG sites throughout the country. Lambert says that the immune responses so far do not look any stronger than with vCP205, but complete data is not yet available.

HIVNET 027, the proposed NIH-funded Phase I trial at Mulago Hospital, will use ALVAC vCP1452 in 50 mother-infant pairs (40 vaccine and 10 placebo). All women and infants in the trial will receive the short-course NVP regimen rather than AZT. Another key difference to the North American studies: if experience holds up, most of the women in the Ugandan trial will choose to breastfeed, so the babies will be exposed to HIV after vaccination. Whether (and how) this affects their immune responses is a question Guay and Mmiro, the trial's two principal investigators, hope to tackle in the study, along with monitoring safety and immunogenicity. They will also monitor the responses to standard childhood vaccines, to be given at staggered intervals between the experimental vaccinations (to help pinpoint the source of any side effects).

Arriving at this plan has been a process extending over several years. The researchers knew that acceptance of a neonatal trial in Uganda would require a vaccine already well-tested for safety in adults and babies, which meant waiting until PACTG 326 was near completion. They also debated whether to go with the existing vCP1452 (based on HIV subtype B) or--since subtype A predominates in Uganda--to wait for the new subtype A vCP1452 developed by

Aventis Pasteur. In the end they opted for the former, since it will take time for the subtype A vaccine to accrue a comparable safety record in adults. (The Walter Reed Army Institute for Research [WRAIR] is expected to submit a Phase I trial protocol of this vaccine for approval in Uganda within the next few months.) Another factor in the decision was the finding that some Ugandan adults showed cross-reactive immune responses in a recent trial of vCP205.

HIVNET 027 will also measure CD8+ T-cell responses, using a modified CTL assay which focuses on a restricted number of antigens. That's due to a key limitation of working with neonates: since blood samples are limited to 2-5ml, it's rarely feasible to repeat a CTL assay or confirm it with other tests. "It's sort of a one-shot deal," admits Guay. They may turn to ELISpot assays in the future, she says, but for now the assay is not standardized well enough for use on neonates.

Infants who become HIV-infected during the course of the trial will continue to be monitored for viral load and immune responses, with other newborns enrolled to maintain a constant sample size. They will also continue to receive vaccine after testing positive, another key difference from the US trial. "We want to know about safety in kids who are already infected," explains Guay, since a neonatal vaccine would presumably be used in settings where HIV infections cannot be definitively diagnosed at birth (which requires PCR-based testing). The infected infants will be offered PCP prophylaxis, free medication for any illnesses and nutritional support, and will be referred to outside facilities, none of which offer ARV treatment at this time. The same care will be available to all mothers. For now, researchers say that antiretroviral treatment is not sustainable. "The research program has a short life of one to three years," says Francis Mmiro. "If we start these children now on antiretrovirals, who is going to take over?"

Now it's all up to the committees on the approvals pathway. Once the US and Ugandan IRB's have signed off, the protocol goes to the Ugandan vaccine review committees for science and ethics and to the National Council on Science and Technology. The final step is approval by the office of the President. Although this process took two years for the first canarypox trial, Guay and Mmiro hope for greater speed this time around in light of the country's prior experience and the increasing amount of HIV vaccine work in Uganda.

A need for new solutions

Studies like HIVNET 027 are part of a growing movement to address breastfeeding transmission. It's a movement fueled by the acknowledgement that formula feeding is not an option in many parts of the world, and that the benefits of breastfeeding may outweigh the risk of HIV transmission. In one study by Ruth Nduati, formula- and breastfed infants had comparable mortality rates--although from different causes--after two years.

Current WHO guidelines for HIV-infected mothers suggest exclusive replacement feeding when it is "acceptable, feasible, sustainable and safe. Otherwise, exclusive breastfeeding is recommended during the first months of life." The Ugandan National MTCT Plan calls for three months of exclusive breastfeeding, followed by a switch to formula. But on the ground, each woman makes her own decision about what is feasible. At Upper Mulago, among the 35% of women who initially opt to formula feed, 56% do not come back to the clinic at six weeks to re-stock their formula supply.

To help get a better picture of what happens during breastfeeding transmission, WHO released a draft in June 2001 of its first guidelines for studies on breastfeeding and HIV transmission. The document notes a serious lack of information and observes that "nearly all studies of transmission through breastfeeding have used customary but now inadequate methodologies." It points out, for example, that studies frequently don't distinguish between exclusive versus mixed breastfeeding. That's an important distinction, since exclusive breastfeeding--which means that infants receive no other fluids for their first 12 months--may carry a lower transmission risk than mixed feeding. The guidelines also call for collection of complete data on

breast health.

Studies by the teams of Ruth Nduati and Anna Coutsoudis (University of Natal) have shed light on several important issues, including the relationship between cell-free viral load in breast milk and transmission risk, and on how transmission risk relates to volume of breast milk ingested. But there are still many open questions--including the exact relationship between viral load in breast milk versus plasma, and whether the latter is a useful correlate of infectiousness in a fluid that teems with immune defenses.

Several research groups are now focusing on these questions. For example, scientists at the Uganda Virus Research Institute in Entebbe are launching a study examining the relationship between mastitis and viral load in breast milk, and asking whether breastfeeding from the non-inflamed breast reduces transmission risk--the type of simple solution that can give additional prevention at no cost.

In the meantime, a flurry of trials are testing new interventions for the infants, with antiretroviral prophylaxis topping the list. For example, this year's multicenter SIMBA trial, which includes a site in Uganda, will test whether weekly doses of NVP or 3TC given for six months can reduce breastfeeding transmission.

A few researchers are also looking at immune-based therapies. One strategy being pursued by Brooks Jackson (Johns Hopkins) and including Guay and Mmiro, is to test whether treatment of newborns with a cocktail of antibodies against HIV (HIV immune globulin, or HIVIGLOB) can provide some protection in the weeks or months after birth, when the risk of transmission seems to be highest. This might mimic the antibody protection that appears to be at work with the Hepatitis B vaccine, which protects 90% of infants who receive it at birth.

Following on early studies that showed HIVIGLOB to be safe and well-tolerated in both pregnant women and newborns, an upcoming NIH-sponsored Phase III study in Uganda (co-sponsored by the Ministry of Health) will compare HIVIGLOB given to pregnant women at 37-38 weeks, along with a single dose to babies within 18 hours of birth, with two different NVP regimens. The protocol is in the final stages of the approval process, and is expected to start enrolling in October. Here, too, a CDC-sponsored substudy of this trial will pose a host of basic science questions about breast milk immunology.

An expanding field

For now, the US and proposed Ugandan ALVAC trials are the world's only neonatal vaccine studies--but there's a push to build interest. This October, the Elizabeth Glaser Pediatric AIDS Foundation will sponsor a two-day meeting on the science and immunology of pediatric vaccines in Dedham, Massachusetts. "A lot of people are thinking about vaccine trials, but very few are thinking about pediatric trials," says Jeff Safrit, the senior program officer at EGPAF who is planning the conference, which will bring together 20-25 mostly US-based researchers, for a mini think-tank. Safrit is excited about developments like polio and measles vectors. "The potential to use these in kids is just amazing."

These trials could bring insights to the adult field, too. In theory, pediatric vaccine efficacy trials could be much more straightforward that adult trials, due to the high incidence of breastfeeding transmission in exposed babies. This means it could take less time and a smaller sample size to determine a vaccine's effect.

But in practice, easy answers may be hard to come by. That's because a neonatal vaccine would not be a stand-alone intervention. Other strategies, such as antiretrovirals and immune-boosters, will be needed to provide coverage right after birth, before the immune responses kick in. And veterans of the neonatal vaccine field like Jack Lambert, are some of the staunchest supporters of the ARV-based approach.

*MOTHER-TO-CHILD TRANSMISSION RATES OF HIV**

Study	Group	Rate of infant HIV infection (%) at:					
		Birth	1.5 months	3 months	6 months	15-18 months	24 months
SOUTH AFRICA[1]	Breastfed (n = 394)	6.9	19.9	21.8	24.2	31.6	— —
	Breastfed (n = 157)	7.6	18.0	18.7	19.4	19.4	— —
KENYA[2]	Breastfed (n = 191)	7.0	19.9	24.5	28	— —	36.7
	Formula (n = 193)	3.1	9.7	13.2	15.9	— —	29.5
BRAZIL[3]	Breastfed (n = 168)	— —	— —	— —	— —	21	— —
	Breastfed (n = 264)	— —	— —	— —	— —	13	— —

**Infants were either breastfed (predominantly mixed breastfed) or fed formula (never breastfed).*

[1]Coustoudis et al., *AIDS*. 2001;15:379.

[2] Nduati et al., JAMA, 2000;283:1167.

[3]Tess et al., *AIDS*. 1998;19:189.

Note: This table only includes cohorts that had at least 100 infants in each of the two feeding groups. Table from: H.M. Coovadia and A. Coutsoudis, AIDScience 1:4, July 2001. Used with permission.

"If an infant is born in Africa and we want to do vaccine studies, we can't say, 'We don't know if antiretrovirals work [in breastfeeding prophylaxis].' It's not proven for health-care workers either," he says. "I think we should have the same vision for infants as for health-care workers and build a vaccine strategy on top of that."

Other researchers and advocates suggest that treating women, at least for the duration of pregnancy and breastfeeding, could have a profound effect on rates of MTCT, as well as providing a foundation for more widespread adult antiretroviral treatment.

Pragmatists counter that while these strategies may be the best, they're not necessarily feasible right now. "We haven't really managed to get a two-tablet regimen out of Kampala," says Laura Guay, who points out that Ugandan efforts to provide NVP nationwide to HIV-positive pregnant women are proceeding by inches, rather than leaps and bounds. Human resources are the major bottleneck, according to Saul Onyango, the Ministry of Health official in charge of MTCT efforts. He points out that training counselors, nurses and physicians takes

time and money that's been slow in coming.

The fledgling field of neonatal vaccine research will face these and other tough issues. Will it be ethical to test neonatal vaccine efficacy if ARV prophylaxis proves effective? If not, will it be enough to measure immunogenicity? How will successive generations of trials address the issue of treating women, especially in light of research by Ruth Nduati suggesting that infants of HIV-positive women are more likely to die, regardless of their own serostatus? It's all part of an expanding vision for MTCT--one which incorporates many long-term threats to infant mortality. "If you keep the mother healthy, you keep the baby healthy--so you build your argument," says Lambert, who adds that vaccine studies can help with the implementation of proven interventions, like NVP. "We should go ahead with vaccine research--and take our known successes further."

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