

HATiP

HIV & AIDS Treatment in Practice

Issue 68 | 23 May 2006



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Integrating prevention research into the provision of HIV care

By Theo Smart

"We are in a situation, especially in KwaZulu Natal, that we cannot ignore treatment and care of these women. I feel that there is a responsibility of [HIV prevention] trials sponsors and researchers to facilitate access to HIV-related care. It needs to be done and we need to do something about it," said Professor Gita Ramjee at the recent Microbicides 2006 conference during a panel discussion on setting standards of care for participants in HIV prevention research trials. Prof. Ramjee is the Director of the HIV Prevention Research Unit (HPRU) of the South African Medical Research Council (MRC) and she was a co-chair of the Microbicides 2006 conference.

Although firmly resolved to help women access care if they screen out of prevention studies because they are already HIV-positive or if they seroconvert during the studies, Prof. Ramjee and other panel members stressed that the provision of HIV care is not an exercise that researchers and trial sponsors should be expected to do alone — rather they should work with and provide additional capacity to the local scale-up of HIV treatment and care. Nevertheless, this represents a significant evolution over the thinking that doomed a couple of earlier prevention studies (see below).

One of the triumphs of the Microbicide 2006 meeting is that researchers demonstrated that the inclusion of the community and the provision of standard of care treatment to participants in prevention studies is a win-win scenario.

"Facilitation is the key word. And the model I use is to integrate prevention, treatment and care," said Prof. Ramjee.

The potential role that prevention research could play in the scale up of treatment and care is considerable. Prevention research by definition requires voluntary testing and counselling and screening of sexually transmitted infections and so can add significantly to laboratory and testing capacity.

It may also feed very large numbers of patients into HIV treatment and care clinics. Globally, ongoing microbicide research trials are enrolling over 30,000 participants, and oral pre-exposure prophylaxis (PREP) studies will also involve thousands of patients. Some studies slated to open in the next year or so, such as the tenofovir gel efficacy studies, will involve at least 10,000 participants each — and possibly many more if sample sizes in the ongoing clinical trials are determined to be too small (and there is a good possibility of this, see

<http://www.aidsmap.com/en/news/DB107459-36CD-4868-9F24-0F36C4B00B88.asp>)

The number of people who screen for these studies is actually much higher than the number needed for enrollment and many screen out because they are HIV-positive (in rates similar to the local HIV prevalence). In the absence of routine HIV testing or dramatically increased uptake of VCT, prevention studies could represent one of the larger sources of potential participants for scaling up HIV programmes. In addition, these individuals could also serve as index cases for partners and/or children who may also need HIV care.

But until only recently, the prospects appeared limited for integrating HIV prevention research into HIV treatment programmes. This was largely because of setbacks — and missteps — in earlier prevention research that may have set back the quest to find an effective prevention technique (besides condoms) by years.

Tenofovir's trials and tribulations

Daily oral tenofovir (as PREP) was one of the first products to move into large-scale efficacy studies for the prevention of HIV. But in 2004 and 2005, several of the studies were derailed largely due to pressure from ACT UP Paris and in some cases, local organisations that claimed that the trials were unethical. Ultimately, the choice of whether this study or any study should continue should be left up to the community in which it is being performed — as long as that community is speaking with a unified voice.

In the case of the tenofovir studies, the story is somewhat mixed. <http://www.aidsmap.com/en/news/3BAF85DA-3C18-49F1-A8A1-49F37C94F8D7.asp>, <http://www.aidsmap.com/en/news/53066193-F3CA-4B1A-8E1E-7B99A7698E76.asp>, <http://www.aidsmap.com/en/news/deab5309-e626-476e-8df8-50d836b26d66.asp>.

In general, activists felt that the community had not been adequately involved in the preparation, design and implementation of the tenofovir trials — and to some extent the problems encountered by the trials are evidence of this. The activists also had several specific complaints especially concerning the standard of care for prevention being offered in the studies and the provisions for standard of care treatment during and after the study.

Activists had the right to be concerned about the adequacy of prevention services offered participants in these studies, however, the issues can be complex. The activists cited Guideline 29 of the Helsinki Declaration on Ethical Principles for Medical Research Involving Human Subjects (<http://www.wma.net/e/policy/pdf/17c.pdf>), which states that new products should be tested against the best treatment or prophylactic interventions available. In the case of HIV prevention, this would clearly include counselling and condoms as well as clean needles.

For example, one complaint, about a jeopardised PREP study in injection drug users (IDUs) in Thailand, is that the study does not provide clean needles to the participants. In this case, the IDU activists are absolutely right — clean needle distribution would markedly reduce HIV transmission in the study population, however, US government policy currently bars federally funded organisations (such as the Centers for Disease Control and Prevention) from supporting needle exchange.

This is a bad policy, and yet, it does not necessarily follow that the trial should be discontinued. One of the goals of the Helsinki Declaration is to try avoid modern day Tuskegee experiments but there is a danger that if guideline 29 were to be interpreted too strictly, trials would be never be able to generate results that are applicable to real world settings. The best way to get useful results is to use a control arm that matches actual practice in the community — although in this case, the IDU community clearly wants the freedom to do more to protect themselves (to access clean needles without police harassment).

But this isn't always the case. For example, ACT UP Paris complained that the tenofovir studies in Cameroon did not provide female condoms. And indeed, female condoms could reduce transmission and supplying them would optimise the standard of

care for prevention in the trial. However, even though acceptability of female condoms was reportedly high in clinical trials, their real world uptake has been very limited perhaps, as mentioned by participants in one Population Council study, because it takes too long to insert (destroying spontaneity), looks ugly and squeaks noisily during sex. Although lowering the price and increased social marketing have led more people to try the product, these efforts have had no impact on increasing consistent use.

Having up a trial because it does not offer a prevention intervention which is not in widespread use would seem not to be in the best interest of people. And if you took this approach (requiring the highest standard of care in the prevention control arm) to its logical conclusion, then prevention studies would have to get women to bring in their male partners for circumcision – as this has also been shown to reduce HIV acquisition in the man, and transmission of HIV to his partner (see <http://www.aidsmap.com/en/news/d775d204-7155-4cdf-acb5-8caa1c6730fa.asp>, and <http://www.aidsmap.com/en/news/37A87885-0A35-431B-8C8C-6D7A4B1BB9F6.asp>.)

But this would be unworkable.

ACT UP Paris also had another related complaint – that there were too few prevention counsellors in the Cameroon study – arguing that one doctor and five counsellors to 400 women was an unacceptably low ratio. (see <http://www.aidsmap.com/en/news/53066193-F3CA-4B1A-8E1E-7B99A7698E76.asp>)

But just how many counsellors and how much counselling is necessary? Five full-time counsellors to 400 people is a lot better than many communities have. That's about two hours of prevention counselling and support for each person per month; certainly much more than the participants would receive outside of the trial.

On top of this, at their monthly clinic visits participants would have received free condoms, repeated tests for hepatitis and for HIV (in itself, a pretty strong incentive to practice safer sex) and free treatment for sexually transmitted infections. In reality, anyone participating in this study would have received prevention that was better than in the real world treatment. Instead, the study in Cameroon was shut down, and those people got nothing.

With the benefit of hindsight, trials presented at Microbicide 2006 suggest that activist concerns about inadequate prevention interventions were unwarranted. For example, participation in a prevention trial in Ghana (of the microbicide Savvy, see <http://www.aidsmap.com/en/news/E31C54A1-F80E-4155-A2CB-0852AF6A04B6.asp>), which offered the same standard of care interventions that were being offered in Cameroon, resulted in extremely low seroconversion rates of ~0.9-1.0 in both the placebo and Savvy arm – and many other trials are also observed lower than expected rates of transmission (Link) .

Unfortunately, misinformation about the study in Cameroon and oral tenofovir received considerable press in in sub-Saharan Africa and did immeasurable harm beyond the permanent closure of the trials. Many people are now convinced that the investigators were trying to give the participants HIV, and that the tenofovir pills – or even microbicides that Western investigators now want to study in them – might actually *contain* HIV.

Even on the other side of the continent, in Uganda, activist Miriam Katende of TASO said during the panel discussion on standard of care, the first thing that people want to know about a study is “is the product free of HIV.” It has affected trust, and people in Katende's community are worried about who is conducting trial “Who is administering the product, and this matters

a lot. Where is this person coming from? Is he coming from the North or the South?” she said.

But the other major concern for the activists and the major reason for the suspension of the tenofovir trials was the absence of a system to guarantee long term provision of ART to those who seroconverted during the trial (in every setting). And the investigators and study sponsors didn't really have a good answer.

One of the difficulties of the tenofovir studies was that it didn't really have a pharmaceutical sponsor. Gilead Sciences, maker of tenofovir, provided free drug but offered no other backing for the studies. The actual trial sponsors/organisers including Family Health International and the US National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases (NIAID) will never be selling the product, nor are they in the business of providing long term treatment. “Not all sponsors are created equal. Our missions can be quite different,” said Dr Monica Ruiz of the US National Institutes of Health. “What we can do in terms of standard of care is determined by our mission.” And the NIH and NIAID do research. To provide longer care, they generally have to partner with other organisations.

And at the time, options were limited in Cambodia and Cameroon. At first, the trials tried to set up a programme of care only for the course of the study or for a two or three year period afterwards; and yet, some of the sponsors now admit that withdrawing support for treatment after a couple of years just wouldn't have been right. “It is neither ethical or practical to offer a standard of care that cannot be sustained after the trial has finished – to do this would be unfair to participants and the community in which the research took place.” said Dr Ruiz.

Of course, it wasn't acceptable to the activists either.

If there are any silver linings in the debacle of these tenofovir trials, it is that researchers have now realised that community participation is absolutely necessary to move forward with this sort of research – and that that will require more than token efforts at inclusion. At the Microbicides meeting, a whole track is now devoted to community involvement, which is seen not only as necessary for trials to run smoothly but as potential allies in the educational programmes, and to sustain support of microbicide research efforts. “Community mobilisation for microbicides should not be limited to awareness raising but should aim at building the capacity of communities to enhance development and/or improving community healthcare systems,” said Katende. The community can thus become a much richer resource for prevention researchers to draw on.

Finally, the controversy has forced researchers and sponsors to consider what is their obligation to provide quality treatment where it is not available. And even if they reject the moral arguments, “existing social and political realities make access to care an essential factor in a trial's ability to go forward,” said Anna Forbes of the Global Campaign for Microbicides.

“Worldwide there is consensus among researchers and sponsors that care should be provided to participants who volunteer for screening and are excluded due to their HIV status and especially to those who become HIV positive during the course of the trial,” said Prof. Ramjee. Who should do it? Increasingly, it is being seen as a collaborative effort between the investigator, sponsor, pharmaceutical company, community and the local health department. Even the NIH is now routinely looking for partnerships to provide long-term care to the participants in its studies, and Dr Ruiz noted, agreeing that “research doesn't happen in a vacuum.”

The HIV Prevention Research Unit Model

Prof. Ramjee believes it is the investigator's responsibility to organise this effort — and she has developed a working model to manage HPRU's seven trial sites involving over ten thousand women, and screening up to twice as many.

"When we talk about care, we need to look at the trialist perspective and the woman's perspective. We need to look at what the trialist can do, and what the woman's needs are," said Prof. Ramjee.

The women who screen out of her trial because they are already HIV-positive may be in the most immediate need of HIV care and possibly treatment. Her model facilitates linkages to care in partnership with local health care providers. "So I have developed a memorandum of understanding between the trial site and each district government referral hospital which will assess the women's need for treatment," she said. Women with CD4s below 200 will be counselled to go on the treatment programme, while women not in immediate need of treatment will receive on-going monitoring of HIV infection. The trial site also provides the government with a regular report on the number of women have been referred from the trial (how they are assisting with the scale-up).

"Of course, the government is already overburdened so what can I do to help in order to help the government in the scaling up of treatment efforts for HIV positive women who are screening out of trials?" She has looked to external donors such as PEPFAR to help carry some of the burden. In particular, she has developed a partnership with Aurum Health, which receives funding from PEPFAR, setting up two sites adjacent to Aurum Health sites. "All the women that we screen out will go automatically to the PEPFAR site where they [receive ongoing HIV care] and when ART is required they will send them to the government hospital. However, if the hospital says that they are overburdened, PEPFAR has the capacity to provide them with drugs as well."

Recently, they've begun a partnership with Broadreach Healthcare — another PEPFAR recipient, which is working with around 100 general practitioners. "I'm really pleased about this and this also deals with my problem working with the women who don't want to go to the hospital where they may know somebody who knows them."

"But eventually, all these women will go into the government system so we need to partner with the government on this." She reiterated: "It's very important that the government needs to be informed of what the memorandum of understanding is, as well as how you are assisting them with their scaling up numbers, because it's very important that we all work together."

For those women who seroconvert during the trial? "Within the trial, there should be the capacity to respond to short term care needs, including ongoing counselling, baseline CD4s, treatment of STIs, and condom promotion," said Prof. Ramjee. The package of short-term care they have developed costs about \$350 per woman per year. They also ask the women who test positive to bring in their partners in so that they can provide them with care.

She also believes the trial should assist the referral site with capacity building.

"They are asking for more counsellors, office space for counselling, for trial doctors to give some time to help manage the workload — so they aren't really asking the earth, but I think we can include that sort of support within the clinical trial budget. Honestly this is not a lot."

For the long-term care, they again develop a memorandum of understanding with the referral hospital. They may also refer the patient to enter other treatment trials or studies and to the PEPFAR sites. "I know that PEPFAR programme is a short term programme and that the money won't be there forever but it does help us scale up our efforts," she said.

And by partnering with other support organisations, she says that the trials are assisting with scale-up of HIV treatment and care. "All we are doing is giving them a little push in to the HIV treatment and care programme. Eventually all of them should get lifelong care."

She believes that the sponsors should provide some form of support (funding) for seroconverters on the study (essentially for their short-term care), and for ART should any patients progress quickly.

She has seen at least one case of rapid progression that required ART. "The non-governmental sponsors provided treatment for that particular woman because it became urgent and the government referral hospital had a one month waiting list at the time, and we couldn't wait. But we aren't looking at thousands of women — these are just a few who will seroconvert — so we need to have some capacity built into the trial."

"As a researcher, my responsibility is to ensure that there is a true partnership with the local government which is transparent so that each [party] knows what contribution the other is making."

But she said that the appropriate linkages must be in place prior to trial implementation. "What are the referral structures? Who do we talk to? What sort of care does the women need. We need to do all of that quite well in advance and the memorandum of understanding is very important."

"I don't think anyone can tell anyone else what the standard of care should be. It's a country specific standard of care plan, which is going to be possible if the researcher works with the local government (gets healthcare approval and understanding) and supported by sponsors. But it is a moving target. Today, I'm quite comfortable with what I've set up but tomorrow it might change, it's a moving target. As a researcher, I feel comfortable that I have sorted out care for my screened out and my seroconverters."

Need to perform follow-up

One thing Prof. Ramjee and HPRU may need to keep an eye on is whether women who screen or test positive actually show up at the referral hospital or PEPFAR site — which is a serious problem according to some presentations. For example, the Savy trial in Nigeria was located in an area with existing HIV care (funded by PEPFAR). Even so, only 15 of 87 women from one trial site and 12 out of 17 at another have attended the PEPFAR clinic. "Some women are reluctant to return to our study clinic for counselling. Others refuse to attend the PEPFAR clinic for evaluation. Staff must use tact in contacting these women, since many have not informed their partners or relations of their serostatus," the authors wrote. Even in South Africa, there are problems accessing referral services. According to Dr Khatija Ahmed of the University of Limpopo, in the Population Council trial of Carraguard, they have conducted a preliminary assessment of the referral centers at the Medunsa/Soshanguve site, where nearly one out of four of those screened are HIV-positive, "which raised concerns that the existing infrastructure in the community might not be adequate to support the increased number of women seeking services." 15 out of 20 women accessed referral services but they complained of long waits (up to seven hours), rude staff, stigmatization, and lack of resources at the clinics. Many women also lacked transportation to the clinic.

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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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