

HATiP

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IAS 2011 conference: summary

This edition of HATIP collects together some of the most important news stories from the Sixth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, which took place in Rome, July 17-21. These stories and others were published at <http://www.aidsmap.com/ias2011>

NAM was official provider of online scientific coverage for the conference. We would like to thank the International AIDS Society for their help in facilitating this news coverage. You can browse and search for conference abstracts and slides at the conference website [here](#).

TREATMENT AS PREVENTION

- Results of the HPTN 052 study showed that when compared to delaying treatment until the CD4 cell count falls to 250 cells/mm³, antiretroviral treatment started at a CD4 count between 350 and 550 cells/mm³ reduced the risk of HIV transmission to an uninfected partner by at least 96%.
- The only transmission that occurred from a person on treatment probably occurred in the first few weeks on treatment, before viral load was fully suppressed.
- The study also found that early treatment reduced the risk of serious illness or death by 40%. However this reduction in risk was largely explained by a reduction in the risk of extrapulmonary TB. Earlier treatment had no significant impact on the risk of death, pulmonary TB, serious illness (WHO stage 4 disease) or severe bacterial infection.
- The study recruited couples in Africa, India and Brazil. There was no difference in the effect of treatment on transmission between regions.
- Reducing new HIV infections by treating more people will require improvements in performance at every stage from HIV testing, retention in care prior to treatment, initiation of treatment, retention in care once on treatment and adherence to treatment.
- WHO plans to look at all its guidelines over the next year in order to produce one simplified set of guidance to replace all current guidelines.
- Community organisations want to see an immediate review of counselling and medical services for serodiscordant couples and pregnant women, and say that every person with HIV should decide for themselves when and how to start treatment, without coercion.

PRE-EXPOSURE PROPHYLAXIS

- Three studies presented at the conference showed that pre-exposure prophylaxis using the antiretroviral drugs tenofovir or *Truvada* (tenofovir / emtricitabine) reduced the risk of acquiring HIV very substantially.
- The Partners study showed that pre-exposure prophylaxis with *Truvada* or tenofovir protected both men and women in serodiscordant couples. PrEP reduced the risk of HIV infection by 62% - 73%.
- The TDF2 study showed that PrEP reduced the risk of HIV infection by 63%.
- The IPrEX study showed that *Truvada* reduced the risk of infection by 42% in men who have sex with men.
- In the TDF2 and IPrEX studies, better adherence was associated with greater reductions in the risk of infection.
- Implementing these findings in a cost-effective way will require careful targeting of an intervention to the right groups. For example PrEP may be suitable for some couples, but a microbicide containing tenofovir might be better for others.

OPERATIONAL RESEARCH

- New point of care CD4 cell counting tests were described at the meeting. The cost-effectiveness of these technologies will be highly dependent on the volume of patients being tested, and the cost of materials.
- The Gene Xpert TB test being rolled out in South Africa is detecting much higher rates of TB and of MDR TB than the existing method of diagnosis.
- It is estimated that Gene Xpert will result in 39% more people on TB treatment in South Africa by 2013, and could cut the time to starting TB treatment by over 50 days, to around 5 days.
- There is controversy over whether Gene Xpert should be used in all people with HIV, regardless of whether they have symptoms of TB, as a screening tool.
- Trials of task-shifting antiretroviral initiation and management to nurses highlighted the tension between rapid devolution of care to the primary health level and the need to fully train staff as this process goes forward.
- The STRETCH trial in South Africa showed that task shifting of ART initiation and management to nurses showed that a nurse-led service delivered ART just as effectively as a physician-led service. However the trial was unable to show that a nurse-led service resulted in a reduction in deaths among people waiting for treatment, or a speeding up of treatment initiation for those waiting.
- Nurses are successfully providing circumcision services in several countries but a shortage of nurses will limit the scale-up of circumcision. Bringing

retired or unemployed nurses back into service might be one way of expanding the workforce.

Treatment is prevention!

By Keith Alcorn

Treatment is prevention: HPTN 052 study shows 96% reduction in transmission when HIV-positive partner starts treatment early

Results from a trial showing that antiretroviral treatment prevents HIV from being passed onto uninfected partners received a standing ovation today at the Sixth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in Rome.

HPTN 052 showed that early treatment – started at a CD4 count between 350 and 550 cells/mm³ – reduced the risk of HIV transmission to an uninfected partner – by at least 96%. Almost all the study participants were heterosexual couples.

The study lends some support to advice given three years ago in the Swiss statement, a document issued by Swiss doctors which stated that, for heterosexual couples where the HIV-positive partner had an undetectable viral load on stable treatment (and no sexually transmitted infections) the risk of HIV transmission through vaginal intercourse was negligible.

But Professor Myron Cohen of the University of North Carolina, who led the study, urged caution in interpreting the results, reminding the audience that the transmission study had followed patients for a median of 1.7 years.

Nevertheless, he said, “these are important results to give to a serodiscordant couple.”

The HPTN 052 study recruited 1763 couples in Malawi, Zimbabwe, Botswana, Kenya, South Africa, Brazil, Thailand, the US and India. The trial recruited serodiscordant couples – one HIV-positive, one HIV-negative – in which the HIV-positive partner had a CD4 cell count between 350 and 550 cells/mm³, and was thus ineligible for treatment.

The HIV-positive participants were randomised either to start treatment immediately, or to defer treatment until their CD4 counts fell into the range 250 to 200, the threshold for starting treatment in national guidelines at the time the study began recruiting.

The overall gender balance in the trial was even, but the HIV-positive participants were significantly more likely to be women in the Africa region.

Approximately 95% of the couples were married, and 6% reported unprotected intercourse in the previous month at baseline.

Of note, just over one-quarter of HIV-positive individuals reported no sexual activity at baseline, and there is some indication that sexual activity actually declined at some points during the follow-up period in both the immediate- and the deferred-treatment arms.

However, condom use was high, reported by 94% of HIV-positive individuals at baseline, and there was no evidence of a decline in self-reported condom use as the study went on.

Results

A total of 39 individuals became infected during the study, four in the immediate-treatment arm and 36 in the deferred-treatment arm, during a median follow-up period of 1.7 years.

A careful genetic analysis of virus samples from the HIV-positive partner and the subsequently infected partner was conducted to

determine how many of the infections could be attributed to the index partners.

Eleven cases of transmission were unlinked, that is, attributable either to sex outside the primary relationship, or else the source could not be confidently determined. There was a strong association between unlinked infection and reporting more than one sexual partner in the three months prior to seroconversion ($p < 0.0001$).

This left 28 infections, of which only one occurred in the immediate-treatment arm. This represented a reduction in the risk of transmission of 96%, and was highly statistically significant ($P < 0.001$).

Sixty-four per cent of transmissions occurred from the female to the male partner, and 82% of transmissions took place at African trial sites.

Surprisingly, the majority of transmission events were estimated to have occurred when the index partner had a CD4 count above 350 cells/mm³, indicating that any potential prevention benefit of treatment might only be maximised by providing treatment above the threshold currently recommended by the World Health Organization. (It recommends that treatment should start once a person's CD4 cell count has fallen below 350.)

In the delayed arm, the median viral load (as measured at the last clinic visit) at which transmission took place was 4.9 log (approximately 80,000 copies/ml), while the median CD4 count was 391 cells/mm³.

In the immediate treatment arm the only verified transmission took place during the early months of treatment, with HIV antibodies fully detectable 85 days after baseline in the partner who became infected. The transmitting partner had a baseline viral load of 87,202 copies, and after 28 days a viral load below 400 copies/ml.

Professor Cohen said that couples need to be counselled about the possible differences in risk between the first few months of treatment and later periods.

Final multivariate analysis showed that baseline viral load was the strongest predictor of transmission in both groups (hazard ratio 2.84, 95% confidence interval 1.51-5.41). Consistent condom use at baseline was highly protective (HR 0.33, 95% CI 0.12-0.91).

Reactions

[The results of the study were announced in late May](#) after the study's independent data and safety monitoring board decided that the magnitude of benefit made it unethical to continue with a randomised study.

The results have fundamentally changed attitudes towards treatment scale-up and the possibility of halting the epidemic, but the hard work of winning funding and implementing wider treatment is not over.

Dr Elly Katabira, President of the International AIDS Society, warned that scientists and activists still have a lot to do to convince policy makers and donors of the importance of the findings and the need for rapid action to translate the findings into treatment expansion in the countries worst hit by HIV.

But Dr Tony Fauci of the US National Institutes of Health told reporters: “You shouldn't underestimate the power of having a scientifically based argument, rather than waving your arms about.”

References

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HPTN 052: early treatment reduces serious illness by 40%

Early treatment in the HPTN 052 study of treatment as prevention reduced serious illness by around 40%, delegates at the Sixth International AIDS Society conference heard – but the effect was almost entirely accounted for by fewer cases of extrapulmonary tuberculosis.

There was no significant difference in deaths, or in the rate of serious bacterial infections or of pulmonary tuberculosis.

The HPTN 052 study was designed to determine whether early treatment for an HIV-infected person would reduce the risk of HIV transmission to his or her regular partner.

The study showed that early antiretroviral treatment – started at a CD4 count between 350 and 550 cells/mm³ – reduced the risk of HIV transmission to uninfected partners by at least 96%.

However, the study also collected information on a number of other endpoints: death, illness, virological and immunological responses to treatment. These data will provide important information on the potential benefits of early treatment in settings where bacterial infections and tuberculosis are more prevalent than in North America and Europe.

The study will also provide information on any differences in rates of clinical or immunological disease progression between different regions of the world, or between men and women. Some studies, but not all, have suggested faster rates of disease progression in sub-Saharan Africa.

The study enrolled 1763 HIV-infected individuals with CD4 counts between 350 and 550 cells/mm³. Participants were randomised either to receive immediate antiretroviral treatment or to defer treatment until their CD4 cell count fell below 250 cells/mm³ on two separate tests. This was the level at which treatment was recommended to begin in national guidelines during the study recruitment period. The study recruited participants in Malawi, India, Zimbabwe, Botswana, South Africa, Kenya, Thailand, the US and Brazil.

The median CD4 count at enrolment was 446 cells/mm³ and the median viral load 4.4 log₁₀ copies/ml (25,000 copies/ml).

Differences between Africa and other regions

Although the proportion of HIV-positive men and women recruited to the study was equal across the study population as a whole, sites in Africa recruited a larger proportion of women than men (58 vs 40%, $p < 0.0001$), reflecting the higher rates of engagement in care by women in sub-Saharan Africa as a consequence of earlier HIV diagnosis through antenatal programmes.

African sites also recruited a larger proportion of participants in the 18 to 24 age group (20 vs 15%, $p = 0.003$). African participants had slightly lower viral loads (4.4 vs 4.5 log₁₀ HIVRNA, $p = 0.006$).

Although there was no significant difference in baseline CD4 count between regions, Africans in the deferred treatment arm were less likely to reach the CD4 threshold that indicated they needed to start treatment. Participants in the deferred arm outside the Africa region were 40% more likely to start treatment, but when the hazard

ratio was adjusted for confounding factors this difference ceased to be statistically significant (aHR 1.30, 95% CI 0.9-1.8, $p = 0.06$).

The median time to starting treatment in the deferred arm was 3.25 years outside Africa, compared to 4.1 years in Africa.

Overall, 21% of participants in the deferred arm needed to start treatment during the follow-up period ($n = 184$), an incidence rate of 12 per 100 person-years of follow-up. However, among Africans the rate of treatment initiation was 9 per 100 person-years, compared to 15 per 100 person-years of follow-up in participants at non-African sites.

Unsurprisingly, the factors significantly associated with the need to start treatment in the deferred treatment arm were lower CD4 count or higher viral load at enrolment (adjusted hazard ratio per increase of 100 CD4 0.6; 95% CI, 0.5-0.7) and higher log₁₀ HIV RNA (adjusted hazard ratio per log increase 1.5; 95% CI, 1.2-1.8).

Overall, 75% of patients in the deferred arm who initiated treatment did so because of a decline in CD4 cell count.

Among those who initiated treatment immediately (886 patients), at a median CD4 count of 442 cells/mm³, 90% had an undetectable viral load (below 400 copies/ml) after one year of treatment. They experienced a mean CD4 cell increase of 158 cells/mm³, to 603 cells/mm³.

In the delayed-treatment group, the median CD4 count at treatment initiation was 225 cells/mm³, and the median time to treatment initiation in the deferred arm was 3.5 years. After one year, 93% had an undetectable viral load (below 400 copies/ml) and CD4 cell counts had risen by a mean of 191 cells/mm³, to 418 cells/mm³.

Virologic failure was rare; only 5% in the immediate-treatment arm and 2.7% in the deferred-treatment arm experienced virologic failure. Of these, 67% in the immediate arm and 60% in the deferred arm switched to second-line therapy.

Clinical outcomes

The effect of early treatment on clinical outcomes was very clear.

Early treatment significantly reduced the risk of clinical illness, but there was no difference in the risk of death between the two study arms.

Primary endpoint clinical events were defined as:

- A WHO stage IV event.
- Pulmonary tuberculosis.
- Severe bacterial infection.
- Death.

Around 7% of participants received cotrimoxazole prophylaxis against bacterial infections, and around 4% received isoniazid preventive therapy to prevent the development of active TB.

A total of 105 participants developed a primary clinical event during 3304 person-years of follow-up. Forty primary events occurred in the immediate arm (2.4 per 100 PY), compared to 65 in the deferred arm (4.0 per 100 PY, hazard ratio 0.59, 95% CI: 0.40 - 0.88, $p = 0.01$).

Early treatment did not significantly reduce the risk of developing pulmonary tuberculosis. There were 14 cases of pulmonary TB in the immediate-treatment arm (0.8 per 100 PY), compared with 16 in the delayed-treatment arm (0.9 per 100 PY). Pulmonary TB cases were diagnosed at a median CD4 count of 521 in the immediate-treatment arm and 295 in the delayed-treatment arm.

In contrast, early treatment did significantly reduce the risk of extrapulmonary TB. Three cases were diagnosed in the

immediate-treatment arm (0.2 per 100 PY), at a median CD4 count of 443, compared to 17 in the delayed-treatment arm (1 per 100 PY), at a median CD4 count of 342.

Bacterial infections occurred somewhat more frequently in the immediate-treatment arm (19 vs 13, 1.1 vs 0.8 per 100 PY). In each arm the most common bacterial infection was pneumonia, and the difference between arms was chiefly driven by four cases of sepsis in the immediate-treatment arm. Three participants in the immediate arm each experienced more than one bacterial infection.

There was no significant difference in the death rate between arms: ten occurred in the immediate arm and 13 in the deferred arm. Deaths were largely attributed to causes other than HIV in the immediate arm: 3 suicides, one stroke, and three unknown causes, with only three deaths due to infection (leptospirosis, TB and sepsis) in the immediate arm. Almost half the deaths in the delayed arm were of unknown cause, with two accidental deaths, one stroke and only two deaths due to infection.

There was no significant difference in severe adverse events between the two arms (14% in each), nor any difference in the distribution of types of adverse event between the two arms.

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Treatment as prevention: what are the next steps?

Turning treatment into a prevention tool that can end the HIV pandemic will require not one, but a host of different improvements, in the delivery of health care to achieve its full impact, and will not succeed without full respect for the human rights of people with HIV, the Sixth International AIDS Society conference heard this week in Rome.

Following Monday's comprehensive presentation of results from [HPTN 052](#), the landmark study which showed that early treatment of HIV-positive people reduced the risk of HIV transmission to their partners by 96%, experts have reviewed some of the challenges in translating these results into action.

Professor Julio Montaner of the University of British Columbia, a long-time champion of treatment as prevention, pointed to the first hurdle: the fact that many people with HIV do not know of their infection, and even if they do, many others are either not in regular care or not on treatment.

Only 19% of HIV-infected people in the United States [are estimated](#) to have an undetectable viral load, Prof. Montaner noted.

Furthermore, 21% of the population of HIV-infected are unaware of their HIV status, yet they are estimated to account for 54% of onward infections in the United States.

Similarly, in Mozambique, [a study that tracked patients from HIV diagnosis through the medical system](#) found that, of 7005 patients who tested positive, 57% were still in care 30 days later. Of these, 77% had a CD4 cell count to determine if they were eligible for antiretroviral treatment (ART). Half of these patients were eligible for

ART, and 471 of these 1506 patients actually started ART within 30 days. Of the original 7005 patients, just 317 made it onto ART and were then adherent for at least six months.

Getting all parts of the process, from the offering of an HIV test through referral to care, starting treatment and ensuring long-term adherence to treatment, will be critical for ensuring that the proportion of people with suppressed viral load is as high as possible.

Couples first

Some voices at the conference are beginning to say that it is unethical not to provide treatment for anyone who is part of a serodiscordant couple.

So should the focus be on population-wide treatment, or should treatment target couples?

Wafaa El-Sadr of Columbia University's International Center for AIDS Care and Treatment Programs (ICAP), which provides treatment to over one million people in 21 countries, pointed out that individuals with HIV who form part of a serodiscordant couple may form a very small part of the total population of people with HIV in some of the countries she works in.

In Lesotho, for example, 15% of couples contained one HIV-positive partner, according to Demographic and Health surveys (see [systematic review by Eyawo et al.](#)), but in Rwanda, only 2.1% of couples tested were serodiscordant. Although high-burden countries are likely to have the biggest proportion of serodiscordant couples, this number is likely to be dwarfed by the number of people who do not know their HIV status.

She argued that any decision made at country level will be highly dependent on population size and on the proportion of diagnosed HIV-positive people in serodiscordant couples. Modelling work by Wafaa El-Sadr and Sally Blower shows that high ART coverage in serodiscordant couples (>70%) could have a substantial impact in Malawi and Lesotho, but a negligible impact in Ghana and Rwanda.

Craig McClure, co-director of Treatment 2.0 activities at the World Health Organization, said: "WHO is very clear that people who are sickest should have first priority for antiretroviral therapy."

"All my patients are in a serodiscordant couple at some point," said Professor Montaner. His comment underlines the artificial nature of the distinction being made if serodiscordant couples are chosen as the priority group on the basis of applying strict criteria that do not extrapolate beyond the population studied in randomised trials (these trials are the gold standard on which WHO must base its guidance).

In addition, any strict definition of a couple is likely to ignore the fact that many people with HIV have multiple partners, are unmarried or have several regular partners, pointed out Professor Helen Rees of Wits Reproductive Health and HIV Institute.

The World Health Organization will be convening a high-level panel to review the role of antiretrovirals for treatment and for prevention over the next twelve months, with a view to simplifying and integrating guidance into one document, said Craig McClure.

Human rights

Eric Fleutelot, director of international programmes for Sidaction, a French HIV organisation, warned that thinking about treatment as prevention needs to put people with HIV at the centre of any strategy.

"It is a revolution in prevention, but is it going to be like the French revolution, in which a new elite of experts and public health people become more powerful, or is it going to be a democratic

revolution in which people with HIV are freed from the fear of passing the virus to their partners?"

"Treatment as prevention offers a wonderful opportunity to discuss about the sexuality of people living with HIV within the context of positive health, rights and dignity. HIV remains a disease that is highly difficult to disclose to family and friends, and highly prevalent among discriminated and marginalised people."

He said that community organisations recommend an immediate review of counselling and medical services for serodiscordant couples and pregnant HIV-positive women, and called for more research to look at the impact of treatment as prevention on sexual behaviour, and on the criminalisation of HIV transmission.

He also called for more research to determine the extent to which transmissions that take place despite treatment are due to sexually transmitted infections.

Finally, he noted, "We need to ensure that early treatment has a clear benefit [for the person who is taking it] and the results of the START trial will be very helpful."

The START trial is a large randomised study which is comparing starting treatment at a CD4 count of 350 – the current WHO recommendation – with starting treatment at a CD4 count above 500, and is expected to report results by 2015.

Waafa El-Sadr commented: "The treatment benefit of HPTN 052 is less compelling than the prevention benefit."

"Every individual with HIV should decide for themselves when and how to start treatment," said Fleutelot. "No one should be forced or coerced into treatment primarily for the benefit of the public health rather than the health or the well-being of the individual."

Pre-exposure prophylaxis

By Gus Cairns, Roger Pebody

Pre-exposure prophylaxis does work for women, two studies find

By Gus Cairns

Two studies of the use of oral pre-exposure prophylaxis (PrEP) in heterosexual people show that oral PrEP will protect women against HIV.

The 6th International AIDS Society Conference in Rome heard the additional data from two trials of pre-exposure prophylaxis in heterosexuals yesterday. First results from these trials, the Partners PrEP trial and the TDF2 trial, [were announced on Wednesday, 13 July](#). This was when the placebo arm of the Partners trial was closed well in advance of the planned ending date as it was realised that there were many more infections in this arm than in people taking antiretroviral PrEP.

The new data on PrEP in men and women were keenly anticipated because another study of PrEP in women, [FEM-PrEP](#), had closed recently after finding zero efficacy for *Truvada*, and it had been theorised that oral PrEP might not work for women because drug concentrations in the genital tract were too low.

The results of the TDF2 trial were planned to be announced at the IAS conference, but in the event were released at the same time as the Partners PrEP results, while a special session was convened at the conference to include more data from both studies.

The Partners study compared tenofovir and tenofovir/FTC (*Truvada*) versus placebo as PrEP in serodiscordant couples (one person HIV-positive, one negative) in Kenya and Uganda, while the

TDF2 study compared *Truvada* versus placebo in heterosexual men and women in Botswana.

In brief, the Partners study found that tenofovir had an efficacy of 62% in preventing HIV infection and *Truvada* an efficacy of 73%; there was no statistical difference between the efficacy of *Truvada* and tenofovir. In the TDF2 study, *Truvada* had an efficacy of 63%, but was 78% efficacious in patients who had last received study drugs less than a month ago and who therefore had pills available.

Efficacy in men and women

In the Partners PrEP study, the HIV-negative partner was female in 38% of the 4758 couples. There was no difference in efficacy of either tenofovir or *Truvada* between men and women. The efficacy of tenofovir was 68% in women and 58% in men versus placebo; the efficacy of *Truvada* was 62% in women and 83% in men. None of the differences between men and women, or between tenofovir and *Truvada*, was statistically significant.

Unadjusted figures in the TDF2 study at first suggested there might be some difference in efficacy between men and women. It is important to note that this study was not 'powered' to demonstrate efficacy; this means that – due to there being fewer infections than expected – even a statistically significant positive result is based on too few cases for it to be regarded as a truly convincing efficacy result. Nonetheless, the headline finding of 63% efficacy against placebo was statistically significant.

In this study, 45% of the 1200 participants were women. The efficacy of *Truvada* in men was 80% (two HIV infections in men on *Truvada* versus ten on placebo) and this was statistically significant. The efficacy in women was 49% (seven infections on *Truvada* versus 14 on placebo), and this lost statistical significance.

However when only participants who had refilled their pills at the clinic in the last 30 days were counted, there were three infections in women on *Truvada* versus 13 on placebo. This was an efficacy of 75.5%, which was statistically significant ($p=0.021$). In men in this group there was one infection on *Truvada* versus six on placebo (82% efficacy), which was actually *not* statistically significant, due to the small numbers.

Other data - Partners study

Because the Partners study has only recently closed its placebo arm, a limited amount of other findings were announced. Placebo-arm recipients will be offered tenofovir or *Truvada*. Recipients already taking active drug will remain blinded (will not know whether they are on tenofovir or *Truvada*) to see if outcomes remain similar.

Presenter Jared Baeten of the University of Washington said that adherence had been excellent throughout, with approximately 97% adherence in all arms, and strong correlation between self-reported adherence and pill count. Baeten speculated that adherence might tend to be higher in couples, especially ones who received adherence and sexual risk counselling together, as they would tend to look after each other. Although 27% of the couples reported unprotected sex in the previous month at baseline, this declined throughout the study to about 10% at month 30.

Initial safety data raised no concerns with similar rates of adverse events and laboratory abnormalities. There were 17 cases of raised creatinine (indicative of kidney malfunction) on tenofovir and 20 on *Truvada* versus twelve on placebo – not a significant difference.

There was a slightly raised incidence of nausea in the first month in patients on tenofovir or *Truvada* (6.3 and 5.9%) versus placebo (4.5%) but no difference after the first month.

Other data - TDF2

Adherence in the TDF2 study was somewhat lower; by pill count it was about 84%, which makes the efficacy measures reported even more impressive. There was no difference in reported adherence between seroconverters and others in the *Truvada* group, though it was slightly higher (93%) in the placebo group. There were no differences observed in sexual behaviour: 14% in all arms reported having had more than one sexual partner in the previous month and 81% reported consistent condom use.

There was a statistically significant difference in nausea between *Truvada* recipients (19%) and placebo (7%) and also in vomiting (11.5 and 7%) and dizziness (15 versus 10.5%), though presenter Michael Thigpen did not specify whether these were concentrated into the first month. There was no difference in the rate of serious adverse events (approximately 9% in all arms).

Forthcoming analyses will include efficacy among participants with varying levels of self-reported adherence, drug level testing for efficacy and adherence, changes in bone mineral density and trends in risk behaviour over time. All participants will now take open-label *Truvada* if they want to.

Acute infections and resistance

Amongst the most important data presented were those concerning acute infection. In Partners PrEP, twelve participants who had tested HIV-negative at screening were found to have acute HIV infection.

In TDF2, there was one case of a participant who started taking *Truvada* while having acute HIV infection, and developed multi-drug-resistant HIV. S/he tested positive for the K65R tenofovir resistance mutation and the M184V FTC mutation; s/he also had a broad-spectrum NNRTI mutation A62V, which suggests that the virus contracted was not wild-type. This individual is currently undetectable on AZT, 3TC and boosted lopinavir.

One seroconverter in the placebo arm was also found to have HIV with low levels of the K65R mutation. This is a reminder that one of the most problematic aspects of PrEP is the need to exclude patients who are in the process of seroconverting to HIV from taking it, and also that it does not protect against drug-resistant virus.

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Gay men's PrEP study final results: near 90% efficacy in men who took drug, but adherence even lower than thought

A completed series of investigations into the iPrEx study of tenofovir/FTC (*Truvada*) as pre-exposure prophylaxis (PrEP) has found that the drug was 92% efficacious in preventing HIV infection amongst those who had detectable drug levels, though only 42% efficacious overall.

An expanded number of drug-level tests show that only 44% of those who did *not* become infected with HIV had drug detectable in their blood and/or cells, suggesting that overall adherence in the study was even lower than thought. This suggests that adherence will be the factor that may limit the effectiveness of this strategy in curbing HIV in many populations, and that it may need to be offered only to people highly motivated to take it.

Efficacy

The iPrEx study [reported its initial findings in November 2010](#). It found at this point that the overall efficacy of the drug in preventing HIV was 44%, in other words that nine HIV infections out of 20 that would otherwise have happened were prevented.

Updated findings, presented at the [International AIDS Society conference](#) (IAS 2011) in Rome by the trial's lead investigator Robert Grant, show that the finally-calculated overall efficacy was 42%. There were 131 HIV infections during the study, 83 in the placebo arm of the 2499-member trial and 48 in the *Truvada* arm. The 95% confidence interval was 18% to 60%, meaning that the 'true' efficacy, allowing for chance, had a 95% chance of lying within these figures. The probability that the finding was a chance one was 0.002, meaning there was only a one in 500 chance that the efficacy observed was purely due to chance.

Efficacy was notably higher in some groups than others. It was 83% in circumcised men and 36% in uncircumcised men. There were relatively few circumcised men in the study, so this could have been a random finding, but this mysterious interaction between circumcision and other prevention methods, which has also been seen in the STEP vaccine trial, needs further investigation.

Efficacy was 52% in those with secondary education or above and only 14% in those with only primary education. It was also, rather discouragingly, only 28% in men aged younger than 25. It is not news that young people find adherence a problem, but given that PrEP might have its highest potential effectiveness if given to young people at their peak of HIV risk, more studies are needed to see if it is feasible as a prevention measure in youth. It was also completely ineffective (efficacy minus 3%) in the small number (1% of the study population) of transgendered people taking it.

None of these differences are statistically significant, but one significant difference was that PrEP was 52% efficacious in men who reported unprotected anal intercourse as the passive partner, and worse than ineffective in men who did not report it. This may indicate that adherence was highest in those who knew they were at highest risk.

Adherence and drug levels

In the initial findings, one unexpected one was that while very few men who caught HIV had detectable drug levels in their blood, the same was true of over half of the men who did not catch HIV, indicating low adherence.

This analysis was only conducted in 34 people who caught HIV and 42 who did not in the original findings. An expanded substudy (Anderson) tested drug levels in all 48 men who caught HIV, each matched with three controls (144 in total) of similar age and background who did not catch HIV.

This found that only 10% of those who caught HIV had detectable drug levels in either cells or blood plasma. However it also found that only 44% of those who did *not* catch HIV had detectable drug in their system either. This may indicate that overall adherence was even lower than thought.

The absence of detectable drug in cells also indicates that most men did not take the drug on an on/off basis: either they did

consistently or they didn't at all. In the 10% of men who caught HIV who *did* have detectable drug, levels were half of those seen in controls; these people may be amongst the minority who took it now and then. Overall, the HIV acquisition rate in people with detectable drug in their system was 87% lower than in those where drug was undetectable.

Another substudy (Liu 1) measured drug levels in hair, and indicator of whether people had ever taken the drug. Drug was detected in 90% of subjects from US and South African sites, who may be more used to randomised drug trials, and only 55% of subjects from the South American and Thai sites.

Risk compensation

Only a minority of people thought they know whether they were taking drug or placebo; 63% didn't hazard a guess and 6% weren't asked. Amongst those who thought they knew, 9% thought they were on placebo and 22% thought they were on *Truvada* – indicating that hope springs eternal, perhaps. They were wrong about their guess exactly half of the time, indicating that the trial remained truly 'blinded'.

During the trial, the proportion of men reporting unprotected receptive anal intercourse declined from 58% at baseline to about 25%. It was non-significantly higher (about 30%) in men who thought they were on *Truvada*, providing very little evidence of behaviour change. Only an open-label study, however, where all subjects know they are taking PrEP, will show if it causes people to change their risk behaviour.

Acute HIV infection and resistance

One concern is whether many people taking PrEP will do so when they already been infected with HIV, but not yet developed antibodies. Because during acute infection viral levels are very high, this provides an ideal environment for the development of drug resistance, and in fact ten men out of the 131 infected during the study in fact had acute HIV infection (virus detectable but not antibodies) at the time they started PrEP. Two of those men appear to have developed resistance as a result of taking PrEP.

This means that one in 250 men in the study had acute HIV at baseline. During the study, however, only one in 1666 subjects actually came down with acute HIV infection while taking *Truvada*, and no one developed resistance.

Depression, adherence and behaviour

Depression has been associated with poor adherence in treatment studies. A substudy (Liu 2) of depression showed that drug levels in hair in people reporting high depression scores were somewhat lower than in other people (70% with detectable drug versus 81%), but this was not statistically significant.

Depressed people were somewhat more likely to have had unprotected receptive anal intercourse in the past three months (29% versus 24%) but had nearly twice the number of partners (an average of 0.8 in three months versus 0.45).

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Antiretroviral prevention methods 'not in competition' with each other

By Keith Alcorn

Antiretroviral prevention methods are not in competition, and policy makers and providers need to start to thinking about how antiretrovirals, pre-exposure prophylaxis and microbicides will be provided as part of a combination prevention package – and who will benefit most from each method, delegates heard at a satellite meeting on the opening day of the Sixth International AIDS Society Conference in Rome.

"You don't want to have the family planning clinic here, the pills clinic here, the injections clinic here, and the microbicides clinic over here," said Dr Stephen Becker of the Bill and Melinda Gates Foundation.

Delegates were discussing the rapidly changing landscape of HIV prevention methods that use antiretroviral drugs. One year ago, at the International AIDS Conference in Vienna, the world heard the results of the [CAPRISA study](#), which showed that a microbicide gel containing tenofovir halved the risk of HIV infection in women who used the vaginal gel consistently.

Since then results from four studies have added to the array of prevention methods that exploit antiretroviral drugs to prevent transmission or acquisition of HIV infection:

- The [iPrEx study](#) showed that taking the antiretroviral combination *Truvada* (tenofovir and emtricitabine (also known as FTC) reduced the risk of HIV infection in men who have sex with men by 44%.
- The [HPTN 052 study](#) showed that early treatment reduced the risk of HIV transmission to an uninfected regular partner by at least 96%.
- The [Partners study](#) showed pre-exposure prophylaxis with *Truvada* or with tenofovir alone reduced the risk of HIV infection by between 62% and 73%.
- The [TDF2 study](#) showed that pre-exposure prophylaxis with *Truvada* reduced the risk of infection by between 62% and 78%.

The first tenofovir-containing microbicide could receive regulatory approval by the end of 2013, subject to positive results from a confirmatory trial now taking place in South Africa. That study is testing exactly the same dosing regimen as that used in the CAPRISA study, the so-called BAT 24 dosing schedule: one dose Before, one After, and no more than Two doses in 24 hours.

A second CAPRISA study (008) is testing the roll-out of tenofovir gel through family planning clinics in KwaZulu-Natal, comparing the monthly testing and follow-up schedule used in the original CAPRISA study with a three-monthly schedule, in order to examine the feasibility and acceptability of providing a microbicide through existing health services that target sexually active women.

Although the South African government has already begun investing in the scale-up of production facilities to manufacture the gel, the extent of demand for the microbicide is still unclear. Studies

of women's attitudes towards the microbicide will be needed to gauge demand, but a lot of work will also be needed to develop demand – and to make sure that women understand how they could benefit from using the microbicide.

"We need to reach out to women who don't perceive themselves to be at risk, and we should be getting communities to rally round to be early adopters of tenofovir gel," said Samu Dube of the Global Campaign for Microbicides.

"We need to get the product to the places where women are: the family planning clinics, the immunisation centres, antenatal clinics. We also need to target the school health system."

However, work will also be needed to convince the providers of those services that they have a role to play in expanding women's opportunities to protect themselves from HIV infection.

"Providers can be major gatekeepers – their attitudes and how they present it to women will be critical. We saw very negative attitudes from the providers towards the female condom. Ideally they should use [the microbicide] themselves at least once," said Catherine Hankins of UNAIDS.

Provider and donor preferences for particular prevention methods could also overshadow the need to think about prevention technologies as a spectrum of methods that will suit different people at different times.

"Is treatment always the best option [as the prevention measure] in the serodiscordant couple? If the index partner can't or won't take pills, or if the HIV-negative partner is having concurrent partners, they might need PrEP or a microbicide," said Professor Myron Cohen of the University of North Carolina, lead investigator on the HPTN 052 study.

He also pointed to the estimated volume of transmission that takes place during the early weeks after infection. In the region of Malawi in which the HPTN 052 study recruited participants, his team calculated that around 30% of HIV infections came from undiagnosed people who had been infected less than six months previously.

In these circumstances, he pointed out, a microbicide or PrEP would still have an important role to play, even if counselling, testing, early diagnosis and treatment could be maximised.

Indeed, defining the niches of different antiretroviral-based prevention methods will depend on up to date information about local epidemics and behavioural patterns, applied through mathematical modelling to generate options for policy makers, what Willard Cates of Family Health International called "the science of prioritisation, to make scarce resources go further to maximise impact".

"Modellers have their hands full at the moment, and that's for good reason. That information needs to go out now [in order to help with prioritisation]," said Peter Cherutich of the Kenyan Ministry of Health.

"It's very important not to pit prevention technologies against each other," said Renée Ridzon of the Bill and Melinda Gates Foundation.

However, microbicides may have unique introductory challenges, said David Stanton of USAID, whose agency is strongly committed to supporting microbicide scale-up in sub-Saharan Africa. The tenofovir microbicide will have to clear the hurdles of confirmatory trials, as well as differences in regulatory requirements between countries before it can even be distributed. The South African Medicines Control Agency has not yet given a clear opinion on what data it will require for registration, leaving the danger that further studies could be needed to achieve registration in South Africa.

There is also the challenge of ensuring that the gel is manufactured to a consistently high standard, so that contains the right quantity of tenofovir in each dose, and the challenge of organising an efficient distribution system.

WHO and UNAIDS are working with CONRAD and the South African Ministry of Science and Technology, two of the sponsors of the satellite meeting, to plan for introduction of tenofovir gel, and WHO will develop guidance on use of the microbicide so that it can be released as soon as the first regulatory approval is granted.

Global Campaign for Microbicides, the third sponsor of the meeting, is working to raise awareness of the choices around prevention technologies, both for policy makers and communities, and to build community awareness and demand for the tenofovir microbicide.

But perhaps the biggest challenge for introduction will be the accessibility of the microbicide gel for a group at particularly high risk of infection in southern Africa – young women and girls. Dr. Sengiziwe Sibeko, a women's health practitioner in KwaZulu-Natal, said that sexually active adolescent girls represented an important group who could benefit from prevention counselling that included discussion of the microbicide gel.

But, said Dr Stephen Becker, "the idea of doing sex education in schools and distributing products for HIV prevention is not a straightforward path and will take a great deal of pushing."

Nevertheless, it highlights one of the key discussions about niches for prevention products that will need to take place: as well as thinking about the characteristics of populations most likely to benefit, a clear strategy will also be needed for overcoming the social, legal and health system barriers that could prevent maximum impact of microbicides.

While circumcising male adolescents is easy and socially acceptable, social and legal constraints on the sexuality of women will continue to undermine the central promise of microbicides – a prevention tool to empower women – unless confronted head-on.

From 'what if' to 'what now': implementing the new prevention technologies

By Gus Cairns

Two consecutive sessions at the sixth International AIDS Society conference in Rome yesterday were devoted, now we have convincing scientific data on the benefits of treatment as prevention and PrEP, to putting these new prevention methods into practice.

"We have moved from 'What if?' to 'What now?'" was the comment of Mitchell Warren, Executive Director of the AIDS Vaccine Advocacy Coalition (AVAC), on what else we need to know, what barriers need to be addressed, and what resources might be required, to maximise the promise of antiretroviral-based prevention.

Anthony Fauci, Director of the US National Institute of Allergies and Infectious Diseases (NIAID), said: "We now have a solid scientific foundation to say that even in the absence of a vaccine we have the capacity to end the epidemic. I can't go to the US President and say: 'We can cure HIV.' But I can say 'Ending the epidemic is scientifically doable'."

Earlier, however, Nancy Padian from the Office of the US Global AIDS Coordinator had outlined formidable challenges still to be answered if antiretroviral treatment could bring about this goal.

She said that questions still needing answers include whether antiretroviral drugs (ARVs) really are a durable and reliable means of viral load suppression over a period of years and whether increasing the proportion of people on treatment would lead to

increased levels of resistance. The biggest practical question, however, was whether treatment as prevention would work in situations where a high proportion of transmissions came from people with acute, recent HIV infections.

The biggest barriers to treatment as prevention, however, are stigma and lack of resources. Implementing ARV-based prevention would not only be expensive in terms of drugs; it would require added human resources and increased training and task-shifting for prevention counsellors so they can deal with biomedical data. There would also be added costs in terms of tests and monitoring.

The other big barrier will be the stigma of being tested, she said, particularly for at-risk populations in societies where injecting drug use, male-male sex, or sex work were criminalised and stigmatised. Treatment as prevention would require people not simply to test and then go to more supportive community organisations for prevention advice; it required a much closer relationship with medical personnel who might be prejudiced or feared to be so.

Mitchell Warren issued a call to action to implement the new strategies, but his presentation was tempered by realism. "We have evidence, we have data, and we now need to make decisions," he said.

Firstly, he said, we need "smart combinations" of prevention interventions tailored to different people and populations. "It can be seen as frustrating to have all these tools (he counted 13 different ones for which there is now evidence) and not know what to choose or how to pay for them," he said, "but it's a better kind of frustration than in 2004" (at the time of the closing of the first PrEP study in Cambodia).

Given that, even now, only 8 to 9% of people who need them have ready access to condoms or clean needles, only 11% of gay men have access to behaviour-change programmes, and only a third of HIV-positive mothers have access to ARVs to prevent transmission to their baby, making ARVs more widely available as prevention or PrEP would be a big challenge.

Using ARVs for prevention would continue to be a behavioural issue, he added, in terms of people coming forward for testing and, crucially, for adherence.

One important consideration was to match the prevention intervention to the person. PrEP, for instance, had been criticised as a 'niche intervention', but niche interventions were important for specific groups of people and could be extremely effective; an example from another context was injectable contraceptives.

Lastly, of course, money and resource allocation would be a huge issue. "Scientific data do not change the world – programmes and policies backed by civil society, donors, implementers and governments do," he said.

In this context, Tim Farley of the World Health Organization, presenting a comprehensive review of the licensing processes needed for ARV-based prevention methods in the USA, Europe and Africa, remarked on the extreme range of prices paid for tenofovir and *Truvada* in different contexts, from \$35.82 as the US list price (almost always discounted) for one *Truvada* tablet, to \$0.87 as the 'no profit' price paid to the developers Gilead in low-income countries and the even lower \$0.28 for a generic equivalent. He noted, however, that Gilead was already licensing generic companies to produce tenofovir and *Truvada* at lower prices.

Helen Rees, University of Witwatersrand in South Africa, said that the new data from the treatment-as-prevention and PrEP studies had come along just as she was involved in writing the country's new National Plan for HIV. She said that the new prevention choices offered could feel bewildering. "Do we put more people on treatment, circumcise all men or buy millions of condoms?" she

asked. As an initial step, the country had extended its CD4 criteria to 350 cells/mm³ in line with WHO guidelines and had decided that, with still only 45% of those who need it on treatment, that treatment access remained South Africa's biggest priority.

She added, however, that the data from serodiscordant-couple studies did not necessarily provide the kind of data needed on the likely effectiveness of treatment as prevention, or of PrEP. "South Africa is a country of female-dominated households and a low level of marriage," she said, "and serodiscordant couples are hard to identify: men still won't come forward." It had been decided that HIV-negative women wishing to conceive who were or might be having sex with HIV-positive men were a logical first population who might need PrEP, but setting up PrEP as a service was a much bigger step than expanding existing HIV treatment, as it involved a new type of service that didn't yet exist.

Myron Cohen, principal investigator of the HPTN 052 study, said that if the world did not pay for ARVs now it would do so later, in terms of an indefinitely increasing number of people needing HIV treatment. He said that his study's findings did not imply a huge expansion of treatment to groups not previously entitled to it; for the study's purposes, it had needed to offer ARVs to people with relatively high CD4 counts but the reduction in infectiousness should apply to people with CD4 counts below 350 cells/mm³ too, and should serve as a further incentive to get ARVs to the two-thirds of people with CD4 counts below this figure who were not yet on treatment.

Above all, moving from the data provided by scientific studies to the business of trying to make HIV prevention work in the real world was an exercise in dealing in uncertainty. Microbicide researcher Ian McGowan of the University of Pittsburgh commented that: "In an ideal world, we'd treat all the HIV-positive people and the negative ones would use condoms. But people may not go on treatment, may fail treatment, and may fail to use condoms. The world has never been black and white, and the debate about moving from treatment, to treatment-as-prevention, to PrEP is the kind of debate we have been having on access to medications for HIV ever since we've had them."

The research agenda for antiretroviral prevention – now it gets complex

By Roger Pebody

We now know that starting antiretroviral therapy early, pre-exposure prophylaxis (PrEP) and vaginal microbicides can all have an impact on HIV transmission, Victor de Gruttola told a satellite session at the International AIDS Society conference in Rome on Sunday. But researchers now need to do more than establish efficacy, he said.

Studies need to identify the mechanisms by which interventions do and do not work in different communities. They need to get to understand the characteristics of sexual networks, sexual behaviour and local epidemiology that influence their effectiveness. And they need to compare the impact of providing a stand-alone intervention with that of combined packages of interventions.

Other speakers at the satellite, which had been organised by AVAC and the European AIDS Treatment Group, emphasised the importance of implementation research – identifying barriers to the implementation of prevention interventions and developing strategies to overcome them.

Both Victor de Gruttola from the Harvard School of Public Health and Timothy Hallett from Imperial College London suggested there

is no single best intervention – or even best package of interventions, but that this will depend on the characteristics of different communities and epidemics.

For different settings, researchers need to identify the combination of prevention interventions which could keep the spread of HIV under control. They also need to establish the breadth of programme coverage that is required.

Timothy Hallett presented some results from a basic mathematical model which aimed to identify the impact and cost of providing antiretroviral therapy to 80% of people at a number of different CD4 counts, PrEP to varying proportions of young people, PrEP to most people of all ages, or a combination thereof.

For each level of spending, Hallett identified the programme that would have the greatest impact – at the lowest levels of spending identified, this would be antiretroviral therapy alone. Should there be budget available to fund more than making therapy available for all with diagnosed HIV, policy makers should then provide PrEP for young people, and then for people of all ages.

But the model's results change if baseline assumptions shift. If the costs of PrEP are actually lower than Hallett estimated (because drug prices come down), or if it turns out to be more expensive to get people diagnosed early and on to treatment (because testing promotion has less impact than anticipated or because new health services need to be provided), strategies with a greater reliance on PrEP would start to make more sense.

And the modelling studies need to consider other issues. Interventions – and combinations of interventions – will have different levels of effectiveness in different places, depending on a vast range of local factors which researchers are only beginning to get to grips with.

For example, Victor de Gruttola mentioned assortativity: the tendency for people who have many sexual partners to choose partners with the same characteristic. When this is the case, interventions will have less impact than when there is less assortativity.

Other important local factors are the number of transmissions that are due to people who are themselves recently infected, the proportion of people with HIV who are diagnosed and linked to care and the proportion of HIV-negative people who can be provided with an intervention.

Timothy Hallett noted that, although we know from the [HPTN 052 trial](#) that early initiation of treatment can reduce transmission to stable partners by 96%, this does not mean that changing treatment guidelines will bring about a 96% reduction in new infections.

Far too many people are diagnosed late for this to be possible. While early treatment strategies rely on early diagnosis, Sheena McCormack of the UK's Medical Research Council said that frequent HIV screening is not always an acceptable intervention.

New modelling work suggests that, even to achieve a 60% reduction in new infections through early treatment, testing would have to be so frequent that 60% are diagnosed within a year of infection, 90% of diagnosed people would have to be treated, 87% would need to be virally suppressed within six months of starting therapy, with only a 1% drop-out rate from treatment programmes.

Just minor modifications in these highly optimistic assumptions can wipe out the predicted impact. On the other hand, a combination of interventions would be more resilient in real-life conditions.

Should there not be the resources to make treatment available for everyone who needs it, its impact could be increased by

prioritising its provision to people at higher risk of passing their infection on.

Sheena McCormack argued that the next prevention trials need to show that it is feasible to deliver interventions in a service setting, rather than with a great number of extra resources or with excessive demands placed on participants. Requirements for clinic visits, HIV tests and laboratory monitoring should be cut back, while users should be advised that PrEP may only be used around the time of sex, rather than on a daily basis. These measures will reduce the cost of interventions and increase their acceptability to users, she said.

She pointed out that a key question for a pilot PrEP study in the UK is whether a significant number of gay men are actually interested in taking it.

More acceptable interventions are more likely to be used consistently, and Sheena McCormack said that adherence is key to all the interventions discussed: "It's all about behaviour," she said. This applies as much to condom users as it does to people using a microbicide, PrEP or antiretroviral treatment.

Operational research: diagnostics and task-shifting

By Theo Smart

How best to deploy point-of-care CD4 cell testing in resource-limited settings?

Widespread introduction of point-of-care (POC) CD4 cell tests that don't require a laboratory technician but can be performed onsite by a nurse, providing results in less than an hour – *while* the patient waits) is expected in the next 12 to 24 months, said Dr Steven Reid of Imperial College, London, during a session on advances in diagnostics on Monday at the International AIDS Society conference in Rome, Italy.

In fact, one such test is already being rolled out in some settings. Speakers during the session described how POC CD4 tests might improve service delivery for people living with HIV, their potential cost-effectiveness and where best to deploy them.

For instance, the availability of POC CD4 cell tests – paired with a mobile HIV counselling and testing service – significantly increased linkage to care for people testing positive for HIV, according to one study.

Dr Reid presented a modelling study suggesting that starting treatment on the basis of POC results would be more cost-effective than with traditional CD4 cell tests, and better than initiating treatment on the basis of clinical (syndromic) management of people living with HIV – potentially adding years to their lives.

However, another study, presented by Dr Ilesh V Jani of the Instituto Nacional de Saúde reported that the cost of implementing POC CD4 would depend upon the clinic and volume of tests it would perform – and that there should be "a more judicious deployment of the technology", prioritising "higher volume sites and clinics that cannot refer samples to laboratories".

CD4 cell tests

CD4 depletion is the hallmark of acquired immune deficiency, and CD4 cell measurements are the best indication of when a person should start antiretroviral treatment – preferably before there is a seriously increased risk of opportunistic infections and tuberculosis. The World Health Organization's 2010 antiretroviral

treatment (ART) guidelines recommend that treatment begin at a CD4 count of 350 cells/mm³ – although not all countries follow this recommendation yet.

But in a number of resource-constrained settings, it is difficult to do CD4 cell measurements to start treatment – and these have instead relied on clinical staging (based upon symptoms and signs of immune deficiency). But a number of studies have shown that clinical staging is inadequate since it misses large numbers of people with very low CD4 cell counts, who are at great risk of catastrophic illnesses.

The gold standard for CD4 measurement is flow cytometry (Becton Dickinson or Beckman), but this equipment is relatively complex and it requires skilled laboratory technicians to perform. Many resource-poor settings simply don't have the infrastructure, human resources or funds to provide convenient access to CD4 cell testing in more remote or rural settings. People either have to be referred to a site that provides CD4 cell testing, or have their specimens sent to the site and return to the clinic to get their results.

Many people simply don't bother because of time, distance or money, and are often lost to follow-up, until they either fall ill, and come in for care again, or die. Researchers have therefore been working to make CD4 cell testing cheaper, more accessible and easier to use.

"The CD4 Initiative was established in 2005 to develop rapid, economical, point-of-care tests for CD4," said Dr Reid. "The aim was to develop tests which require limited or no infrastructure – no electronics, simple to use, and cheap."

Such CD4 cell results could then be introduced into the most remote rural settings to put people onto ART on the basis of CD4 counts rather than clinical staging. The new tests would also facilitate the delivery of ART in decentralised settings (including the primary health care clinic) and possibly improve retention into ART programmes, by speeding the time it takes between when a person gets tested and when he or she goes onto ART, and by reducing loss to follow-up.

The new generation of CD4 cell tests

Dr Reid listed three of the leading POC CD4 products.

[Alere's PIMA](#) is already in use (in both the mobile clinic study and in Mozambique). It consists of a disposable CD4 cartridge containing sealed reagents and a portable analyser to produce a CD4 cell test from either a fingerstick or venous whole blood sample within 20 minutes.

A finger prick is made with a sterile lancet to collect 25µL of capillary whole blood into the cartridge, without manual sample handling or processing. The reagents (all dried and requiring no refrigeration) are sealed inside the cartridge. The cartridge is then inserted into the battery (or A/C) powered portable analyser, which automatically begins the testing process, providing a direct CD4 measurement in 20 minutes.

[Daktari CD4](#) is another POC test, that requires no pipetting, labels or reagents. Its cartridge is then placed into an analyser that reads electrical signals, and reports the CD4 count within minutes, according to the manufacturer's site.

The third POC test, from [CD4 Initiative working with Zyomyx, Inc.](#), is a single disposable unit that can deliver an absolute CD4 count without complex electronics and instrumentation. It is the first *readerless* point-of-care, that is, without an analyzer. Instead, the healthcare worker reads the CD4 cell count by a simple visual inspection of the test tube-like unit.

Modelling

Despite the promise of POC CD4 cell tests, "the impact of introduction is not obvious", said Dr Reid. So he adapted a published model of ART initiation, to compare the impact on life-years saved (LYS) of syndromic management and the two CD4 counting strategies (flow cytometry and POC CD4 tests), adding in costs for the CD4 cell monitoring technologies. He adjusted a number of parameters in the model (based upon the POC test's expected impact on retention), and used two different CD4 cell initiation thresholds (250 and 350 cells/mm³) and different estimates for the CD4 cell costs.

He calculated high and low costs for the CD4 cell technologies based upon costs of reagents and the test price, the staffing, personnel costs needed to perform the test, infrastructure, laboratory costs (when needed), the overhead for hospital or laboratory (if needed), referring to data on costs from Zimbabwe and Uganda. The unit costs were higher on the POC CD4 test, but reagents and other expenses made the centralised flow cytometry test more expensive overall.

In the model, initiation based upon syndromic management clearly cost the least (almost half of POC), but has the poorest outcomes in terms of life-years saved. Initiation on the basis of flow cytometry and POC CD4 would have similar overall costs, but POC CD4 cell tests would result in more life-years saved and thus be more cost-effective.

However, these results are entirely dependent upon the cost calculations and assumptions about how the availability of point-of-care testing would affect retention and the timely initiation of ART. Other reports presented at the conference were conflicting on some of these points.

Increased linkage to care

For instance, there was a poster presentation of data from Themba Lethu Clinic in Johannesburg, previously reported at the 5th South African AIDS Conference, showing that having a POC CD4 test available didn't dramatically shorten the time between testing positive and going onto ART. The lack of impact was primarily due to the fact that 39% of the people rejected the offer of POC CD4.

However, another study from the same researchers in Johannesburg, presented by Dr Bruce Larson, reported much greater acceptance – 90% – of the Pima POC CD4 cell test when it was piloted to a few hundred people testing positive at a mobile HIV counselling and testing service.

The study involved phone interviews of people who had been offered the test versus those who had not. There was a 26% increase in referral uptake (those making their first visit to the referral site within eight weeks of testing positive).

"The increase in referral completion went from 38.5% to 64.7% (a 68% improvement)," said Dr Larson.

He said the difference in the uptake of the offer for POC CD4 between the mobile clinic and Themba Lethu clinic was puzzling, but he noted that the Pima test provided results within about 20 minutes, while the test used at Themba Lethu took much longer (closer to an hour). "Once it was explained how long it would take, many of the patients at Themba Lethu may simply not have wanted to wait around that long," he said.

Likewise, Dr Jani mentioned similar data from a study he conducted in Mozambique, which found that nurses in primary health clinics can accurately perform CD4 counting using point-of-care devices.

Comparing percentages of patients getting and returning to the clinic at baseline to post-piloting of the POC CD4, there was a clear reduction in pre-treatment loss to follow-up. At baseline, only 55.2% got their CD4 cell results, compared to 92.9% afterwards, while only 28.4% returned to the clinic for care, versus 79.4% after the introduction of POC CD4.

Costs depend on throughput needed — deploy carefully

However, Dr Jani presented data on indicating that the cost of implementing POC CD4 could be significant, and suggested that programmes may want to consider carefully where they want to install POC CD4 cell monitoring.

The traditional CD4 test has several things going for it: a higher throughput (50 to 75 tests per day), a large installed base (>1000 instruments across Africa), already existing infrastructure in some settings, and it may be more efficient and cheaper due to economy of scale. POC CD4 however can only perform 5 to 20 tests per day, and is new technology — although it does not require significant infrastructure and can be performed by non-specialised personnel.

He developed a different costing model based upon data gathered from health facilities across 13 countries in sub-Saharan Africa, looking at reagent, control, and consumable costs, equipment and maintenance costs, lab infrastructure and overhead costs, sample transport costs, human resource salaries, and site patient volumes.

These data were used to calculate a total cost per test for a site with a known testing volume to determine if it would be less costly to refer samples to an existing CD4 laboratory or to implement POC CD4 testing on-site (with the PIMA test).

The cost of conventional CD4 cell testing actually varied significantly by site (due to reagent costs), while POC CD4 costs were more stable. At sites with average throughput, the costs of testing were similar: \$10.50 for the conventional CD4 and \$11.78 for the POC CD4.

However, for increasing volume, the cost per test for POC CD4 drops dramatically (though it will increase again if more than 5000 tests are performed a year — because a second analyser would be needed).

The cost of POC CD4 versus conventional CD4 is about equal if ~2,900 tests per year are performed by a site.

“Sites above 2900 tests per year comprise more than 90% of CD4 test demand, but it is more intuitive that POC would belong at small, remote sites,” said Dr. Jani.

But even though it may be less costly to put the POC CD4 tests at a number of higher volume sites, Dr Jani stressed site selection should depend on other factors than simply cost, including universal access, equity, distance to laboratories, patient loss-to-follow-up, size of catchment area, ART coverage, HIV prevalence, and PMTCT services.

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Despite challenges, South Africa successfully scaling up GeneXpert TB test — but concerns about the cost of rapid full implementation

South Africa has quickly and successfully scaled up the first phase of implementation of the new diagnostic test for tuberculosis, the GeneXpert MTB/RIF assay, as the first-line TB test in 25 sites, achieving two to threefold higher rates of TB and drug-resistant TB diagnoses in many of the facilities, according to a late breaker presentation at IAS2011 in Rome. However, switching over from relying on smear microscopy-based diagnoses to using the new test presents a host of challenges.

“It changes everything we do,” said Professor Wendy Stevens of the University of Witwatersrand and the National Health Laboratory Service, who added that, despite the expected substantial increase in people put on earlier treatment, the cost of rapid full implementation has the programme quite “anxious.”

“Our initial algorithm is an expensive one, which may well have to be modified as confidence in technology and data emerges,” she said.

TB in South Africa

The rates of TB, HIV-related TB and MDR-TB in South Africa are among the highest in the world — with case detection and cure rates that are below WHO targets. This failure to diagnose and effectively treat TB leads to the alarming overall rate of TB, around 980 cases per 100,000, much of which is fuelled by the HIV epidemic. 70%-80% of the country's TB suspects are infected with HIV, generating one-fifth of world's reported HIV-associated TB cases.

Even if case detection were at recommended levels, the currently used first line diagnostic tests are notoriously outdated and insensitive, especially for detecting TB in smear-negative individuals, and for detecting extrapulmonary TB. Both smear negative and extrapulmonary TB are much more common in people living with HIV.

Patients seeking a diagnosis for TB and treatment have to make multiple clinic before they are finally diagnosed and access treatment. Culture takes weeks or months and cannot be not performed on all suspects. While a WHO-recommended algorithm exists to empirically manage suspected smear-negative TB, it relies on cough as a gatekeeper symptom, and thus may not be sensitive enough to capture many people living with HIV, and requires a return clinic visit before an empirical diagnosis can be made.

New diagnostic techniques have been under review over the last few years. The GeneXpert MTB/RIF assay has seemed one of the most promising technologies — a self-contained TB diagnosis system that automates sample processing on sputum and provides real time PCR results within about two hours.

The test also screens for the presence of resistance to rifampicin, which is used as a surrogate for MDR-TB, and should therefore speed the time to diagnosing drug-resistant TB as well. As previously reported, the test requires minimal specimen handling and could be theoretically be performed by trained nurses.

Recently, after a review of the new test, the WHO gave it strong recommendation: “The new automated DNA test for TB [GeneXpert]

should be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV/TB."

South Africa already has a well resourced TB diagnostic infrastructure, according to Prof. Stevens. It has 244 microscopy centres that last year performed over 4 million smears, and 16 culture labs that did 1 million cultures and thousands of line probe assays.

"Despite this we are not making the diagnosis adequately in most of our patients. Our smear sensitivity rates in HIV are about 35-40%, and delay in the results from culture frequently lead to loss to follow-up," she said.

Scaling up Gene Xpert

South Africa began to implement a pilot roll-out of Gene Xpert in March 2011, after Health Minister Aaron Motsoaledi ordered a radical change in the country's policy on TB diagnosis. He instructed the NHLS to get the first pilot sites up and running within six weeks.

The selection of the pilot sites was based upon burden, with 30 instruments installed at 25 of the highest burden districts in each province. The initial rollout was at microscopy centres, which generally provide about 11% of national coverage for TB diagnosis based upon smears.

"The decision at the time was to replace smears with one GeneXpert test for diagnosis. What has happened subsequently is that a lot of work has gone into the development of an algorithm," said Prof. Stevens. The plan for the near future is that all patients will get the GeneXpert test up front. If the test fails (due to an error, such as lack of an adequate specimen), the test is repeated. If the TB result is positive, they are diagnosed with TB. If the test shows rifampicin resistance as well, the results must be confirmed by TB culture and drug sensitivity testing (DST).

One of the problems with this algorithm is that requiring only one GeneXpert test could miss a high percentage of people living with HIV who have smear-negative TB. The GeneXpert test is able to detect TB in many – though not all – smear-negative people living with HIV, but more can be detected by performing a second or a third test – which of course, increases the cost of diagnosis.

NHLS had a very limited time to perform the activities needed to support the rollout. Site assessments had to be done at all 25 sites, with a checklist developed to looking for network points, power, space, air conditioning, and adequate human resources. Standard operating procedures had to be developed and 80 laboratory technologists had to be trained (54 were trained by World TB Day) with an intensive two day centralised training – so far, these have largely been microscopists who had previously been doing first line diagnosis.

All instruments have been interfaced with the laboratory information management system (LMIS). A Lab-Track LIS interface was developed to automatically report the lab number, instrument, cartridge number whether or not TB was detected, and whether RIF resistance was detected or not.

"This is so we can automatically collect data in real time," said Prof Stevens. "We have also developed an external quality assurance programme using dried culture spots. We quantitated TB bacteria by flow, placed it on a dried culture spot, and every module that gets placed in the field is tested in this way."

The next steps were the development of the further implementation plan, the budget plan and a national TB Costing Model (NTCM).

Results

All the sites were launched by World TB day, and most were operating at full capacity by April. Cumulatively, between March and June, 50,093 people were screened with the test – yielding a TB diagnosis in 8591 cases.

"We have identified a positivity rate of 17.15%, which is *huge*," said Prof. Stevens. The test failure rate was 4.02% (these tests must be re-run). "For rifampicin resistance, in the same population, we have picked up 7.3% (n=630), which is literally triple what has been identified in the population previously," she said.

Indeed, if these rates are accurate it would suggest that around 30,000 to 40,000 cases of the 400-500,000 notified TB cases in South Africa are MDR-TB – which would have profound implications for South Africa's TB programme. However, she added that the test is known to produce false positives for rifampicin resistance, so those findings should be seen as preliminary.

Indeed, in a newly published study by Lawn et al, Gene Xpert correctly identified rifampicin resistance in four cases of multidrug-resistant TB but incorrectly identified resistance in three other patients whose disease was subsequently confirmed to be drug sensitive by gene sequencing. This means that the test is highly sensitive, but has a specificity of 94.1%; and a positive predictive value of 57%. Even at that predictive value however, the burden of MDR-TB in South Africa could be substantially greater than previously thought.

There was significant geographical variation in rates of M.TB positivity, and the rates of rifampicin resistance to a lesser extent. Excluding the Western Cape (which does not seem to have reported many test results), KwaZulu Natal has the highest rate of TB diagnoses (20.51%) ranging down to 10.91% in Limpopo; while the Northwest Province reported the highest rate of rifampicin resistance (9.3%).

Focusing just on the eThekweni District (Durban), the GeneXpert more than doubled TB diagnoses to 19.71%, compared to 8-9% for the same period in 2010.

Challenges and lessons learned

"We've learned that the algorithm development is complex and time is needed to get consensus," said Prof. Stevens. Switching over to diagnostic platforms meant sweeping changes had to be made to the TB guidelines, request forms, training and resistance reporting.

"Training needs to focus on items like sample preparation and good laboratory practice. We're also running into regulatory issues such as who can do the test, when scope of work is well-defined in South Africa," she said.

The error rate of about 3-4% is a cause for concern because it adds to the cost of implementation and delays diagnosis. Some of these errors are well characterised, such as one resulting from putting an insufficient volume of sputum into the cartridge. But the most common error code being seen appears to be unique to South Africa and is being investigated at the current time. "Electricity is also critical for the good running of the instrument," said Prof. Stevens. "As is good temperature control."

Pace of implementation, cost modelling and anticipated impact

But the biggest challenge could be the cost, which could clearly affect the pace to full implementation.

There are two timelines for phased implementation on the table, a fast-scale up scenario, with full coverage with GeneXpert by December 2012 and a slower scale-up scenario, with full coverage by September 2013.

"The minister would prefer the first one," said Prof. Stevens.

The first phase of implementation is already completed. The second phase will be to fully capacitate the high burden districts. Phase 3a/3b will be part of a Gates funded, cluster-based randomised trial to analyse cost effectiveness and impact on patient outcome.

But the capital expenditures for the equipment alone will be significant, at around (US) \$21 million for 238 machines (65 G4, 169 G16 and 4 G48s)..

"This is a huge capital outlay, and we are looking at this with great anxiety," said Prof. Stevens.

This costing model adjusts for a 10% increase in TB suspects coming in for screening — but this estimate may be low given the intensified case finding campaign and routine TB screening of people coming through the HIV counselling and testing campaign.

The cost of each test itself, or rather the cartridge, is currently 161.45 Rand, but there are a number of hidden costs including staff costs, the cost of calibrating the equipment, consumables, waste disposal (the cartridges are bulky), transport and logistics, training and quality assurance and overhead. Costs will also vary dependent on implementation rate, exchange rates, global volumes, negotiations, and freight costs.

When hidden costs are included, the model projects that the actual cost of performing a test will be R 216.30 (around US \$36) between 2011 to 2014, decreasing to 189.85 Rand (\$26) per test from 2014 to 2017.

The NHLH has also developed a National TB Cost Model to estimate the incremental costs to the national health service of switching to the new diagnostic platform, under routine care conditions and at costs incurred by the government.

"We think that the programme costs per suspect will increase by about 53%, and that the cost per case, for diagnosis alone will increase by 17%. Having said that, we will probably identify 30% more cases, 76% more MDR-TB and by 2013, if everything goes to plan, initiate 39% more people on treatment," said Prof Stevens.

The increase in initiation of treatment is only one of the benefits however. According to a study by Boehme et al, the test will lead to dramatic reductions in the time to initiating treatment from 56 days (39–81) currently to 5 days (2–8). Currently, only 46% of patients are diagnosed by their second visit to the clinic, and another 40% only by the third visit. In contrast, at full GeneXpert coverage, 83% of patients will be diagnosed by their second visit and 89% by visit three.

Meanwhile, there should be reductions in the use of other TB diagnostics. AFB microscopy — a time-consuming task — will still be necessary for monitoring treatment response, but the number of smears from 4.1 million per year currently to 1.5 million per year. Use of culture should also decrease by about 30%.

A leap into the well-modelled

Although switching to use of GeneXpert for first-line diagnosis is a radical step, so far it has gone well, and one cannot fault the South African National Health Laboratory Services for lack of preparation.

"Significant changes to the national TB programme are envisaged," she said. "What we have already identified is that it is beginning to facilitate [TB/HIV] integration at both the laboratory, clinic and programmatic level because people are being forced to analyse their budgets and look at putting clinics together."

"I think it is a brave bold step, and we are hoping that by the end of full Xpert implementation, the bulk of our patients will be diagnosed by Xpert, and the bulk of our patients will be diagnosed

before 5 days. We are completely aware of the implications this will have on our treatment programme."

However, it should be pointed out that the current algorithm is relatively conservative. Other presentations at the conference (and in a series of articles just published in *PLoS Medicine*) argue for much broader use of GeneXpert, with repeated testing to diagnose more smear negative TB in people living with HIV. However, this would increase financial outlays significantly — and not everyone is convinced that the expenditures are the best use of limited programme funds.

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Should the GeneXpert test be performed on all people living with HIV before initiating ART?

Symptom screening and smear microscopy should be replaced by Gene Xpert in patients initiating ART in South Africa," said Dr Jason Andrews of Massachusetts General Hospital, who presented findings at the International AIDS Society conference in Rome of a cost-effectiveness analysis comparing different TB screening strategies in people with more advanced HIV.

This proposal is based on data demonstrating GeneXpert is more sensitive than smear microscopy, and the premise that symptom screening might miss a substantial proportion of active TB cases — as suggested by another study presented at the conference by Dr Tolu Oni of Imperial College, London, and the University of Cape Town. That study found 'subclinical TB' (M. TB that could be cultured from induced sputum even though there were no symptoms of TB) in 8.5% of HIV-positive people at a site in Khayelitsha.

Similar data were published in *PLoS Medicine* this week, from a study by Lawn et al on the use of GeneXpert, notably conducted in the same setting. When including 'asymptomatic culture-confirmed TB' Lawn et al concluded that the GeneXpert was 73.3% sensitive for TB in people living with HIV. The sensitivity for smear-negative disease was lower than previously reported: 43.3% versus 72.5% using one sputum sample; 63.3% versus 85.1% using two samples). Dr Andrew's cost analysis was at least partially based on Lawn's data.

However, the conclusions of each of these reports are somewhat controversial because there is no clear consensus on the meaning of culture-positive TB without symptoms, which could result from primary TB infection or re-infection (that would be common in this community with one of the highest rates of TB transmission in the world). Although finding such cases is certainly an important observation from a natural history and epidemiological perspective

— the clinical implications of primary infection are different (see below).

Furthermore, the cost analysis doesn't really consider the diagnostic strategy currently being proposed in South Africa's new first-line TB diagnostic algorithm or the costs of implementing and performing GeneXpert at a scale significantly beyond the already ambitious targets set by South Africa's Department of Health for switching over from smear microscopy to GeneXpert-based diagnosis. Notably, Professor Wendy Stevens of South Africa's National Health Laboratory Services presented significantly different costing data during a late breaker session of the conference.

Analysing all the real costs versus the full potential downstream benefit of implementing a new diagnostic strategy is complex, however. As Dowdy et al wrote in another article in *PLoS Medicine* this week, "standard cost-effectiveness analyses may give misleading results when applied blindly to the scale-up of TB diagnostics. Challenges in economic analysis of TB diagnostic tests include: underestimating the cost of false-positive diagnoses, overlooking operational and clinical impact of diagnostics, and utilizing unrealistic cost-effectiveness thresholds."

Screening for and diagnosing TB

Stopping the spread of TB is dependent upon rapidly detecting and treating active TB, reducing new TB infections (through measures such as TB infection control), and preventing activation of latent TB infections.

The inability to rapidly detect TB has been a major impediment to this strategy. It is widely acknowledged that smear microscopy is an outdated, insensitive and appallingly inadequate way to diagnose TB, particularly in people living with HIV, who are far more likely to present with smear-negative disease.

Culture is considered the gold standard for detecting the presence of replicating TB bacilli in a specimen, but is a more expensive, technically complex, and time-consuming process. Even with automated liquid culture equipment, culturing can take two to three weeks to make a diagnosis. Culture-based drug susceptibility testing (to detect drug resistant TB) takes even longer.

Consequently, the development of new, simple inexpensive point of care diagnostic test for TB (and drug-resistant TB) has been a major focus of research in the last five or six years. Unfortunately, a handheld dipstick-like test (like a rapid HIV test) that could be deployed anywhere people present for care is still a long way off.

However, as described elsewhere, the GeneXpert MTB Rif test is a dramatic step forward in diagnostic technology, with much greater sensitivity and specificity for smear-positive TB, and to a somewhat lesser extent, smear-negative TB. It could be performed by a trained nurse and deliver results within two hours.

It has been recommended by WHO as the initial diagnostic test in individuals suspected of MDR-TB or HIV/TB.

However, the equipment and test requires electricity and temperature control, and is too expensive for the equipment to be deployed at the primary care level in most countries.

South Africa, however, has taken the ambitious step of implementing the technology at all smear microscopy sites. As it is being implemented, the test won't really be point-of-care, but it should generate a more rapid diagnosis in more people.

But the first challenge to rapidly detecting TB is the failure to look for it in the first place — which is particularly egregious in people living with HIV who are at much greater risk of developing and dying from TB.

For this reason, WHO recommends intensified case finding in people living with HIV, using a simple symptom screen. People with

symptoms should be effectively referred to the TB diagnostic process, while those without symptoms should be given isoniazid preventive therapy (IPT), a low cost intervention, to prevent the re-activation (and perhaps acquisition) of TB disease. It is well recognised that there may be breakthrough TB cases that are missed and which develop despite IPT — thus, people should be rescreened for TB symptoms each month when they pick up their month's supply of IPT. South Africa has adopted this policy — though not all provinces are implementing it equally.

In addition, WHO recommends earlier antiretroviral therapy — when people's CD4 cell counts fall below 350 — partly because ART reduces the risk of TB as well. Aside from people who already have TB, and pregnant women, South Africa has not yet adopted this policy.

It is within this context that these reports (of asymptomatic TB in people living with HIV and the recommendation to use GeneXpert to screen all South Africans living with HIV before starting ART) must be considered.

Questions regarding TB 'without symptoms'

The study presented by Dr Oni evaluated the prevalence and outcome of 'subclinical TB disease' in people not eligible for ART in Khayelitsha. It included 274 asymptomatic persons from pre-ART wellness clinic or from the HIV counseling and testing site (who were compared to 162 symptomatic TB cases). Participants were screened for TB symptoms, given a tuberculin skin test (TST) and a chest X-ray if their TST was above 4mm. Culture positive cases were spoligotyped to exclude cross-contamination.

As already noted, there was an 8.5% (95% C.I. 5.1-13.0%) prevalence of asymptomatic TB disease. 71% of those with TST \geq 5mm (which, it should be noted, is an indication of TB infection, but not active TB) had normal chest X-rays.

Similarly, Lawn et al reported that the WHO TB symptom screen only detected 85% of the cases of 'culture confirmed TB' in that cohort, which included people with more advanced HIV disease qualifying for ART. In other words, 15% had no symptoms of TB when they were screened.

Dr Oni's findings suggested that these patients were clearly at a much earlier stage of disease.

"The findings suggest the asymptomatic cases had a lower bacterial burden compared to symptomatic TB cases," said Dr Oni. "These patients had higher CD4 counts, a higher proportion were smear-negative but culture-positive with longer days to culture positivity." Culture positivity occurred within a median of 17 days (interquartile range 12-39) in the asymptomatic compared to symptomatic TB patients (7 days; IQR 6-12).

She suggested that culture should be performed after testing positive for TB in settings with a high burden of HIV/TB, especially in people with TST \geq 5mm (OR 4.96; $p=0.064$), lower CD4 counts (OR 0.996; $p=0.06$), and longer histories of HIV (OR 1.006; $p=0.056$).

"However, there are logistic difficulties in performing culture. It is labour intensive and there is the need for laboratory infrastructure, so these findings highlight the need for new rapid and affordable point-of-care diagnostic tests to identify persons with clinical and subclinical TB disease," she concluded.

She reported that treatment was started earlier than if these patients had waited for symptoms to develop — and that all of these patients had completed TB treatment and remained in care 6-12 months later.

However, some experts are not convinced that all of these culture confirmed cases are truly 'active TB.' Despite the general assumption that culture-confirmed TB is re-activation TB (full-blown

TB), it could be also be primary TB or perhaps TB re-infection. TB transmission is ongoing in high burden settings.

There are many cases in the literature of culture confirmed primary infection in children. For instance, back in 1999 van Rie et al reported a significant number of TB cases were due to exogenous re-infection. A study in 1996 reported clustering of spoligotypes in 24 out of 34 homeless patients with culture-confirmed TB in Los Angeles — documenting that these were cases of primary infection TB (or just post-primary TB). Culture positive primary infection TB has also be documented in individuals on immunosuppressant therapy.

Such cases may not present with some TB symptoms, but might not quickly progress to active disease and could even be suppressible with IPT.

Professor Ben Marais of Stellenbosch University recently wrote a letter on the issue to the Editor of the *American Journal of Respiratory and Critical Care Medicine*.

"Transient M. tuberculosis excretion has been well documented in children following recent primary infection and there is no reason to expect that this phenomenon is restricted to children. A survey conducted among randomly selected adults in South Africa identified a significant number of "asymptomatic" individuals, both with and without HIV, from whom M. tuberculosis was isolated. This presents a clinical dilemma and it would be important to differentiate transient organism excretion, after primary infection or reinfection, from active disease.

The likelihood of M. tuberculosis infection depends on the level of ongoing transmission in a particular setting, which is difficult to quantify. The annual rate of TB infection (ARTI) has been used as a surrogate, but the age restriction applied introduces severe selection bias and probably underestimates the infection pressure experienced by adults within the same community.

It can be argued that the risk posed to a patient who is infected with HIV and immune-compromised is self evident, which obviates the need to distinguish transient organism excretion from active TB. However, it remains an open question if a completely asymptomatic person with sputum smear-negative "culture-confirmed TB," who has no clinical or radiological signs suggestive of active disease, represents a true case of TB. With poor epidemic control, M. tuberculosis infection (both primary infection and reinfection) events are common. In these settings, careful reappraisal of TB case definitions seems warranted, especially among those without significant immune compromise."

Dr Oni reported that 56% of the asymptomatic did progress clinically (a median of 28 days later), however, it remains an open question whether this would have occurred if WHO policy (IPT and ART) had been followed in these patients.

Gene Xpert for all people with HIV

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The current South African TB diagnostic algorithm using the GeneXpert test (at least once) should pick up many more cases of TB among symptomatic people living with HIV and those who are household contacts of active TB cases. But it will not pick them all up.

Lawn's et al's study found that 'compared to the strategy of doing an Xpert assay on one sputum sample from patients with a positive symptom screen, a strategy of doing two Xpert tests on all patients was associated with 22.9% higher sensitivity for TB and the fewest missed cases. Although the latter strategy would require a large absolute number of tests, at a TB prevalence of 20%, one extra TB case would be diagnosed for every additional 6.3 tests done.

Dr Andrews and colleagues established a costing model based on Lawn et al's data, the costs of performing different screening strategies (including performing one GeneXpert test versus two, in symptomatic or everyone with HIV) to determine whether this was cost effective as defined by incremental cost-effectiveness ratio (ICER), which divides the cost by the additional benefit.

According to his calculations, the incremental cost per year of life saved for performing two GeneXperts on everyone qualifying for ART (the CD4 count in Lawn's study was 177) would be \$5,200, more cost effective than the other options - except for just using smear microscopy - which was still more cost effective at \$4000 if just performed in symptomatic patients and \$4200 if performed in all people living with HIV about to start ART.

Because of the decreased sensitivity of the GeneXpert to detect smear negative TB cases (once these asymptomatic cases are included), Dr Andrew's study concluded that performing two GeneXpert tests on every person with HIV about to start ART in South Africa would be cost effective — partly because it was assumed that these cases would otherwise lead to active disease. It is not clear that this would be the case.

The cost analysis was also only based upon the cost of the GeneXpert cartridge, estimating a test cost of only \$22 — and doesn't include the hidden costs mentioned in Prof. Steven's presentation or the cost of scaling up the capacity to perform these tests more widely. Further costing analysis studies on the South African programme will be presented at the Union World Conference on Lung Health in October.

From a patient perspective, anyone who presents to care with low CD4 cell counts should get the best diagnostic services that can be made available in order to avoid a life-threatening case of TB — as long as scaling up these services does not put other aspects of their care in jeopardy — which is a concern in the current economic clinic

From a public health perspective, implementing existing policies to prevent TB may have greater impact on a larger number of people. As Dr Carlton A. Evans, of Imperial College, London, wrote in an opinion piece commenting on the recent series of articles:

"This new test must not divert resources from preventive efforts and well-established TB diagnostic and treatment systems that already have the potential to have considerable impact upon TB morbidity and mortality."

"With tiered pricing for low-income countries, each MTB/RIF test machine currently costs US\$17,000–\$62,000. More importantly, each disposable test-cartridge costs US\$17–\$120, which is comparable with the per capita annual health expenditure in the countries with the highest TB burdens... For example, it has been estimated that in India, providing the MTB/RIF test to only 15% of the suspected cases of TB would consume the annual budget for the entire TB control program."

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Task-shifting of HIV care to nurses: successes, but problems to watch out for

“A nurse-led service can deliver ART care as effectively as a doctor-driven one, and even improves quality of care, but this pragmatic trial did not result in increased access to ART,” said Lara Fairall of the University of Cape Town. She was describing the results of the STRETCH study, a cluster-based randomised controlled study of nurse-managed and initiated antiretroviral therapy (ART) presented at the sixth International AIDS Society conference, held in Rome this week.

Another presentation in the session suggested non-physician health workers could be mobilised to respond to AIDS in prevention services – notably male circumcision.

Meanwhile, an observational cohort study presented by Dr Megan McGuire of Epicentre, a public health research unit of Médecins Sans Frontières, suggested that HIV-care provided by nurses in Malawi was superior to that provided by clinical officers. However, as McGuire herself pointed, the clinical officers primarily managed the sickest patients with the most advanced disease. This was not an entirely fair comparison.

All these reports recommended task-shifting HIV care to nurses at the primary healthcare level. But the session also highlighted the tension at the conference between those lobbying for a quick shift to task-shifting and decentralisation in order to reach goals for universal access to HIV treatment, versus those warning that task-shifting may not be an overnight solution to the crisis in human resources for health care. Rather, there are indicators suggesting programmes must be aware that there can be gaps and problems in the transition for doctor-based to task-shifted care.

Nurses can make the cut

Several large, randomised studies have reported that male circumcision significantly reduces the risk of HIV acquisition among heterosexual men, and the World Health Organization has recommended that services offering male circumcision should be incorporated into national HIV prevention activities in

high-HIV-burden settings. As a result of news reports and prevention campaigns, demand for the procedure outstrips supply in some sub-Saharan African settings.

“The shortage of health professionals poses a critical challenge to the male circumcision scale-up,” according to Dr Kelly Curran of JHPIEGO in Baltimore.

However, programmes have identified a number of potential approaches to expanding the numbers of health workers who can offer the intervention.

In Kenya, procedures and policy were adapted to empower nurses to safely perform male circumcision. After two campaigns, the programme has delivered 268,000 male circumcisions within 2.5 years.

In Swaziland, a survey was performed to identify existing nurses who were under-utilised: in other words, registered but unemployed nurses (many of whom were Zimbabwean), those recently retired or recently graduated, and often working abroad (mainly in the UK). At least 259 were found who could be trained to do the procedure.

Some public critics have been concerned that HIV services for treatment – not to mention prevention interventions, such as male circumcision campaigns – might draw healthcare staff away from other critical health care services, but Dr Curran pointed out that the Swaziland approach might remedy that to an extent.

“My lesson learnt from our efforts in Swaziland is that the first place where we should go is the unemployed healthcare workers, as well as the recently retired yet still energetic. In many of the countries where we work, retirement age is as low as 55 – many of those nurses would happily still be employed. They may not want to do surgery all day on their feet but they could happily do post-operative reviews or staff recovery rooms,” said Dr Curran. “So I think the key here is really to look everywhere you can first before engaging nurses or other healthcare workers away from service provision of other critical health interventions.”

Programmatic data on nurses and clinical officer-based care in Malawi

Malawi has a severe shortage of doctors, and yet over the last several years has ramped up a massive HIV treatment and care programme with very few resources. For example, in 2010, there were roughly 14,000 HIV consultations, 700 program enrollments and 400 ART initiations.

This was achieved with a mixed model of care, shifting ART initiation and management to clinical officers and nurses.

Dr Megan McGuire presented the findings of a study comparing treatment outcomes of 10,112 adults patients receiving ART between 2007 and 2010, who were cared for either by nurses, clinical officers or both in a large HIV programme in rural Malawi.

However, nurses were only supposed to care for patients who were antiretroviral naïve and starting on first-line treatment, with WHO stage 1 or 2 disease, CD4 cell counts above 100 and BMIs over 17. In practice there were some exceptions, but in general, patients cared for by nurses had less severe HIV disease and wasting than those cared for by clinical officers.

The nurses provided the majority of care for 1901 patients and the clinical officers 3386, while 4825 patients received mixed care.

At baseline, BMI was under 18.5 in 15.4% of those cared for by nurses, 35.4% of those cared for by clinical officers, and 25.9% who received mixed care.

Similarly, median CD4 cell counts at baseline were 195, 147 and 182, respectively, for the nurse, clinical officer and mixed-care cohort. The difference in severely symptomatic disease was more pronounced, with 19.1, versus 58.9 and 33.1% with WHO stage

III/IV disease for the nurse, clinical officer and mixed-care cohorts, respectively.

Follow-up was right-censored at the earliest of the following dates: death, transfer out, last visit or 24 months of follow-up. Not surprisingly, more of those receiving care from clinical officers (the sicker patients) were around 5 times likely to die (around 20% vs. less than 5% for both nurses and mixed care) within 2 years of follow-up. Similarly about 40% of the clinical officer cohort was lost to follow-up, versus around 10% for the nurses, and just over 5% for those receiving care for both.

Acknowledging that some of this may have been due to ill health at baseline, the analysis was restricted to less severely ill patients ($n=3846$) with BMI>18.5, WHO stage 1 or 2, and CD4>100. The aIRR (95% confidence interval) for mortality was 3.42 (2.60-4.48) for those in the clinic officer cohort and 0.63 (0.47-0.86) for those receiving mixed care (versus those getting nurse-provided care).

However, this was an analysis based upon the health of the patient at baseline – and a serious long-term illness developing after entry into care (such as TB) would have led to the patient being referred to (and having more visits) with a clinical officer. Tellingly, CD4 cell counts were somewhat poorer for the clinical officer group at 12 months, but there was not much difference at 24 months.

It is possible that nurse care was indeed better for retention and health outcomes, but this was not a randomised study and cannot be used to reach that conclusion.

STRETCH

The STRETCH study (Streamlining Tasks and Roles to Expand Treatment and Care for HIV) was randomised – but because it was performed in real-world conditions, at a time and place (the Free State Province in South Africa) where nurses were *in the process of being trained up to provide ART*, it may not serve as the final word for whether nurses can provide ART care just as well as doctors or other clinicians.

Thirty-one clinics were randomised: 16 operated the STRETCH protocol, alongside 15 control clinics. The study had two parts: one ($n=6321$ patients) was to show whether nurse-led clinics could maintain patients who had been stable on ART for at least six months as well as clinics with more doctor-based care or support – as measured by viral load. This they could do easily.

The second part of the study evaluated whether task-shifting to nurse-led clinics would reduce mortality in people on ‘waiting lists’ for treatment by improving access and initiating ART among those with CD4 cell counts below 350 (9252 patients).

This study was unable to show this. However, Fairall pointed out that the nurse-led clinics began initiating ART gradually.

The results were previously presented at the 5th South African AIDS Conference, and reported in much more detail in [HATIP 179](#).

Discussion

Audience members asked whether it was too much to ask nurses to take on the additional burden of ART initiation and management – and whether this was reflected by STRETCH's inability to increase access to ART during the study period.

“We did monitor [the adverse consequences of task-shifting on the nurses] during the trial. And yes, nurses are very burnt out. So one has to be very cautious about how and when one can delegate the clinical responsibility. So that really is ... a cause for consideration,” said Fairall.

“But going back to this concept of task-shifting – I think we’ve seen nurses as really having extremely broad shoulders and able to take on more and more and more. That does have consequences. The nurses in our trial didn’t seem to mind the new duties but they were well supported by our provincial co-ordinator, with whom they had a direct personal relationship,” she added.

Indeed, nurses need encouragement and support – and nurses should not be expected to handle the most complicated cases. Part of the STRETCH programme involves training nurses when to recognise the need to refer patients for doctor-based management.

The need for more specialised clinical support is recognised in Malawi as well – the goal is to be less reliant on it, however.

Dr McGuire said that they were now looking at whether it was possible to space out clinic appointments further, so that patients visit the clinic once every six months, or even once a year if they are stable.

Another important aspect of shifting more of the burden of care to nurses involves shifting some of their existing duties to less highly trained health workers, such as expert patients.

A number of other studies at IAS 2011 reported on how lay personnel can dramatically improve outcomes such as initiation of ART and retention in care. Conversely, the failure to make certain that such support services are available at the primary healthcare level could be one reason behind some of the disappointing results on the decentralisation of ART services reported during other sessions of the conference. Both these issues will be addressed in subsequent articles on www.aidsmap.com.

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about HATiP

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