

# HATiP

HIV & AIDS Treatment in Practice

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## In this issue:

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### News from CROI 2010; *page 2*

- About CROI
- ART roll-out
- PMTCT
- Treatment as prevention
- Long-term toxicities
- Cancers
- Epidemiology

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### HIV and TB in Practice; *by Keith Alcorn page 14*

- More evidence supports isoniazid for TB prevention in people with HIV

## News from CROI 2010

### About CROI

The Seventeenth Conference on Retroviruses and Opportunistic Infections took place February 16-19 in San Francisco.

This edition of HATIP is devoted to news reports on research of specific relevance to resource-limited settings presented at the conference.

To view the full range of [aidsmap.com](http://aidsmap.com) news reports from the conference, go to our [CROI 2010](#) page. You can also download an easy-to-read overview of key research presented each day at the conference in English, French, Spanish, Portuguese or Russian.

To view [conference abstracts](#), and slides and audio from conference sessions, visit the [conference website](#). Please note: if you have a slower internet connection the slides will take a long time to load into the online viewer; we have found that even with relatively fast broadband connections in the UK, these presentations can take 2-3 minutes to fully load.

Prior to the conference the TB/HIV Working Group of the Stop TB Partnership organised a Research Frontiers meeting to review recent findings on isoniazid preventive therapy, discussed in this month's HIV and TB in Practice column in this edition of HATIP. You can download all the slides presented at that meeting, including draft WHO recommendations on intensified case finding and IPT, at the [TB/HIV Working group meetings web page](#).

### ART roll-out

#### One-quarter died on HIV treatment waiting list in South Africa's Free State province

By Carole Leach-Lemens

Almost a quarter of patients eligible for HIV treatment in South Africa's Free State province died before getting it, a further 13% disappeared from the healthcare system and 5% were still on a waiting list, according to a review of three years of progress in the province's public sector antiretroviral treatment (ART) programme.

The findings were reported on Thursday at the Seventeenth Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco.

As scale-up progresses important measures of a programme's success include how many of those who meet the criteria to start treatment do in fact start, as well what proportion die before beginning treatment.

Until recently the primary focus has been on the outcomes of patients who start treatment. However, the highest rates of mortality happen within the first month on treatment, raising the question: what happens to the people who are caught in the system, waiting to start on treatment?

At last year's International AIDS Society conference in Cape Town, South African HIV Clinician's Society president Dr Francois Venter warned that South Africa's health system was doing bad job of getting people on to treatment early enough and quickly enough.

This analysis looked at how well one province in South Africa is doing in ensuring that patients with HIV receive prompt treatment once they become eligible for it.

Free State has the third-highest HIV prevalence rate among the nine provinces of South Africa.

From May 2004 until December 2007 all ART eligible patients (with a CD4 cell count under 200 cells/mm<sup>3</sup>) enrolled at the clinics

in the Free State treatment programme were followed until December 2008. Time was measured from the (first) baseline CD4 count until whichever event came first: the start of antiretroviral therapy or death.

Data are collected routinely from enrolment and are linked to the national death register and National Health Laboratory Service (NHLS) database.

Of the 59% (12,963) who started antiretroviral therapy, men had a higher risk of death (hazard ratio [HR] 1.29 95% confidence interval [CI]: 1.22-1.36) and were less likely to start treatment compared to women (HR 0.83 95% CI: 0.80-0.86).

The lower the CD4 cell count at eligibility the higher the proportion of those likely to die before starting ART and the greater the probability of not starting treatment. Of the 15% (3207) with a CD4 cell count under 25 cells/mm<sup>3</sup> at eligibility, close to 50% died before starting treatment.

Survival improved over time. Of those who enrolled in 2007 56% more had started treatment compared to those who enrolled during 2004 or 2005 and were less likely to die (HR 0.64 95% CI: 0.59-0.68).

Among 2991 patients with a median CD4 cell count of 260 (interquartile range [IQR] 227-318), and so not yet eligible for treatment, the median time to their next CD4 cell count measurement was, in accordance with national guidelines, six months (183 days, IQR 105-309). Subsequently their median CD4 count for eligibility was 101 (IQR 47-154) with a median decrease between CD4 count measures of 113 (IQR 70-183).

These findings provide further evidence for reducing pre-ART mortality and improving survival by getting those who are most severely immune-compromised on to treatment as soon as possible, as well as improving access for men.

National treatment guidelines have recently changed to recommend earlier treatment at a CD4 count below 350 cells/mm<sup>3</sup>, so those starting treatment will do so at a higher CD4 count. However, as the Free State study shows, patients with higher CD4 cell counts are being monitored too infrequently for the timely start of treatment, undermining the value for the health system and the individual of recommending earlier treatment.

#### Reference

Ingle S et al. *Pre-treatment mortality and probability of starting ART in patients enrolled in the Free State ARV program, South Africa: implications for treatment guidelines*. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 108, February 2010.

#### Further information

You can [view the abstract on the official conference website](#).

You can also [view a webcast and slides of this session on the official conference website](#).

#### Immune restoration in DART study: late start means low CD4 count for years

By Carole Leach-Lemens

HIV-infected adults participating in the DART trial in Uganda and Zimbabwe who began antiretroviral treatment with CD4 counts below 125 cells/mm<sup>3</sup> were very unlikely to see a restoration of immune function to a level of 250 cells/mm<sup>3</sup> or greater, after a year on first-line treatment according to findings presented at the 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco.

While improvement was seen over several years, it remained insignificant for those who began treatment with very low cell counts.

A CD4 cell count decline is seen as a marker of immune deficiency and so a predictor of death in untreated HIV infection. Getting a CD4 count back to at least 500 cells/mm<sup>3</sup> is suggested as a goal for effective antiretroviral therapy.

Patients with CD4 counts below 200 cells/mm<sup>3</sup> remain at high risk of opportunistic illnesses despite antiretroviral therapy, and prophylaxis against opportunistic infections is recommended for this group of patients. Findings from South Africa [presented at last year's conference](#) show that the disadvantage caused by a late start to treatment can persist for years, with patients in this group at a continuing high risk of death.

Nevertheless, it is common in resource-poor settings for patients to be diagnosed at a late stage in the disease and so to begin antiretroviral treatment with advanced immunodeficiency. Few will attain the treatment goal of a CD4 count of 500 cells/mm<sup>3</sup>. So the probability of lowering the risk of death and disease over time is significantly reduced for this population.

Accumulating evidence, particularly at this conference, suggests that a very low CD4 count before starting treatment, and subsequent poor immune restoration, is associated not only with an increased risk of death after starting antiretroviral treatment (ART) due to infectious causes, but also to a prolonged increased risk of cardiovascular disease and cancers despite long-term viral suppression.

For all these reasons, the World Health Organization's (WHO) recently revised treatment guidelines support earlier diagnosis and treatment.

The DART study was designed to test treatment monitoring strategies in Africa, and is the largest and longest randomised study of antiretroviral treatment to take place in a resource-limited setting. The [headline results from the study](#) were presented in 2009 at the International AIDS Society conference in Cape Town.

In the randomised DART trial, 3316 ART-naïve adults began antiretroviral treatment in Uganda and Zimbabwe. First-line regimens included zidovudine/lamivudine and tenofovir, or abacavir, or nevirapine and comprised 74%, 9% and 16% respectively. All participants had their CD4 counts monitored every 12 months. The decision to switch to a second-line regimen was made after a new or recurring WHO clinical stage 4 illness and/or a CD4 cell count below 100 cells/mm<sup>3</sup>.

Over a five-year period, of the 3158 patients who had two CD4 counts following enrolment, 19% reached a CD4 count of 500 cells/mm<sup>3</sup> or greater and 69% reached 250 cells/mm<sup>3</sup> or more on a first-line regimen.

On first-line regimens the median time to reach a CD4 cell count of 250 cells/mm<sup>3</sup> was 1.8 years (interquartile range [IQR] 0.7-3.3) and to reach 350 cells/mm<sup>3</sup> it took 3.9 years (IQR 2.1-over 6), whereas it took over six years to reach CD4 cell counts of 500 cells/mm<sup>3</sup> or more.

After one year (48 weeks) on first-line treatment 10% still had a CD4 cell count ranging from 0 to 99, 38% were in the range 100 to 199, 39% in the range 200 to 349, 10% in the range 350 to 499 and only 2% had reached a CD4 count of 500 cells/mm<sup>3</sup> or more. This did improve over time and around 21% reached CD4 cell counts over 500 after five years on treatment.

The researchers suggested that these findings raise the question of whether to switch those with CD4 cell counts still below 125 cells/mm<sup>3</sup> at week 48 to a second-line regimen, in order to improve the rate of immune restoration. (Some protease inhibitor-based regimens have been associated with greater CD4 cell count gains.)

Dr Munderi concluded that these findings "highlight the importance of expanded earlier diagnosis and initiation of treatment at higher CD4 counts".

#### Reference

Munderi P et al. *Immune restoration over 5 years on ART among patients initiating treatment with advanced immune deficiency in the DART trial in Uganda and Zimbabwe*. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 110, 2010.

#### Further information

You can [view the abstract on the official conference website](#).

You can also [view a webcast and slides of this session on the official conference website](#).

#### Goosby warns of need for long-term funding for AIDS, says financial trades tax is 'interesting'

By Keith Alcorn

International donors need to start looking at a 30 to 40 year time frame for 'long-term sustainable support' to manage the global response to AIDS, US Global AIDS Coordinator Eric Goosby told a press conference on the opening day of the Seventeenth Conference on Retroviruses and Opportunistic Infections (CROI) today in San Francisco.

He also said that US officials charged with global health are looking with great interest at a new proposal from non-governmental organisations for a financial transaction tax to raise money for global health and development.

A 0.05% levy on financial transactions such as currency trades and financial derivatives might raise \$150 billion per year, campaigners say, and largely affect speculative trades of 'no economic value', according to UK Financial Services Authority regulator Adair Turner.

A transaction tax is gaining international support from influential figures as a means of providing an insurance fund against future bank crashes. The German Chancellor Angela Merkel and French President Nicolas Sarkozy have endorsed the proposal, as has British Prime Minister Gordon Brown.

Some of the money raised would repay the vast sums used by governments to stabilise banks during the 2008-2009 crisis, or form the basis of an insurance fund that would protect against future banking crises.

However advocates are also proposing that the tax could generate substantial funds for global development. This position has not yet been endorsed by governments, but a growing civil society campaign is attempting to build support for a 'Robin Hood' tax that would be split between global and domestic priorities.

However for a tax to be implemented, it will need to garner support from most of the G20 group of major economies that includes China, India, Brazil and Russia, together with the United States.

Ambassador Goosby's comments are the first hint that figures in the US administration are looking seriously at the transaction tax as a means of generating financial support for global health. Up until now any interest in a tax on banks was thought to focus on taxes on individual banks as a means of establishing an insurance fund against future bank crashes.

"We are very interested by innovative strategies and we're looking at this with great interest...This could be a big one," he said.

However he emphasised that the US was also looking for ways to maximise support for multilateral partners, a coded reference to the fact that European governments – particularly France, Germany and Italy – have a persistent track record of low contributions to the Global Fund proportionate to their economic output.

## PMTCT

### Missed opportunities for HIV testing of pregnant women By Carole Leach-Lemens

Kenyan women are becoming infected with HIV during pregnancy at very high rates, and repeat testing prior to delivery or at the earliest possible opportunity after birth should be encouraged in order to reduce mother to child transmission, Kenyan researchers reported last week at the Seventeenth Conference on Retroviruses and Opportunistic Infections in San Francisco.

When mothers who tested negative before giving birth were retested six weeks after having given birth at six health clinics in Nairobi and Western Kenya, they showed a significant HIV incidence researchers reported last week at the 17th Conference on Retroviruses and Opportunistic Infections in San Francisco.

Women in Western Kenya, where the HIV prevalence rate of 15% is over twice the national rate, were at especially high risk for seroconversion during pregnancy.

Prevention of mother-to-child transmission (PMTCT) programmes have focused primarily on preventing transmission from an HIV-infected woman to her infant. Little attention has been given to the other key elements of a globally recognised comprehensive strategy that includes prevention of HIV in women, prevention of unwanted pregnancies as well as care and treatment for the HIV-infected woman and her family.

An estimated 1.4 million pregnant women in low- and middle-income countries are living with HIV, of which 90% are in sub-Saharan Africa. Only an estimated 21% of pregnant women received an HIV test in 2008 and 45% received drugs to prevent mother-to-child transmission.

Most of the women who attend PMTCT programmes are HIV negative. Yet evidence suggests that there is a high incidence of HIV infection during pregnancy and the immediate period after having given birth. Identifying co-factors for HIV infection during this time will help develop needed strategies to reduce the rate of seroconversion.

Mothers who brought their infants for routine childhood immunisations at six maternal-child clinics in Nairobi and Western Kenya were offered HIV testing. Questionnaires were completed before testing.

HIV-negative mothers who subsequently tested positive were compared with those who did not seroconvert.

2,035 (95.3%) of women who had tested negative before giving birth agreed to be re-tested. Fifty-three (2.6%) tested positive with an estimated HIV incidence rate of 6.8 per 100 woman years (95% CI: 5.1-8.8). The incidence rate was considerably higher in Western Kenya than in the capital Nairobi (13.8 per 100 women years, 95% CI 9.6-18.9 versus 3.9 per 100 women years, 95% CI 2.4-5.8). Being employed (45.3% versus 29.0%  $P=0.01$ ), married and from a high prevalence region increased the likelihood of seroconversion.

For married women in a polygamous relationship the possibility for seroconversion increased significantly (19.6% versus 6.7%,  $P<0.001$ ).

In a multivariate analysis both region (OR: 3.6 95% CI: 2.1-6.4) and being employed (OR 1.9 95% CI: 1.1-3.3) were independent predictors of seroconversion.

The researchers highlighted the limitations of the study that included no data on the timing of the first HIV test and no data on the partner's HIV status.

Acceptance of repeat early testing following birth is high and resulted in significant rates of HIV incidence. The findings of high

HIV incidence among women who had participated in PMTCT programmes supports the need for "urgent review of services provided to HIV uninfected women", said John Kinuthia of Kenyatta National Hospital, Nairobi, presenting the findings.

He noted that the HIV incidence seen in pregnant women in this study was as high as in cohorts of sex workers, indicating that pregnant women are a high risk group for seroconversion.

"Preventing incident infection during pregnancy is critical because of the high viral load associated with primary HIV infection," he went on.

PMTCT interventions need to address HIV-negative as well as HIV-positive women, he explained, and should not assume that because a woman tests HIV-negative, no risk of HIV transmission exists.

In particular there is a need for couples counselling, and where women test alone it is important to encourage her partner to be tested, he said. Where women test HIV-negative, partner testing remains important because it may identify women in discordant relationships, while counselling may expose other risk factors that need to be addressed.

A second study, carried out in Swaziland, showed that where repeat testing can be implemented during labour or delivery, it results in increased use of nevirapine prophylaxis.

Mary Pat Keiffer of the Elisabeth Glaser Paediatric Foundation reported on an intervention in Swaziland designed to increase uptake of single-dose nevirapine through a number of measures:

- Provision of HIV testing and counselling to all women who arrived at maternity services with unknown HIV status.
- Offer of nevirapine prophylaxis to all women who declined an HIV test.
- Routine re-testing for HIV of all women who had tested negative more than three months prior to delivery.
- Ensuring that all women with HIV, known or newly diagnosed, took ARV prophylaxis as prescribed.

Maternity nurses received a one-day training to ensure that they understood their roles, and they actions they needed to take, to ensure these outcomes. The effectiveness of the intervention was evaluated through a study of six EGPAF-supported maternity units, which were randomised to receive the intervention or act as control sites.

The primary outcome of interest in the study was the percentage of infant cord blood samples which were HIV-positive and contained nevirapine, as an indicator of the proportion of women with HIV who had been reached with nevirapine prophylaxis at the time of delivery.

The study enrolled 2444 women, of whom 2211 had undergone HIV testing previously (91%). A further 215 women had an unknown HIV status at the time they arrived at the maternity clinic to give birth.

Analysis of cord blood samples (2386 samples) showed that HIV-positive women who attended intervention clinics were significantly more likely to have taken nevirapine (80% vs 69%,  $p=0.0001$ ).

When the results were broken down by HIV status on arrival at the maternity clinic, it was clear that women who had not already been diagnosed prior to their delivery were much less likely to have taken nevirapine.

However, women attending the intervention clinics had a significantly higher frequency of detectable nevirapine, regardless of whether they were already known to be positive, diagnosed at the maternity clinic or with unknown HIV status at the time of delivery.

HIV incidence among pregnant women was extremely high, at 16.75 seroconversions per 100 person-years. In comparison, noted the presenter, incidence among pregnant women in the Rakai population study, reported in 2005, was 2.3 per 100 person-years, while incidence among non-pregnant women was 1.1 per 100 person-years in that study.

ARV provision to women who seroconverted during pregnancy doubled at the intervention sites (54% vs 26%,  $p=0.03$ ).

The proportion of HIV-negative women retested in maternity clinics was significantly greater in intervention clinics, but still low, due to Swazi guidelines which recommend that repeat testing should take place at least 90 days after a previous negative test. (14% at control sites vs 45% at intervention sites,  $p=0.0001$ ). Thirty-eight per cent who seroconverted had been tested less than 90 days before delivery, and so were not re-tested.

Reaching women who are infected late in pregnancy should not be an afterthought for PMTCT programmes, said Mary Pat Keiffer.

In the discussion following the presentation, there was controversy over whether the higher rates of seroconversion in pregnant women were due to biological or behavioural vulnerability. At present there is no evidence that pregnancy increases a woman's biological vulnerability to infection, but behavioural factors may contribute to the high rate of seroconversion seen in various populations of pregnant women.

"Part of the behavioural risk that we're finding in Swaziland is that when women are pregnant, they are considered safe to have sex with," said Mary Pat Keiffer.

## References

Keiffer MP et al. *Repeat HIV testing in labor and delivery as a standard of care increases ARV provision for women who seroconvert during pregnancy*. Abstract 156

Kinuthia J et al. *Co-factors for HIV incidence during pregnancy and the postpartum period*. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 155, 2010.

## Treatment as prevention

### HIV treatment may prevent at least nine out of ten transmissions

By Gus Cairns

A study of HIV transmission between long-term, HIV-serodiscordant heterosexual couples in Africa has found that the chance of transmission is reduced by at least 90% if the HIV-positive partner is on antiretroviral therapy.

As a comparison, this is better than the efficacy of 100% attempted condom use, which is in the order of 85% (with a high margin of uncertainty).

There was one transmission from a partner who was taking HIV therapy, however, and presenter Deborah Donnell said that this indicated that the advice to serodiscordant couples that they should maintain safer sex should not change, even when the HIV-positive partner was on treatment.

The proportion of couples who had unprotected sex actually decreased when the HIV-positive partner started treatment, allaying fears about behaviour change, at least in this population and in the short term.

The other important finding from this study was that untreated partners with CD4 counts under 200 cells/mm<sup>3</sup> were approximately five times more likely to transmit HIV than those with CD4 counts over 350 cells/mm<sup>3</sup>, strengthening the case for extending antiretroviral (ARV) provision to all people with low CD4 counts.

This was a substudy in the Partners in Prevention study, a large randomised controlled study designed to see if treatment for the genital herpes virus HSV-2 could reduce HIV transmission.

[The main study, as reported at last year's IAS Conference in Cape Town, found that herpes treatment was ineffective as HIV prevention.](#)

This substudy was purely observational – it did not randomise people to HIV therapy – so its results can't be regarded as conclusive. Donnell remarked that for that we will have to await the results of [the HTPN 052 study](#), which is currently underway.

In the study, 3381 serodiscordant couples from seven countries from south and east Africa were included. The average age of women in the study was 29 and men 37, and two-thirds of the HIV-positive partners were women. All the HIV-positive partners had HSV-2.

At baseline about 30% of partners reported having unprotected sex with their main partner in the previous month.

None were on HIV treatment at baseline, and one of the study inclusion criteria was that the positive partner had to have a CD4 count over 250 cells/mm<sup>3</sup>. The average baseline CD4 count was over 400 cells/mm<sup>3</sup>.

CD4 counts were taken every six months and HIV status assessed. ARV therapy was ascertained by self-report: there was no independent confirmation that people were indeed on HIV therapy. Women taking short-term therapy for the prevention of mother-to-child transmission (PMTCT) were not counted as being on ARVs, and about one-third of women in fact took ARVs for this purpose at some point.

During the study 349 people, about 10% of the total, initiated HIV treatment. Approximately half of people initiating treatment had CD4 counts under 200 cells/mm<sup>3</sup> at initiation and one-third between 200 and 350 cells/mm<sup>3</sup>.

There were 151 new HIV infections in the study. One important aspect of the study was that HIV viruses in transmitting and infected partners were sequenced to show that the new infection had indeed come from the long-term partner, and 108 were thus linked: so 28.5% of infections came from someone who was not the primary partner. Five of these 108 transmissions were excluded because the partner's ARV status was unknown, and one because the positive partner was a woman taking ARVs for PMTCT.

Only one of the transmissions came from a partner taking ARVs.

When HIV incidence was calculated in terms of person-years of follow-up, antiretroviral users and their partners had a transmission rate of 0.39 per 100 person-years (1 case ÷ 256 person-years) (95% confidence interval [CI], 0.09-2.18). Antiretroviral non-users and their partners had a transmission rate of 2.23 per 100 person-years (102 cases ÷ 4851 person-years) (95% CI, 1.84-2.70).

This meant the relative risk of transmission from a partner taking ARVs, when adjusted for time on study and CD4 count, was 0.08; a 92% reduction in HIV transmission.

Some significant differences were observed among subsets of study participants. A higher proportion of men (12%) than women (9%) initiated antiretroviral therapy ( $p=0.01$ ). Men initiated antiretroviral therapy at a median CD4 cell count of 192 cells/mm<sup>3</sup>, while the median for women was 204 cells/mm<sup>3</sup> ( $p=0.05$ ).

The single case of transmission involved a man who initiated ARVs 18 days before his 12-month study visit. At this visit his partner tested positive for HIV, having been negative at month 9. His CD4 count was in the 200 to 350 cells/mm<sup>3</sup> range.

Untreated partners were far more likely to transmit HIV if they had low CD4 counts. Annual HIV incidence among HIV-negative partners was 8.79% if their partner had a CD4 count under 200 cells/mm<sup>3</sup>, 2.79 for CD4 counts between 200 and 350 cells/mm<sup>3</sup>,

1.70 between 350 and 500 cells/mm<sup>3</sup>, and 1.82 for CD4s over 500 cells/mm<sup>3</sup>.

Unprotected sex declined when partners started ARVs. Before ARV treatment, 6.2% of partners reported unprotected sex in the previous month; 3.7% reported it after treatment initiation. There was no change in sexual frequency.

This study had a number of limitations: it was not randomised, ARV status relied on self-report, and transmission and behaviour data were only followed for a maximum of two years. Using a single transmission to calculate the risk of infection by a person on ARVs involves sophisticated statistical analysis and, as noted above, very wide confidence intervals.

Audience members also commented that the incidence of sexually transmitted infections was low (as, of course, were herpes symptoms) and that a similar study needed to be conducted in gay men.

Nonetheless, Donnell commented, ARVs appear to confer a significant prevention benefit across all CD4 ranges, and this study goes some way towards quantifying that more accurately.

### Reference

Donnell D et al. *ART and risk of heterosexual HIV-1 transmission in HIV-1 serodiscordant African couples: a multinational prospective study*. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 136, 2010.

### Treatment drive in British Columbia produces modest declines in diagnoses and viral loads

By Gus Cairns

An expansion in the numbers of people with HIV in the Canadian province of British Columbia diagnosed and on treatment has started to produce modest reductions in HIV diagnoses and in the average viral load in the community, the 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) heard today.

The trends seen were similar to those reported from San Francisco in a similar presentation the previous day – [see this report](#).

[In 2008 the health minister for British Columbia announced that the province would pursue an aggressive ‘test and treat’ strategy in order to reap the public health benefit of reducing the average viral load in people with HIV.](#)

However Dr Julio Montaner of the British Columbia Centre for Excellence in HIV/AIDS, the prime mover behind this strategy, told the conference that the ‘second wave’ of increased HAART (highly active antiretroviral treatment) coverage actually started prior to the adoption of this strategy, which in itself does not appear to have further increased access.

Antiretroviral (ARV) coverage started in the province in 1996 and had reached 2500 patients by 1999. After this it reached a plateau. Dr Montaner commented that the steady state observed appeared to be connected to a lot of patients in that era choosing to take treatment interruptions.

Starting from the beginning of 2004, a second wave of treatment uptake began, which continues to this day, and there are now 5000 people in the province on treatment. Many of these people were not drug-naïve but re-started treatment after the Centre undertook a campaign of contacting people on treatment interruptions and suggesting they resume.

It is worth noting that there is room for considerable further expansion of treatment in British Columbia, as this figure represents less than half of the estimated number of people who have tested

HIV-positive, and a third of the estimated total number of people with HIV.

The proportion of patients on treatment with a viral load under 50 copies/ml increased from 66% in 2000 to 88% in 2008. Montaner commented that concerns had been raised that encouraging people to return to HIV treatment might result in increased drug resistance, as the proportion of patients with poor adherence would increase. In fact, despite this doubling of ARV coverage, the number of new cases of HIV drug resistance declined from 270 in 2000 to 80 in 2008.

Since 2004 there has been a modest, but statistically significant, decline in the number of new HIV diagnoses per year, from 440 in 2004 to 370 in 2009. However this is entirely accounted for by a decrease in diagnoses in injecting drug users (IDUs), which halved during this period, from 150 in 2004 to 80 in 2009.

Montaner said that the reductions appeared to be driven by antiretroviral take-up, rather than changes in risk behaviour, as British Columbia already has a long history of harm reduction schemes for IDUs. The reductions coincided with an outreach campaign to get injecting drugs users on to HIV treatment, though the study could not prove that one caused the other.

The decline in HIV among IDUs was mirrored by a decline in hepatitis C diagnoses in the province. The annual incidence rate in the general population has declined from 0.12% in 1999 to 0.073% in 2004 and 0.055% in 2008. This contrasts with the figures for sexually transmitted infections: syphilis rates have plateaued since 2004 but gonorrhoea and chlamydia rates have continued to climb.

The proportion of non-IDU patients with a viral load under 500 copies/ml increased from 43% in 2004 to 77% in 2009 and the proportion of IDUs from 34% to 74% – nearly the same as other patients. This represents a considerable achievement in a province with a very specific HIV epidemic concentrated in aboriginal Canadians living in remote communities, as well as HIV-positive injecting drug users. Montaner commented that the reductions in viral load were not restricted to Vancouver, but were spread throughout the province.

He also produced an approximate measure of ‘community viral load’: the average viral load within the HIV-positive community at large. Montaner’s way of doing this was to measure the total number of patients ever given a viral load test in the province, minus those known to have died or moved away. This number amounted to 7400 in 2004 and had increased to 10,200 in 2009. He then determined the proportion of tested patients whose viral load was in one of five different viral load strata (under 500, 500 to 3500, 3500 to 10,000, 10,000 to 50,000, and above 50,000) at the end of any given year.

The absolute number of patients with a viral load test result over 500 copies/ml at last test decreased modestly, from 4800 to 4100, between 2003 to 2009, but as a proportion of the total they decreased from 65% to 40%. This represents a rough measurement of the proportion of patients likely to be infectious.

“Our results show an association between expanded HAART coverage, decreased provincial plasma viral load, and decreased new HIV diagnoses,” said Montaner.

“Seek, Test, Treat and Retain (STTR) strategies targeting HIV-positive individuals who meet criteria for HAART initiation should proceed expeditiously,” he added.

### Reference

Montaner J et al. *Association of expanded HAART coverage with a decrease in new HIV diagnoses, particularly among injection drug users in British Columbia, Canada*. 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 88LB, 2010.

### Further information

You can [view the abstract on the official conference website](#).

You can also [view a webcast and slides of this session on the official conference website](#).

### Increased testing leads to decrease in viral load and infections in San Francisco, and in late diagnosis in Washington

By Gus Cairns

The HIV infection rate in San Francisco appears to be falling, and the fall is associated with a reduction in the average viral load in HIV-positive people, due to more people on treatment, the 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) heard on Wednesday.

Dr Moupali Das from the San Francisco Department of Public Health (DPH) told the conference that the reduction in infections was ultimately due to an increased frequency of HIV testing. It is estimated that only one in seven people with HIV in the city is unaware of their infection, one of the lowest undiagnosed rates in the world.

Between 2004 and 2008, Dr Das said, the number of HIV diagnoses in San Francisco fell by 45%, and the average viral load amongst the HIV-positive population by 40%. The DPH also estimated that the actual HIV incidence – the true number of new HIV infections, diagnosed and undiagnosed – fell by one-third between 2006 and 2008.

During the four-year period, the proportion of people taking HIV tests who had tested less than a year previously rose from 65% to 72%, and the proportion testing within the last six months from 41% to 53%. It was estimated that during this time the proportion of people with HIV unaware of their infection fell from 24% to 14.5%.

The proportion of people diagnosed with HIV linked to care rose to nearly 80%, and the proportion of those in care who were on antiretrovirals rose from 78% to 90%, with nearly three-quarters having an undetectable viral load (under 75 copies/ml).

San Francisco City's HIV surveillance system includes mandatory reporting of viral loads, and the DPH was able to calculate two different measures of so-called 'community viral load' (CVL) in the HIV-positive population attending care. They calculated both the mean of the most recent viral load test reported for all individuals in care, and also the cumulative sum of all viral loads.

"Community viral load acts like a virometer," said Dr Das, "a measure of the temperature of the epidemic."

They found that the mean CVL was about 23,000 each year between 2002 and 2005, but then started to fall and was around 15,000 by 2008.

At the same time the number of new HIV diagnoses fell from 796 in 2004 to 434 in 2008. The association between reduction in viral load and new diagnoses was statistically significant ( $p = 0.019$ ). However it is important to note that this is only a measure of the correlation between viral load and diagnoses: it doesn't prove one caused the other.

A Centers for Disease Control (CDC) algorithm, which calculates the likely true incidence of HIV from the diagnosis and testing-frequency data, enabled the researchers to estimate that the actual number of HIV infections in the city fell in two years by 34%, from approximately 930 in 2006 to 620 in 2008. However, due to the margin of error in this method of calculating incidence, this was not statistically significant ( $p = 0.3$ ) so cannot be said to prove that a real decline is yet happening.

The study has one significant limitation in that it could not include the viral load from undiagnosed individuals in its calculation

of CVL, though a reduction in the undiagnosed proportion would lead indirectly to a reduction in CVL due to more people on treatment.

Interestingly, the reduction in new diagnoses and estimated incidence occurred within a context of significant increases in sexually transmitted infections (STIs) including rectal gonorrhoea and syphilis. Dr Das said that serosorting practices between gay men may be the reason this rise did not appear to impact on new infections.

"Our findings support the hypothesis that wide-scale early antiretroviral therapy can have a preventative effect at population level," commented Dr Das. She said that CVL was a useful 'upstream' predictor of the likely number of new infections, and could therefore be used to calculate future resources and prevention needs.

### Testing increases 'exponentially' in Washington DC

Meanwhile on the east coast of the USA, a comprehensive drive to increase HIV testing in Washington, DC has led to a significant rise in the CD4 count of those tested and a near-halving of the proportion who develop AIDS symptoms in the first year after diagnosis, though it has not yet led to falls in HIV diagnosis.

Washington DC has the highest HIV prevalence in the general population of any US city – around 3%. From 2006 three separate campaigns were initiated to increase the number of sites that performed opt-out HIV testing in routine medical settings and the number of tests they did; to encourage members of the public to test; and to improve the proportion of people who test positive who access care.

There had been approximately 20,000 HIV tests performed in Washington DC in 2004, and 35,000 at the start of the campaign in 2006. By 2009 this had risen to 93,000.

The number of HIV diagnoses increased by 17% between 2004 and 2007, from approximately 1100 to 1300, and this was significant. An apparent fall to 1100 diagnoses in 2008 reflects reporting delays.

In the DC setting, unlike San Francisco, increasing testing increased the number of new diagnoses, as many testers had never tested before and were late-presenters. But the increased testing rates did shorten the average time between infection and diagnosis.

Median CD4 count at diagnosis increased from 216 in 2004 to 343 in 2008 ( $p = <0.05$ ), and the proportion who had AIDS-related symptoms within the first year after diagnosis fell from 47% to 28%.

Linkage to HIV care improved. A quarter of patients diagnosed in 2004 had not attended an HIV clinic for a follow-up appointment within a year of diagnosis; by 2008 this fell to just over 5%.

There was no increase in the number of medical providers performing tests, but a significant increase in the number of tests each one performed, and a significant increase in the number of non-medical sites offering tests, such as community-based organisations.

One of the most significant contributors to the increase in both testing and linkage to care, commented presenter Amanda Castel, was the involvement of the Washington DC jail in the testing programme. One-third of the patients who had rapid, as opposed to conventional, HIV tests were tested in prison, and the jail also has an active programme linking released prisoners to care, providing 28 days' worth of antiretrovirals on release.

### References

Das-Douglas M et al. *Decreases in community viral load are associated with a reduction in new HIV diagnoses in San Francisco*. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 33. 2010.

Castel A et al. *Monitoring the impact of expanded HIV testing in the District of Columbia using population-based HIV/AIDS surveillance data*. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 34, 2010.

#### Further information

You can view [abstract 33](#) and [abstract 34](#) on the official conference website.

You can also [view a webcast and slides of this session on the official conference website](#).

## Long-term toxicities

### Antiretroviral drugs have variable effects on bones and fat, lipodystrophy uncommon with modern regimens

By Liz Highleyman

Different antiretroviral regimen components are linked to varying changes in bone mineral density and body fat, according to a sub-study of the US ACTG 5202 trial reported at the 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) last week in San Francisco. Tenofovir/FTC (*Truvada*) led to greater bone loss, whilst boosted atazanavir (*Reyataz*) produced both more bone loss and greater limb and trunk fat gain.

ACTG 5202 was a phase IV clinical trial that compared four commonly used combination regimens. More than 1800 previously untreated participants were randomly assigned to receive either *Truvada* or abacavir/3TC (*Kivexa* or *Epzicom*) as a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) 'backbone'. They also received either ritonavir-boosted atazanavir or efavirenz (*Sustiva* or *Stocrin*) as a 'base' drug on an open-label basis.

The final results of the parent study were also [presented at CROI](#). In brief, the various regimens produced comparable viral suppression in people with baseline viral load below 100,000 copies/ml, but showed some differences in side-effects.

ACTG 5224s was a sub-study of the larger trial that looked at two types of side-effects, bone loss and body fat changes. Grace McComsey and colleagues used dual energy X-ray absorptiometry (DEXA) scans to measure bone mineral density changes in the lumbar spine (lower back) and hip bone, as well as changes in limb fat and trunk (primarily abdominal) fat.

They also looked at the number of bone fractures and the percentage of people who developed lipodystrophy, or fat loss in the limbs and face, after 96 weeks of therapy. For this study, lipodystrophy was defined as a 10% or greater loss of limb fat from baseline. Dr McComsey described this degree of fat loss as "mild", a change that might not be visually evident to patients or clinicians.

The sub-study included 269 participants, with similar numbers taking each of the four regimens. Demographic and HIV status were similar across all groups. Most participants (85%) were men, about half were white, the median age was 38 years, and the median body mass index (BMI) was 24.9, the top of the normal range.

The participants had relatively advanced HIV disease, with a baseline median CD4 cell count of 233 cells/mm<sup>3</sup>, and just over 40% having fewer than 200 cells/mm<sup>3</sup>; 41% had a high viral load of 100,000 copies/ml or more. None had diabetes or other conditions known to affect bone or body composition.

#### Bone density

All regimens led to an initial steep drop in bone mineral density soon after starting treatment, which then rose and stabilised at a somewhat higher level – though not back to the baseline level –

after about a year. There was no evidence of any significant interactions between the NRTI backbones and the base drugs.

In the primary intent-to-treat analysis at week 96 comparing the NRTI backbones, people taking *Truvada* had significantly larger decreases from baseline in lumbar spine and hip bone density compared with *Kivexa* recipients (-1.3% vs -3.0% for spine; -2.6% vs -3.9% for hip).

Looking at the open-label base components, atazanavir/ritonavir was associated with more bone loss than efavirenz at both sites, but the difference was only significant for the lumbar spine (-1.7% vs -3.2% for spine; -3.1% vs -3.4% for hip).

Though the primary analysis was at week 96, Dr McComsey also showed longer follow-up data through week 192, at which point approximately 45% of the initial participants were still being followed. Bone density continued to rise with *Kivexa* (plus either efavirenz or atazanavir), but there was a downward turn with *Truvada* starting around week 144.

Overall, 5.6% of participants had at least one bone fracture, all of them traumatic (due to injury). The researchers also reviewed data on fractures in the ACTG 5202 parent study. In this larger group, the fracture frequency was 4.3% (a rate of 1.7 per 100 person years); 12.7% of these were non-traumatic (spontaneous). Despite variations in bone mineral density, there were no significant differences in fracture frequency between the NRTI arms or between the base drugs in either the sub-study or parent study.

#### Body fat

Turning to fat, Dr McComsey reminded listeners that fat gain in the arms and legs is considered good, relative to the lipodystrophy seen in the past. (People often gain a modest amount of weight after starting antiretroviral treatment.)

Trunk or central fat gain is often unfavourable, but could also signal a "return to health" in people with wasting due to advanced HIV disease.

Overall, 16% of participants had a 10% or greater limb fat loss (protocol-defined lipodystrophy) at week 96, and there were no statistically significant differences between either the NRTI backbones or the base drugs (intent-to-treat analysis). The frequency of lipodystrophy was 14.3% for *Truvada* plus efavirenz, 15.6% for *Truvada* plus atazanavir/ritonavir, 18.9% for *Kivexa* plus efavirenz and 16.3% for *Kivexa* plus atazanavir/ritonavir.

Dr McComsey told a subsequent press conference that the measure of lipodystrophy used in this study was very strict, and that for lipodystrophy to be noticeable to patient and doctor, limb fat loss of 40 to 50% would need to occur. In this population limb fat loss of 10% represents a total loss of around 1kg (2.2lbs) over two years.

The researchers also added a post-hoc (unplanned) analysis of the percentages of people who experienced a 20% or greater limb fat loss. This showed more variation: 8.9%, 0%, 3.8% and 6.1%, respectively.

By week 96, the average amount of limb fat had increased for both *Truvada* and *Kivexa* recipients, with average gains of 1.1 vs 1.7 kg, respectively, in the intent-to-treat analysis, not a significant difference. Percentage changes were also statistically similar. After 96 weeks, limb fat continued to rise with both NRTI backbones.

In an analysis of patients as treated (that is, taking into account treatment discontinuations and switches), limb fat gains were 1.2 kg with *Truvada* vs 2.1 kg with *Kivexa*, which did reach statistical significance. The difference in percentage change, however, remained non-significant. After 96 weeks, limb fat continued to rise with *Truvada* but fell with *Kivexa*.

With regard to the open-label base drugs, the amount of limb fat rose more with atazanavir/ritonavir than with efavirenz by week 96 (1.9 vs 1.0 kg, respectively), and the percentage increase was about

twice as large with atazanavir/ritonavir (roughly 15% vs 30%, respectively); both were significant in an intent-to-treat analysis. With longer follow-up, efavirenz appeared to catch up by week 192.

In an unplanned analysis of trunk fat, average amounts gained (about 1.5 to 2.0 kg) and percentage changes (about 25%) were similar in the *Truvada* and *Kivexa* groups. As with limb fat, these changes were modest.

Trunk fat rose significantly more with atazanavir/ritonavir than with efavirenz (about 1.2 vs 2.5 kg, or roughly 20% vs nearly 40%, respectively).

Summing up, the researchers found that all regimens appeared to produce an initial bone loss, with subsequent stabilisation after week 48. *Truvada* led to greater bone mineral density loss in the lumbar spine and hip than *Kivexa*, and atazanavir/ritonavir led to greater bone loss in the lumbar spine (but not hip) than efavirenz. Fractures were similarly distributed amongst the study arms.

Further, regimens containing *Truvada* or *Kivexa* increased both limb fat and trunk fat, and were not significantly different in an intent-to-treat analysis. Boosted atazanavir led to greater gain in limb fat and trunk fat than efavirenz.

The investigators concluded that lipoatrophy – even the mild protocol-defined form – occurred in about 16% of participants, and was not significantly different between *Truvada* and *Kivexa* or between atazanavir/ritonavir and efavirenz.

Speaking at an accompanying press conference, McComsey said that regimens containing *Truvada* "did worse" than those with *Kivexa*, keeping in mind that bone loss is bad and limb fat gain is good.

These findings are important, she added, because they can help clinicians tailor regimens for people who have a higher risk of bone loss, such as post-menopausal women.

With regard to limb fat, she said the lipoatrophy rates were "very low", which offers "very encouraging news" that these modern regimens do not cause some of the problems seen with some of the older drugs.

#### Reference

McComsey G et al. *Bone and limb fat outcomes of ACTG A5224s, a substudy of ACTG A5202: a prospective, randomized, partially blinded phase III trial of ABC/3TC or TDF/FTC with EFV or ATV/r for initial treatment of HIV-1 infection*. Seventeenth Conference on Retroviruses and Opportunistic Infections, abstract 106LB, San Francisco, 2010.

#### Further information

You can [view the abstract on the official conference website](#).

You can also [view a webcast and slides of this session on the official conference website](#).

### EuroSIDA study suggests tenofovir increases risk of chronic kidney disease

By Liz Highleyman

An analysis from the large EuroSIDA study found that people who take antiretroviral regimens including tenofovir (*Viread*) appear to be more likely to develop chronic kidney disease, researchers reported at the 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) last week in San Francisco. Weaker associations were seen for indinavir (*Crixivan*) and atazanavir (*Reyataz*).

People with HIV are known to have an elevated risk of kidney impairment compared with the general population, but it is not clear whether this is due to chronic infection itself, antiretroviral drugs, traditional risk factors or some combination of factors.

While some studies have shown an increased risk of kidney disease in people who take tenofovir, other studies have failed to find the same relationship.

The EuroSIDA review presented at CROI is the largest study to date, with a substantial period of follow-up, and shows clearly that people taking tenofovir were more likely to suffer a decline in kidney function.

However the study also found that two other drugs – indinavir and atazanavir – were associated with an increased risk of kidney disease, with lopinavir/ritonavir also implicated in the development of kidney disease, although less so.

EuroSIDA investigators performed a study of rates and risk factors for chronic kidney disease – a persistent reduction in glomerular filtration rate (GFR) to less than 60 ml/min/1.73m<sup>2</sup> or presence of albumin (a blood protein) in the urine. GFR is a measure of how efficiently blood is filtered in capillary bundles in the kidney called glomeruli.

For this study, confirmed chronic kidney disease was defined as persistent (two assessments at least three months apart) estimated GFR (eGFR) of 60 or less if the level at baseline was above 60, or a 25% decline if it started at 60 or below, using the Cockcroft-Gault formula.

EuroSIDA is an ongoing prospective observational study that now includes more than 16,500 HIV-positive participants seen at 103 centres. In the kidney disease study, researchers analysed data from 6843 cohort participants who had at least three available serum creatinine measurements (used to estimate GFR). They were followed for an average of about four years, accumulating a total of 21,482 person-years of data.

Three-quarters of the participants were men, more than 85% were white, and the median age was 43 years. Looking at kidney disease risk factors, about 23% were co-infected with hepatitis C, 22% had high blood pressure, and 5% had diabetes.

About 90% had ever been exposed to antiretroviral drugs. Current CD4 cell count was relatively high, at 450 cells/mm<sup>3</sup>, but about one-third had a prior AIDS diagnosis.

A total of 225 study participants (3.3%) progressed to chronic kidney disease during follow-up, for an incidence rate of 1.1 per 100 person-years. The rate increased over time, from less than 0.5% after the first year, to 1.5% after the second year, to about 4.5% after four years of follow-up.

The researchers then assessed the link between specific antiretroviral drugs and development of kidney disease. Exposure duration was divided into four categories: never used, 0-1 years, 1-2 years, 2-3 years and more than three years. There are not yet enough follow-up data to determine associations with the newest agents including darunavir (*Prezista*), etravirine (*Intence*), maraviroc (*Celsentri*) and raltegravir (*Isentress*).

Cumulative exposure to four drugs was linked to higher likelihood of developing chronic kidney disease: the nucleotide reverse transcriptase tenofovir (*Viread*, also in the *Truvada* and *Atripla* combination pills), and three protease inhibitors, indinavir (*Crixivan*), atazanavir (*Reyataz*) and lopinavir/ritonavir (*Kaletra*).

People never exposed to tenofovir had an incidence rate of 0.7 per 100 person-years, whilst people with three or more years of exposure had an incidence rate of 2.4 per 100 person-years. Considering drug exposure alone, the incident rate ratio (IRR) was 1.32, or about 32% higher. After adjusting for other factors, IRR fell to 1.16, which remained statistically significant.

For indinavir, the incidence rate was 0.6 per 100 person-years without exposure compared to 1.9 per 100 person-years with the longest exposure. The IRR was 1.18 – or 18% higher – in isolation and 1.12 after adjustment (also statistically significant).

For atazanavir, the incidence rate was 0.8 per 100 person-years without exposure vs 3.9 per 100 person-years with the longest exposure. Here, the unadjusted IRR was 1.48 and the adjusted IRR was 1.21 (again significant).

Lopinavir/ritonavir showed the weakest link with kidney disease; unlike the other three drugs, risk did not rise consistently with longer exposure, though it was higher after three years. The unadjusted IRR was 1.15 and the adjusted IRR was 1.08; this was statistically significant, but by a narrower margin.

Overall, general patterns for the four drugs were similar when two other methods (MDRD and CKD-EPI) were used to calculate eGFR, when applying alternative definitions of chronic kidney disease, and when 'censoring' other implicated drugs used at the same time.

No other specific antiretroviral drugs or regimen types were significantly associated with a higher risk of chronic kidney dysfunction. However, male sex, older age, lower baseline eGFR, AIDS during follow-up, higher viral load, high blood pressure, diabetes, hepatitis C, and non-AIDS malignancies were independent predictive factors.

Among study participants who stopped taking tenofovir during follow-up, the risk of developing chronic kidney disease was fourfold higher compared with never-exposed patients during the first 12 months (IRR 4.05), but was similar thereafter (IRR 1.12).

Presenter Ole Kirk suggested the high rate during the first year probably reflected patients who discontinued tenofovir due to kidney concerns. Among people who stopped atazanavir or lopinavir/ritonavir, the kidney disease risk was similar to that of unexposed patients.

The EuroSIDA investigators concluded that increasing exposure to tenofovir was associated with a higher risk of chronic kidney disease. An association was also identified for indinavir and atazanavir, but results for lopinavir/ritonavir were less clear. These findings, they noted, are consistent with other studies.

The researchers suggested that long-term kidney impairment may be due to differing mechanisms: glomerular and tubular dysfunction for tenofovir, and build-up of drug crystals or kidney stones for the three protease inhibitors.

Although biologically plausible, they added, the exact pathogenesis behind these findings remains to be elucidated.

## References

Kirk O et al. *Chronic kidney disease and exposure to ART in a large cohort with long-term follow-up: the EuroSIDA study*. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 107LB, 2010.

## Further information

You can [view the abstract on the official conference website](#).

You can also [view a webcast and slides of this session on the official conference website](#).

## Cancers

### Chemotherapy plus ART best treatment for Kaposi's sarcoma in South African study

By Keith Alcorn

Treating severe Kaposi's sarcoma in South Africa is more likely to be successful when chemotherapy is used alongside antiretroviral therapy, researchers from the University of Kwazulu-Natal reported this week at the 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco.

Kaposi's sarcoma (KS) is a skin cancer that is considered to be an AIDS-defining illness. In Europe and North America the condition

occurs largely in men who have sex with men, but in sub-Saharan Africa it is seen in all exposure categories.

The incidence of Kaposi's sarcoma has been rising in recent years as the number of severely immunosuppressed people grows in sub-Saharan Africa, and in Kwazulu-Natal the incidence is estimated at 30 cases per 100,000 inhabitants per year.

Although milder cases of Kaposi's sarcoma often fade away after antiretroviral therapy is begun, more severe disseminated cases that affect the internal organs such as the lungs, or which are widespread over the body, may not resolve as immune status improves, and the prognosis of people with advanced Kaposi's sarcoma is relatively poor.

Researchers at the University of Kwazulu-Natal designed a study to determine whether chemotherapy provided alongside antiretroviral therapy would be safe and effective.

The KAART study was an open-label, randomised controlled trial. All the patients were starting HIV treatment for the first time and had biopsy-proven Kaposi's sarcoma.

A total of 59 patients were randomised to receive antiretroviral therapy alone (3TC, d4T and nevirapine in the combined pill *Triomune*). A further 53 patients were randomised to receive both *Triomune* plus anti-KS chemotherapy consisting of bleomycin, doxorubicin, and vincristine (the ABV regimen). This regimen was chosen because it is the most commonly available in southern Africa.

Response rates were evaluated according to established prognostic factors. Using an intent-to-treat analysis, the investigators compared clinical response rate between the two arms after twelve months of treatment, as well as rate of response, overall survival and quality of life.

Most of the patients had poor prognostic factors. KS was staged as T1 (poor risk) in 89% of individuals, 58% had a CD4 cell count below 200 cells/mm<sup>3</sup> and 42% had another serious illness, tuberculosis being the most common (34%).

The twelve-month overall response rate was significantly better in the patients who received chemotherapy in addition to antiretroviral therapy (66% vs 39%,  $p = 0.005$ ). The response rate was also significantly faster in this group of patients ( $p < 0.001$ ).

However, overall twelve-month survival was comparable between the two arms of the study at 76%.

Adherence, CD4 cell count increases, fall in viral load and the frequency of side-effects were comparable between the two groups of patients.

The most important factor associated with overall response was KS disease staging and the presence of systemic disease (opportunistic infections such as tuberculosis) ( $p = 0.03$ ).

Quality of life information was available for 111 patients. This improved significantly from a score of 50 at baseline to 67 after one year of treatment ( $p < 0.001$ ). Improvements were observed in emotional wellbeing, cognitive ability, social functioning, and most symptoms. There was no difference in quality of life changes between the two arms of the study, but there was a strong, though non-significant, trend towards greater improvement in pain in the chemotherapy group.

Presenting the findings Dr Anisa Mosam of the University of Kwazulu-Natal said: "Early addition of chemotherapy plays an important palliative role in patients with Kaposi's sarcoma in sub-Saharan Africa.

## Further information from aidsmap.com

A detailed clinical review of the management of Kaposi's sarcoma in resource-limited settings was published in *HIV & AIDS Treatment in Practice* in [February 2008](#).

## Reference

Mosam A et al. *The KAART trial: a randomised controlled trial of HAART compared to the combination of HAART and chemotherapy in treatment naïve patients with HIV-associated Kaposi's sarcoma in KwaZulu Natal, South Africa*, NCT 00380770. Seventeenth Conference on Retroviruses and Opportunistic Infections, abstract 32, San Francisco, 2010.

## Preventing cervical cancer: good outcomes from screening programme for HIV-positive Zambian women

By Keith Alcorn

Researchers estimate that a cervical cancer screening programme for HIV-positive Zambian women prevented one death from cervical cancer for every 32 women screened.

Cervical cancer is the biggest cause of cancer deaths among women in sub-Saharan Africa, due in large part to lack of screening.

However, HIV infection and immunodeficiency exacerbate the progression of pre-cancerous lesions, and the high prevalence of cervical cancer and pre-cancerous changes in women with HIV has led to efforts to incorporate cervical screening into HIV clinics and other health services in countries with a high burden of HIV infection.

Dr Groesbeck Parham of the University of Alabama at Birmingham reported to the 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) on one of these pilot programmes, in Zambia.

A pilot study by Dr Parham and colleagues to assess the need for cervical screening among women with HIV had found in 2006 that among a cohort of 150 women, almost one in five had signs suggestive of cervical cancer and only 6% of women had a normal PAP smear. Almost 50% had high-grade cervical changes.

In response to these findings a screening programme was implemented at 15 public-sector health facilities in Lusaka.

The programme used the most basic method of screening available in order to detect abnormalities. Cotton wool soaked in vinegar was applied to the cervix for three minutes, long enough to ensure that any abnormalities would show up as white or red marks.

Nurses were trained to evaluate patients via visual inspection and digital cervicography, which stored digital photographs that could be sent to a gynaecologist for a second opinion where necessary.

Women with grade 3 SIL (squamous intraepithelial lesions) were offered immediate cryotherapy; those with major lesions were referred for excisional biopsy.

The programme used community volunteers to promote cervical screening to women with HIV at local health centres, but once word got round that screening was available, HIV-negative women also began to turn up to request screening.

Between January 2006 and December 2008 21,000 women were screened, of whom 6572 were HIV-positive.

Among the 6572 HIV-positive women screened, 3523 (54%) had abnormal results. Those women were either offered immediate cryotherapy, if they met treatment criteria ( $n = 2062$ ), or were referred for further evaluation ( $n = 1461$ ).

Seventy-eight percent of the women offered cryotherapy underwent the procedure.

Forty-nine percent of the women referred for further evaluation underwent histological confirmation, which led to the diagnosis of 235 pre-cancers (CIN [cervical intraepithelial neoplasia] 2/3); 79

early-stage cancers (stage 1A-1B); and 36 late-stage cancers (>stage 2A). Most of the early stage cancers (78%) were stage 1A (micro-invasive).

The full cohort of HIV-positive women had a median CD4 cell count of 188 cells/mm<sup>3</sup> (interquartile range, 100-302 cells/mm<sup>3</sup>).

Researchers used published estimates of disease progression rates, cure rates and prevention rates to assess the impact of the programme on women's health. Going on the premise that treatment would be provided to all women who needed it, they concluded that the intervention prevented 203 cases of invasive cervical cancer among the 6572 HIV-positive women screened.

Multivariate analysis showed that a low income (<500,000 kwacha per month), abnormal bleeding and discharge, number of lifetime partners and pregnancies were associated with an increased risk of cervical cancer, while age over 45 and no history of condom use were moderately protective. (Dr Parham suggested that these factors may have been protective because they were associated with women in long-term relationships.)

The 'screen and treat' service may provide a potential platform for the introduction of a cervical cancer vaccine, said Dr Parham, but ensuring long-term follow-up of women will require a significant investment of time to ensure that women return to the clinic.

## Reference

Parham G et al. *Effectiveness of a program to prevent cervical cancer among HIV-infected women in Zambia*. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 29, 2010.

## Further information

You can [view the abstract on the official conference website](#).

You can also [view a webcast and slides of this session on the official conference website](#).

## Epidemiology

### Vitamin D deficiency extremely common among HIV-positive patients in diverse regions

By Derek Thaczuk

New analyses have found widespread vitamin D insufficiency among American, Italian and Swiss cohorts of HIV-positive patients. These data were presented in a poster session and related discussion at the 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI).

Vitamin D deficiency was consistently less frequent in Caucasians than in other races. Otherwise, the studies were not entirely consistent as to other risk factors, such as duration or type of antiretroviral treatment.

At the CROI discussion session on Wednesday, moderator Peter Reiss from the University of Amsterdam began by noting that vitamin D deficiency can result in bone density loss, cardiovascular disease, diabetes and insulin resistance, kidney disease, and other metabolic conditions commonly seen in patients with HIV.

Vitamin D levels are generally assessed as blood levels of 25-hydroxyvitamin D, also expressed as 25(OH)D. According to a widely accepted reference scale, 25-hydroxyvitamin D levels are:

- "sufficient" if  $\geq 75$  nmol/l ( $\geq 30$  ng/ml),
- "insufficient" if between 50-75 nmol/l (20-30 ng/ml), and
- "deficient" if  $< 50$  nmol/l ( $< 20$  ng/ml).

However, Reiss pointed out that these values are not universally used (even within the studies in this session), that they do not account for seasonal variation or ethnic differences (as darker skin

is less able to produce vitamin D, and levels are higher in the summer months), and that optimal levels for health have not been well established.

Despite these uncertainties, these newly reported studies were consistent with previous reports in identifying very high rates of vitamin D insufficiency or deficiency among HIV-positive people. (See, for instance, [this Dutch study](#) and [these US and UK studies reported at IAS 2009](#).)

#### United States: the SUN study

Christine Dao from the Centers for Disease Control presented data from the SUN study, a prospective observational cohort of 700 HIV-positive adults enrolled at clinics in four US cities from March 2004 to June 2006.

The findings were based on 672 participants who had had baseline serum 25-hydroxyvitamin D determinations, and who were not taking vitamin D supplements. The cohort was 77% male, 30% black and 10% Hispanic, median age was 41 years, median CD4 count 471 cells/mm<sup>3</sup>, and most (74%) had viral loads < 400 copies/ml.

In this cohort, 71.6% (95% confidence interval [CI] 68.1 to 74.9) were deemed vitamin D insufficient, defined as serum 25-hydroxyvitamin D levels <30 ng/ml. In multivariable analysis, sex, age and bone mineral density (BMD) had no association with vitamin D levels. The following factors were independently associated with higher risk of insufficiency:

- black race (adjusted odds ratio [aOR] = 4.50, 95% confidence interval [CI] 2.59 to 7.85),
- Hispanic ethnicity (aOR = 2.78, 95% CI 1.31 to 5.90),
- lower exposure to ultraviolet light, as estimated from National Weather Service data for the month of sampling (aOR = 1.28, 95% CI 1.17 to 1.40),
- hypertension (aOR = 1.88, 95% CI 1.10 to 3.22),
- lack of exercise (aOR = 3.14, 95% CI 1.80 to 5.47), and
- exposure to efavirenz (aOR = 1.98, 95% CI 1.18 to 3.34).

Lower odds of vitamin D insufficiency were seen in patients with renal (kidney) insufficiency (GFR <90 mL/min/1.73m<sup>2</sup>) (aOR = 0.55, 95% CI 0.36 to 0.83) and exposure to ritonavir (aOR = 0.56, 95% CI 0.35 to 0.89).

#### United States: the WIHS

The Women's Interagency Health Study (WIHS) is a longitudinal study of women with and at risk for HIV. The substudy reported here looked at a cross-section of 609 WIHS participants (480 HIV-positive, 122 HIV-negative) from Chicago and New York. Vitamin D deficiency (defined as 25-hydroxyvitamin D levels ≤ 20 ng/ml) was found in 60% of these women, and insufficiency (20 to ≤30 ng/ml) in 23.5%.

Age, HIV status, and CD4 count were not predictive of vitamin D deficiency in this group. In multivariate analysis, black race was the only significant predictor of deficiency, with an odds ratio [OR] of 3.16 compared to white race (95% CI, 2.06 to 4.89).

Bacterial vaginosis was found in 19% of the study group and was strongly correlated with vitamin D level ( $r = -0.14$ ,  $p < 0.001$ ). Risk of bacterial vaginosis increased with worsening deficiency: compared to sufficient vitamin D levels, the odds ratio was 2.12 for insufficiency and 3.55 for deficiency.

#### Italy: ICONA

Findings from an analysis of the Italian ICONA cohort were presented next. A total of 1505 plasma samples from 856 patients were analysed; 262 before ART initiation and 1243 after a median of 14 months of ART. The median age was 36 years, and most patients (93%) were from Italy.

In this cross-sectional sample, vitamin D insufficiency (defined as 25-hydroxyvitamin D levels <75 nmol/l) was found in 54% of the samples, and deficiency (levels <30 nmol/l) in 7%.

Levels varied seasonally (much lower in winter and spring). In multivariable analysis, older age increased risk of deficiency (odds ratio [OR] = 1.53 per 10 years older, 95% CI 1.11 to 2.09,  $p = 0.009$ ). The following factors decreased risk:

- Caucasian origin (OR = 0.17, 95% CI 0.07 to 0.42,  $p = 0.0001$ ),
- higher CD4 count (OR = 0.90 per 100 cells/mm<sup>3</sup> higher, 95% CI 0.82 to 0.99,  $p = 0.04$ ),
- higher body mass index (BMI) (OR = 0.90 per unit higher, 95% CI 0.83 to 0.98,  $p = 0.01$ ), and
- type of ART (PI use decreased risk compared to NNRTI use: OR = 0.47, 95% CI 0.27 to 0.84,  $p = 0.01$ ).

#### Swiss HIV Cohort Study

The third study presented was a retrospective analysis of 25-hydroxyvitamin D levels in stored serum from 211 Swiss HIV Cohort participants (75% male, 88% Caucasian, median age 37 years). Samples were taken at three time points: before initiating ART, and at twelve and eighteen months after starting ART. Seasonality was thus controlled, as the second sample was taken during the same season as the first, and the final sample in the opposite season (spring/fall, summer/winter).

At the time of the first (baseline) sample, vitamin D deficiency (defined as 25-hydroxyvitamin D levels <30 nmol/l) was found in 14% of participants in fall and 42% in spring. These levels were essentially unchanged twelve months after ART initiation (14% in fall, 47% in spring), but showed the expected seasonal change at 18 months (deficiency levels were higher in the spring and lower in the fall).

By multivariable analysis, apart from seasonal variation, the following factors increased vitamin D levels:

- Caucasian ethnicity (multivariable coefficient 14.1, 95% CI 6.0 to 22.1,  $p = 0.001$ ), and
- duration since HIV diagnosis (6.4, 95% CI 1.2 to 11.7,  $p = 0.02$ ).

Factors that decreased vitamin D levels were:

- injection drug use (-11.2, 95% CI -21.0 to -1.5,  $p = 0.02$ ), and
- NNRTI use (-8.2, 95% CI -13.3 to -3.0,  $p = 0.002$ ).

In a subset of 74 patients, the study researchers also looked at levels of 1,25(OH)<sub>2</sub>D, the actual active molecule of vitamin D which the body produces from the parent molecule 25-hydroxyvitamin D. By multivariate analysis, higher 1,25(OH)<sub>2</sub>D levels were found with higher BMI and with use of tenofovir; lower levels were found with higher CD4 cell count, hepatitis C infection, and a previous AIDS diagnosis.

#### Tanzania

Rather than assessing prevalence and risk factors for vitamin D deficiency, this study looked at health outcomes in Tanzanian women with low vitamin D levels. In the first two years of follow-up, compared to women with adequate vitamin D levels, women with low vitamin D status (defined as 25-hydroxyvitamin D <32 ng/ml) had:

- a 45% higher chance of wasting (reaching a body mass index <18 kg/m<sup>2</sup> (incidence rate ratio [RR] = 1.45; 95% CI, 1.04 to 2.01),
- a 28% higher chance of acute upper respiratory infections (RR = 1.28, 95% CI, 1.05 to 1.55), and
- a 192% higher chance of thrush (RR = 2.92, 95% CI, 1.43 to 5.96).

#### Conclusions

These studies add to a growing body of evidence that insufficient or deficient vitamin D levels are extremely prevalent among people with HIV. While prevalence figures (and the cut-off values used to define them) vary, these studies reported insufficiency rates of 54% to 72%; figures which are generally consistent with other reports. Studies in women linked vitamin D deficiency with risk of bacterial vaginosis, thrush, and other health problems.

The single factor invariably associated with insufficiency or deficiency was non-Caucasian race. Otherwise, reported risk factors were not entirely consistent, although several studies identified NNRTI and/or efavirenz use.

Investigators agreed that vitamin D deficiency is prevalent among HIV-positive individuals, has harmful effects on health, and is easily addressable through supplementation. Remaining research questions include the link between deficiency and clinical health outcomes, the impact of supplementation, the best doses for supplementation, and closer comparisons of deficiency rates in people with HIV and in the general population, where deficiency is also common.

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### Further information

You can view [poster abstract 750](#), [poster abstract 751](#), [poster abstract 752](#), [poster abstract 753](#), and [poster abstract 754](#) on the official conference website.

You can also [view a webcast and slides of this session on the official conference website](#).

## Overall HIV prevalence stabilises at 11% in South Africa, with decreases in younger age groups

By Gus Cairns

Results of three national HIV household surveys spanning six years, presented at the 17th Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco, indicate that HIV prevalence has stabilised at 11% in South Africa, with signs that the rate of infection is falling in younger age groups.

Five and a half million South Africans live with HIV, almost a quarter of the total in sub-Saharan Africa.

The household surveys were conducted in 2002, 2005 and 2008, and another is planned for 2011. They collected data on HIV status, sociodemographic characteristics and behavioural factors of adults and children at 1000 sites throughout the country.

The first survey tested saliva specimens for HIV while the second and third surveys tested dried blood spot specimens.

Nearly 8500 people were surveyed in 2002 and 16,000 and 15,000 respectively in 2005 and 2008.

Overall HIV prevalence has stabilised, with the surveys showing an HIV prevalence of 11.4% in 2002 and 10.9% in the other two years.

Among children aged 2 to 14, HIV prevalence decreased significantly from 5.6% in 2002 (95% confidence interval [CI], 3.7-7.4) to 2.5% in 2008 (95% CI, 1.9-3.5), probably due to increasing coverage of prevention of mother-to-child transmission.

HIV prevalence has stabilised, or is possibly starting to go down, in young people aged 15 to 24: it was 9.3% in 2002 and 8.7% in 2008. It increased in the core group of adults aged 15 to 49 from 15.5% in 2002 to 16.2% in 2005 and 16.8% in 2008. In neither of these age groups, however, were the changes statistically significant.

South Africa also now has the largest HIV treatment programme in the world, with an exponential expansion in the numbers of people taking treatment from nearly 33,000 in January 2005 to 744,000 in March 2009. Rather than ask people directly, the 2005 and 2008 surveys screened the blood specimens of HIV-positive people for antiretroviral drugs. In 2008, antiretroviral drugs were detected in 16.6% of specimens.

The researchers calculated that the effect of highly active antiretroviral treatment (HAART) at present was to increase HIV prevalence due to lower mortality: they estimated that without treatment prevalence among adults aged 15 to 49 would have been 1.7% lower in 2008, i.e. 15.2% instead of 16.9%.

HIV incidence was calculated using two methods. One, which calculated the incidence in young people by extrapolating directly from new infections and estimating the percentage that were recent, found that annual incidence in 18 year olds had declined from 1.8% in 2005, the peak incidence year, to 0.8% in 2008.

The second method of calculating incidence involved observing prevalence in sequential age groups. For instance, if prevalence is compared in 15 to 25 year olds in 2002 versus 18 to 28 year olds in 2005 and 21 to 31 year olds in 2008, an estimate can be made of the number of new infections that were occurring per year. The fact that three surveys have now been done then allows for this cumulative incidence to be compared with the same age groups in subsequent surveys.

This measure yielded an estimate of annual incidence of 2.0% in 2002-05 compared with 1.3% in 2005-08 in 15 to 49 year olds. This 35% decline did not reach statistical significance. However incidence declined more dramatically in young women aged 15 to 24, among whom there was a statistically significant decline in estimated annual incidence from 5.5% in 2003-05 to 2.2% in 2005-08.

Two trends are probably responsible for these estimated changes in incidence. Among survey respondents aged 15 to 49, reported condom use at last sex increased significantly from 31.3% in 2002 to 64.8% in 2008. There were particularly significant increases among women aged 15 to 49 and people aged over 50.

At the same time, the proportion of people who had ever been tested for HIV increased significantly from 25% to 56% between 2003 and 2008, while the proportion tested in the last twelve months increased from 12% in 2005 to 25% in 2008.

No changes were found in levels of other risk factors such as intergenerational sex or multiple partners.

Presenter Thomas Rehle commented that the observed figures for HIV prevalence masked two different trends, increasing coverage of ARVs and increased condom use, and these needed to be disentangled to unearth actual trends. A much higher coverage of ARVs over a longer period would have to happen for HIV treatment to have a positive effect on incidence, he added.

He recommended incorporating the testing of dried blood spots for antiretroviral drugs into routine surveillance as a means of estimating antiretroviral uptake levels.

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#### Further information

You can [view the abstract on the official conference website](#).

You can also [view a webcast and slides of this session on the official conference website](#).

## HIV and TB in Practice

By Keith Alcorn

**This regular feature on HIV/TB integration is kindly supported by the Stop TB department of the World Health Organization.**

### More evidence supports isoniazid for TB prevention in people with HIV

Two new studies presented last week at the 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco add weight to a growing expert consensus that isoniazid preventive therapy (IPT) should be provided to people with HIV in order to reduce the risk of developing active tuberculosis (TB).

Although, as TB expert Richard Chaisson pointed out at an expert discussion on IPT prior to the conference, IPT is proven to reduce the incidence of TB in people with HIV, there are still many unanswered questions, including its effect on overall mortality, the optimum TB preventive regimen, and the effect of IPT on secondary transmission of TB in the household and among close contacts.

The studies presented this week offer new insights about the additive benefit of IPT in people taking antiretroviral drugs, and provide evidence about a potential alternative to the use of isoniazid alone.

#### IPT in people taking antiretroviral therapy

Dr Craig Innes of the Aurum Institute in South Africa presented results of an observational analysis of patients receiving IPT through a workplace programme in South Africa.

The study looked at the effect of IPT on mortality in a population of South African adults, predominantly male (93%), who started antiretroviral therapy (ART) between January 2004 and December 2007, comparing outcomes in those who received IPT and those who did not.

Individuals receiving health care through the Aurum programme were eligible for ART if they had a CD4 count below 250 cells/mm<sup>3</sup> without symptoms, if they had WHO (World Health Organisation) stage 4 disease, or if they had WHO stage 3 disease with a CD4 count below 350 cells/mm<sup>3</sup>.

Isoniazid preventive therapy was recommended if a patient had no history of TB in the past three years and if current TB could be excluded, although prescription was less than universal due to fears of isoniazid resistance among some physicians if they could not exclude active TB.

The study population comprised 3258 patients who started ART, of whom 910 received IPT. The only significant differences between those who received IPT and those who did not were history of previous TB ever (2.5% vs 8.9%), WHO stage 3 or 4 disease (30% vs 50%) and haemoglobin (13.4 vs 12.9) (all differences  $p < 0.001$ ).

The study showed a significantly lower mortality rate for those who received IPT: across a number of analyses, which adjusted for potential confounding factors, the risk of death was approximately halved if an individual received IPT in addition to antiretroviral therapy.

In the first analysis, which included individuals with a previous history of TB and which adjusted for age, WHO disease stage, CD4 count, haemoglobin count and year of ART commencement, the risk of death was 53% lower in those who received IPT (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.30-0.72,  $p < 0.001$ ).

Some patients received IPT despite guidelines indicating that they should not, and this might have diluted the effect of IPT that would be observed if the guidelines had been strictly observed. In a sensitivity analysis which excluded those with a prior history of TB, the risk of death was 54% lower, indicating no substantive effect of prior TB (HR 0.46).

Another way of looking at the question of whether, if used strictly according to guidelines, the results might turn out differently, is to exclude all patients who had symptoms associated with TB at ART commencement, no matter when they received IPT. This would tend to cast a wider net for those patients who had active TB when exposed to isoniazid, and who might therefore have shown less benefit.

In this analysis, the risk of death was 53% lower (HR 0.47, 95% CI 0.28-0.79,  $p = 0.05$ ).

Only when participants were stratified according to whether they commenced IPT within three months of starting ART, or delayed IPT for more than three months, did a marginal difference emerge. Those who started IPT less than three months after ART had a 61% reduction in the risk of death, whereas those who started IPT more than three months after ART had a 46% reduction in the risk of death when compared to those who did not receive IPT.

The chief limitations of the study are its observational nature – there could have been biases in who received IPT, although the analyses controlled for known confounding factors – and the fact that causes of death were not captured in this study. It is not clear whether the effect of IPT on mortality is solely driven by a reduction in TB-related deaths, or whether protecting IPT has a wider effect.

#### The interaction between ART and tuberculin skin test status

The Aurum Institute study did not control for tuberculin skin test (TST) status, a test that can positively confirm that someone is latently infected with TB. In the BOTUSA IPT study, (which compared 6 and 26 months of IPT in people with HIV), previously presented at the World Lung Health conference in Cancun in December 2009, and presented again this week at CROI, TST-positive patients who received antiretroviral therapy alongside six months of isoniazid experienced a 50% reduction in the risk of developing active TB during the three-year follow-up period when compared to people who received six months of isoniazid alone.

In TST-positive people who received 36 months of isoniazid however, the additional benefit of antiretroviral therapy was

marginal, reducing the likelihood of developing active TB by just 4% in comparison to the no-ART group.

In TST-negative people – those who either had no prior exposure to TB, or else hadn't enough immune function to respond to TB antigens in the skin test – antiretroviral therapy halved the risk of developing active TB in those who received six months of isoniazid, and reduced the risk of active TB by around 45% in those who received 36 months of isoniazid when compared to isoniazid alone.

### A new regimen for TB prevention?

A randomised study conducted by the Tuberculosis Research Center in Chennai, India, showed that a six-month course of isoniazid and ethambutol, another antibiotic used in TB treatment, was just as effective as a 36-month course of isoniazid in people with HIV, most of whom were not receiving antiretroviral therapy.

The Indian study was designed to test whether an alternative regimen to isoniazid alone was safe and effective in a setting where 15 to 20% of patients have isoniazid-resistant TB at diagnosis, and where rifampicin, another TB drug tested as a preventive measure, is strictly reserved for treatment of active TB in order to limit the development of resistance to the drug. The study was also designed to compare the feasibility of a short-course regimen of six months against a longer-term regimen that might be expected to offer greater protection against exposure to TB during the study period itself, especially in immunosuppressed people who may be at higher risk of rapid TB progression.

The study was conducted by the Tuberculosis Research Center in Chennai, and began recruiting patients for the three-year study between 2001 and 2005.

All participants had TB confirmed by sputum culture wherever possible, and the study excluded any person with HIV who had a previous history of TB.

During the study patients received a clinical review every three months to check for symptoms of TB and other health problems, and underwent chest X-ray every six months.

Participants were randomised to receive a daily regimen of isoniazid 300mg and ethambutol 800mg for six months, or 36 months of isoniazid alone, and all patients with a CD4 count below 250 cells/mm<sup>3</sup> received cotrimoxazole. Antiretroviral therapy became available in the public sector in 2004 to patients with WHO stage 4 disease, or WHO stage 3 disease and a CD4 count below 200 cells/mm<sup>3</sup>.

The study randomised 683 patients, and 37 cases of TB occurred during the three years of follow-up, 16 of which were bacteriologically confirmed. The incidence of TB was not significantly different in the two arms of the study (2.4 cases per 100 person years in the ethambutol arm, 1.6 cases per 100 person years in the isoniazid arm), and death rates were also similar.

The low rates of TB in the study compared to the historical incidence previously measured in the Chennai cohort (6.9 cases per 100 person years) may in part be attributable to the screening by culture at baseline. Screening picked up 30 cases of active but asymptomatic TB that otherwise would have developed into incident TB cases during the trial.

In both arms, most cases of TB – and most deaths – occurred during the first 12 to 18 months of follow-up, but only three deaths were a result of TB.

Regardless of the regimen received, individuals with a baseline CD4 count had a fourfold higher incidence of TB, while TST-positive individuals (TST >5mm) had a 40% higher risk of developing TB.

Among the TB cases that were bacteriologically confirmed, six had isoniazid resistance (five in the ethambutol arm and one in the isoniazid arm).

There was no difference in the development of adverse events between the two arms: three severe events occurred in the ethambutol arm and two in the isoniazid arm, and overall the regimens were very well-tolerated. Rates of adherence were also very high, with around 93% in each arm judged to be more than 80% adherent by unannounced home visit pill counts.

Dr Swaminathan commented that the high adherence rates, the high study retention and the low rates of TB in the study may have been due to the high level of preparation and screening that patients received before entering the study. Patients in the trial received free HIV care, and for many, it may have been their first experience within the Indian health system of good-quality care and support, leading to a high level of patient loyalty to the programme, and a reluctance to be referred on for care at other centres when the trial was over.

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### Further information

You can view [abstract 102](#), [abstract 104LB](#) and [abstract 103](#) on the official conference website.

You can also [view a webcast and slides of this session on the official conference website](#).