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HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

We thank those organisations for recognising the importance of providing widely distributed free access to information both to people living with HIV and to the healthcare professionals involved in their care. We also thank them for permission to distribute their excellent work and we encourage HTB readers to visit the source websites for further access to their coverage of HIV treatment.

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EDITORIAL

An important focus at CROI this year was the direct impact that current treatment is already likely to be having on reducing transmission.

The results are particularly important given that many treatment programmes in developing countries are under increasing pressure to limit enrollment of new patients, while 70% of people in immediate need of ARVs globally have yet to access them.

When treatment is pitched against prevention for funding, the phase 'we can't treat our way out of the epidemic' is often used, and CROI provided new data challenges this misconception.

Another prominent statement is that 'for every person put on treatment, there are two new infections'.

The CROI data challenges this too, though it has always been flawed logic to link these two unconnected figures.

The numbers accessing treatment are driven by the effectiveness of treatment programmes. Double the programme and the equation equalises. Scale treatment up four times and the impact is reversed: 'for every two people on treatment only one person becomes infected' etc.

When this connection is made it is insidious, because it implies that people on treatment are driving new infections. It is challenging and undermining our right to care. It seeks to connect two broadly different groups of people. New infections are predominantly driven by people who themselves are recently infected but currently unaware of their new HIV status, whereas people on treatment are likely to already have modified risks for onward transmission.

So, post-CROI, based on very conservations data from the PARTNERS and other studies, lets revise the link between treatment and prevention and say clearly that 'every person on treatment prevents at least nine new infections'.

Southern African HIV Clinician's Society

Since its inception in 1997, with a membership of approximately 250 members, the Southern African HIV Clinician's Society has grown to a membership of over 15 000 in the Sub Saharan region and internationally - a clear recognition of the services and support provided.

The Southern African HIV Clinician's Society is the largest special interest group within the South African Medical Association (SAMA). It is also the largest HIV interest group in the world.

The Society is thrilled to be part of the HIV Treatment Bulletin South initiative. This is a valuable publication for all Health Care Practitioners. This publication has essential, current and scientific information about research and HIV treatment updates with particular implications for clinical practice.

For more information about the Society or on how to become a member please visit:

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CONFERENCE REPORTS

16th Conference on Retroviruses and Opportunistic Infections

16-10 February 2010, San Francisco

troduction

The 17th Conference on Retroviruses and Opportunistic Infections (CROI), one of the most important annual HIV meetings, was held this year from 16-19 February. As with previous meetings, much of the conference is published online including all abstracts and webcasts of oral presentations including poster discussions.

Making this scientific content available without login or subscription is itself a significant achievement. It is a model for broadening access to medical research to a degree that is currently unmatched by any other meeting.

The webcasts this year include oral presentations, poster discussions, the opening lectures and the pre-meeting set of training workshops for young investigators.

The conference website also includes a searchable abstract database.

We encourage readers to view these lectures directly.

http://www.retroconference.org/2010/Abstracts/38289.htm

http://www.retroconference.org/2010/data/files/webcast_2010.htm

Lectures are also available as audio downloads and podcasts which include slides as audiobooks.

Our first articles covering this meeting are:

- Treatment reduces infections by over 90%: a theme that is here to stay
- ACTG 5205: atazanavir/ritonavir vs efavirenz in treatment naïve patients
- Pipeline compounds and new approaches to treatment
- Clinical benefits of stopping smoking: CVD and CHD risk returns to that of 'previous smoker' in HIV-positive people within three years
- HIV increases the risk of lung cancer, independent of smoking status
- HIV-positive people in the HOPS cohort have 4-fold risk of fracture compared to general population in the US
- OCTANE 2: nevirapine and lopinavir/r are similar when used with tenofovir and FTC in treatment-naïve women
- HIV incidence and retesting in pregnancy
- Efavirenz use in pregnancy and birth outcomes
- Pregnancy outcomes in women using non-AZT HAART in Europe
- When should HAART be initiated in pregnancy to achieve an undetectable viral load?
- Pregnancy outcomes in infants exposed to maternal antiretrovirals in utero
- Maternal TB, HIV and pregnancy
- Botswana IPT trial: Continuous isoniazid superior to 6 months short course

More to follow next issue...

Treatment reduces infections by over 90%: a theme that is here to stay

Simon Collins, HIV i-Base

CROI was important this year because of the profile given to further studies supporting the role of treatment as prevention. Together they support the argument that universal treatment is perhaps the most powerful prevention tool we are likely to have for many years, perhaps with the potential to even eradicate the virus on a population level.

In a lecture prior to the main conference, Brian Williams from the South African Centre for Epidemiological Modelling and Analysis, Stellensbosch, detailed the modeling data for the direct and indirect impact of ARVs on prevention, [1] elaborating on the research paper published last year in the Lancet. [2]

At its most optimistic, this includes the potential for universal treatment to eliminate new infections in South Africa within 5-10 years on a cost neutral budget, at the same time saving millions of lives (and preventing millions of new infections). The science on which the model is based shows an impact on dramatically reducing infections that few can ignore.

The epidemiology for the model included low HIV infectivity (~0.001 per heterosexual encounter), 10-fold individual variability in infectivity, a slow epidemic doubling time (~1-3 years), a long period of potential infectiousness (5-15 years) and an average case reproduction number (~7 additional people infected per case): leading to a calculation showing that virtual eradication of HIV could be achieved if transmission could be reduced by 7-fold.

Viral load is commonly reduced by 10,000 times on treatment, and although infectivity reduces in smaller proportions (roughly in relation to the cube route of viral load), the net impact of treatment on infectivity was estimated to be a 96% reduction.

The impact on reducing TB and for continuous treatment after pregnancy were also included, and for interventions based only on PrEP alone or in combination with ARVs. For South Africa, the model was based on a conservative treatment programme, treating at a CD4 count of 200 cells/mm3, but similar costs and benefits were shown when starting universal treatment at 350, 500 or even at diagnosis. The initial outlay (an adjusted US $60 billion) was compensated by lower cost of hospitalisations and reduced new infections, and saved an additional 3 million lives over 40 years, at stable costs.

The discussion after the presentation stressed the need for pilot operational research on each aspect of a universal treatment model, including willingness to test, virological response rates with earlier treatment, the actual impact on transmission - and the need to develop new heath structures to allow such scale-up.

A first step in confirming treatment reduces HIV transmission in real world settings was shown in results from the Partners in Prevention HSV/HIV Transmission (PARTNERS) Study in over 3400 serodifferent heterosexual couples in seven southern African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia). The HIV-positive partner was a man in 32% and a woman in 68% of couples. [3]

This study previously reported that HSV therapy with daily acyclovir failed to protect against HIV infections, explained by a massive increase in localised CD4 target cells, and persistence for up to two months after the healing of HSV lesions.

All HIV-positive partners entered the study with CD4 counts >250 cells/mm3 and were not on treatment. Over two years, approximately 10% of study participants required HIV treatment for their own care, and this allowed for the HIV transmission rates to be compared by use of ARV treatment. Intensive risk reduction support was supplied throughout the study, to minimise HIV risk for the HIV-negative partners.

People with more advanced HIV at baseline were more likely to start treatment; with higher baseline viral loads (mean 4.4 vs 3.9 log copies/mL, p<0.001), and lower CD4 counts (375 vs 540 cells/mm3, p<0.001). A higher proportion of men than women (12% vs 9%, p=0.01) strated treatment, at slightly lower median CD4 counts (192 vs 204 cells/mm3, p=0.05). People starting treatment were also older (mean 35.2 vs 32.7 years, p<0.001).

ART was initiated at CD4 counts <200 cells/mm3 in 52% patients, between 200 and 349 cells/mm3 in 33%, and ≥350 cells/mm3 in 15% (30% of this group were for prevention of mother to child transmission).

New HIV infections were detected in 151 of the HIV-negative partners, over 24 months of follow-up, with testing and prevention support provided every 3 months. Phylogenetic analysis suggested that slightly less than one third (43/151) of the infections were not from the relationship partner. Five cases were excluded from the transmission analysis due to uncertain use of ARVs.

This left an overall transmission rate in 103 remaining transmissions of 2.1%.

Of these, 102/103 were in the non-ARV group (102/4558 person years; rate 2.24 95%CI 1.82-2.72) compared to 1/103 from partners using ARV treatment (1/233 person years; rate 0.37 95%CI 0.09-2.04). This produced an unadjusted relative risk of 0.17 (p=0.037), which became even more significant when adjusting for time on study and CD4 count, showing a 92% reduction in risk: RR=0.08 (95%CI 0.002, 0.57, p=0.004).

The single transmission case occurred in someone whose partner started treatment 18 days before the 9 month assessment, when they were still HIV-negative (details on whether this was by HIV-antigen or PCR testing were not provided), but who seroconverted by the month 12 evaluations. Viral load was undetectable at month 12 in the HIV-positive partner.

Details on CD4 count in the HIV-positive partner showed transmissions at all CD4 levels, with a considerably higher risk when the partner had a count <200 cells/mm3 (rate = 8.79 vs 2.79 at 200-350 and 1.7 at 350-500).

This is likely to be an indirect marker of higher viral load relating to more advanced infections, but surprisingly, the presentation provided no further information on viral load levels of the source partner, other than showing that after a median of 7 months treatment (IQR 3-12months) the median viral load dropped to undetectable, indicating excellent responses.

Importantly, and perhaps showing the positive results from the behavioural interventions, the percentage of visits at which people reported unprotected sex dropped from 6.2% to 3.7% at the pre- and post-treatment visits, respectively, with no change in frequency of sex.

Two other studies at CROI, in a largely MSM population in San Francisco, supported the impact of ARVs to reduce transmission.

Moupali Das-Douglas and colleagues from the San Francisco Department of Public Health and the University of California presented results from a model that estimated values for average and total community viral load (CVL) from 2004-2008 and then compared these with the expected and actual number of new diagnoses over the same period. [4]

Average CVL was defined as the mean of the most recent viral load of all reported HIV-positive individuals in a particular population, divided by the number of reported HIV-positive individuals in the population. Total CVL was the sum of the most recent viral loads of all HIV-positive individuals in a particular population.

The context for this study was an effective 'test and treat' programme that from 2004 to 2008 increased the percentage of MSM testing within 12 months from 65% to 72% and within 6 months from 41% to 53%. The percentage of HIV-positive MSM unaware of their status dropped from 24% to 14.5% (comparable UK figures vary from 30-50%). By 2008, 90% of patients in care were on HAART, with 72% virologically suppressed (<75 copies/mL).

The decreases in mean CVL and reductions in actual diagnoses (from 798 in 2004 to 434 in 2008) were both statistically significant (p=0.005), as were the decreases in total CVL (p=0.019) and percentage of virologically suppressed patients (p=0.002). The presentation acknowledged that a limitation in these results is that cases may be diagnosed chronic rather than new infections, which was addressed in methodology for expected and actual incidence rates.

However, using a more conservative meta-regression analysis (different to the reported abstract), the 30% reduction in CVL and almost 40% reduction in incidence (rather than cases) was not significant (p=0.3) due to the degree of imprecision in the estimates.

While this makes it too early to link CVL with incidence, the reductions in newly diagnosed and reported cases, at the same time as increased testing, greater ARV coverage and greater virological suppression strongly support close following of subsequent data from this model.

In a related poster, Edwin Charlebois and colleagues modeled the impact of earlier treatment and broader test and treat programmes in San Francisco, suggesting that HIV prevalence could fall from the current 25% to around 10% by 2030 if the programme shifted to universal test and treat. [5]

As this issue of HTB went to press, a policy shift in San Francisco to offer HIV treatment to all newly diagnosed patients, regardless of CD4 count or viral load, was announced by public health officials. [6]

COMMENT

The positive correlation between viral load and risk of transmission for every route, whether sexual, from shared injection equipment, during pregnancy, at birth and from breast milk, and from needle stick exposure to health workers, is now convincingly demonstrated. For some of these transmission routes, antiretroviral treatment to reduce viral load is already widely used to reduce transmission (principally for mother to child transmission, PEP and PEPSE).

Treatment dramatically extends life, reduces morbidity and should now be additionally valued for reducing transmission. An estimated 70% of HIV-positive people globally in need of immediate treatment for their own care are still unable to access it.

References:

Unless stated otherwise, all references are to the Programme and Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. 16-10 February 2010, San Francisco. All oral abstracts are available as webcasts.
http://www.retroconference.org

1. Williams B and Dye C. Put your money where your model is: ART for the prevention and treatment of HIV/AIDS. Webcast: Guiding the global response. Tuesday 2.30pm.
2. Granich RM et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. The Lancet, Volume 373, Issue 9657, p48-57, 3 January 2009. doi:10.1016/S0140-6736(08)61697-9.
3. Donnell D et al. ART and risk of heterosexual HIV-1 transmission in HIV-1 serodiscordant African couples: a multinational prospective study. 17th CROI 2010. Oral abstract 136.
http://www.retroconference.org/2010/Abstracts/39222.htm
Webcast: New Insights into Transmission and Acute Infection. Friday 9.30am.
http://www.retroconference.org/2010/data/files/webcast_2010.htm
4. Das-Douglas M et al. Decreases in community viral load are associated with a reduction in new HIV diagnoses in San Francisco. 17th CROI 2010. Oral abstract 33.
http://www.retroconference.org/2010/Abstracts/38232.htm
Webcast: Testing and Transmission. Wednesday 9.30am.
http://www.retroconference.org/2010/data/files/webcast_2010.htm
5. Charlebois E et al. Effect of Expanded ART Strategies on the MSM HIV Epidemic in San Francisco. 17th CROI 2010. Poster abstract 996.
http://www.retroconference.org/2010/Abstracts/39042.htm
6. San Francisco endorses starting HIV treatment immediately after diagnosis. (5 April 2010)
http://www.aidsmeds.com/articles/treatment_HIV_diagnosis_1667_18253.shtml

ACTG 5205: atazanavir/ritonavir vs efavirenz in treatment naïve patients

Simon Collins, HIV i-Base

The few randomised clinical trials using currently licensed antiretrovirals worth highlighting from CROI partly stood out because there were fewer comparative studies that at previous CROI meetings. Of these, ACTG 5205, and its metabolic sub-study ACTG 5224s, generated most attention.

ACTG 5205

ACTG 5205 enrolled over 1850 treatment naïve patients from 2005-7 and followed them through to September 2009. The study was designed to compare efavirenz to atazanavir and tenofovir/FTC to abacavir/3TC by randomising equally to one of four groups. Patients were stratified by baseline viral load (above vs below 100,000 copies/mL). [1, 2]

Baseline demographics included 83% men/17% women; 40% white (non-Hispanic), 33% black, 23% Hispanic; median age 38 years median viral load ~50,000 copies/mL, and median CD4 230 cells/mL, Primary efficacy endpoints were time to confirmed virological failure (>1,000 copies/mL) at or after 16 weeks and before week 24 or viral load >200 copies/mL at week 24. Safety endpoints included time to first grade 3/4 event or laboratory abnormality at least one grade higher than baseline (excluding unconjugated hyperbilirubinaemia). Tolerability was assessed as time to change of treatment.

In February 2008, following a DSMB review, patients with baseline viral load >100,000 copies/mL who were using abacavir/3TC were unblinded and recommended to change to tenofovir/FTC due to significantly poorer virological responses. [3, 4]

Interpreting the final results now is further complicated because HLA-B*5701 testing was not available when the study started. Also, and perhaps more surprisingly, baseline resistance testing was performed in less than half the study group. In practice, this means that the most relevant results from the whole study relate to the comparisons between efavirenz vs atazanavir/r.

Using the primary virologic endpoint, there were no significant differences between atazanavir/r and efavirenz with either abacavir/3TC (HR 1.13, 95%CI 0.82–1.56) or tenofovir/FTC (HR 1.01, 95%CI 0.70, 1.46). The differences for the safety endpoint report benefits for atazanavir/r over efavirenz only with abacavir/3TC (HR 0.81, 95%CI 0.66–1.0; p=0.05), probably driven by a caution over management of rash and a potential hypersensitivity reaction when NNRTIs are prescribed with abacavir. This was seen even more in the tolerability analysis (HR 0.69, 95%CI 0.55, 0.86; p=0.0008).

Cardiovascular and renal events, non-AIDS malignancies and bone fractures were broadly similar in each group.

Again, as seen in other PI vs NNRTI studies, patients with virological failure were significantly more likely to develop resistance on the NNRTI compared to the PI regimen (approximately 60% vs 20% of virological failures included ≥1 major mutation in the efavirenz vs atazanavir/r group respectively).

The only signficant differences in CD4 responses were seen when atazanvir/r group was compared to efavirenz, but only when tenofovir/FTC was used as the nucleoside backbone (+252 vs +221 cells/mm3 at 96 weeks, p=0.002).

Lipid differences were more complicated, and while statistically significant for some values, may or may not be of clinical relevance.

In an on-treatment analysis at week 48, efavirenz was consistently associated with significantly greater increases in total cholesterol, LDL and HDL regardless of nucleosides (all comparisons p<0.001, except LDL with TDF/FTC, p=0.002). Increases were also consistently greater with abacavir/3TC compared to tenofovir/FTC. There were no significant differences

for triglycerides although there was a trend for greater increases with atazanavir/r compared to efavirenz, when used with tenofovir/FTC (p=0.07). Despite this, there were no significant differences in total cholesterol:HDL ratio in any comparisons.

Finally, creatinine clearance dropped by approximately -3.0 mL/min at week 96 (as-treated analysis) when atazanavir/r was used with tenfovir/FTC compared to slightly higher increases in the other three groups (p<0.001). These differences were described as modest and <5% of patients in any arm experienced changes of greater than 25% decline.

ACTG 5224s

The metabolic substudy ACTG 5224s provided data on bone mineral density (BMD) and limb fat changes in 269 patients in ACTG 5202 (approximately 65 from each of the four comparative regimens). [5, 6]

Exclusion criteria for the substudy included diabetes or other complications including use of medication related to bone or body composition. DEXA evaluations (whole body and bone) were taken at baseline and at 24, 48 and 96 weeks, then annually. CT abdominal scans were taken at baseline and at week 96.

When no interaction was seen between either the RTI component or third drug components, factorial analyses were performed comparing pooled results for each dual RTI, and for atazanavir/r to efavirenz.

Primary endpoints included percentage changes in hip and lumber spine between the two RTI components, and changes of >10% loss of limb fat. Secondary analysis included fracture rates and the same bone and fat changes in the PI vs NNRTI groups.

Baseline demographics broadly reflected the main study and were balanced between groups. Of note, baseline rates of osteopenia (T-score <1.0) were 35% at lumbar spine and 23% at the hip.

Mean values for BMD at lumbar spine dropped in all groups over the first year of treatment and then recovered by about 50% over the subsequent year. These declines were more significant in the tenofovir/FTC compared to abacavir/3TC (approximately -3.5%% vs -1.5% at week 96, p=0.004) group and in patients using atazanavir/r compared to efavirenz (-3.2% vs -1.7, p=0.035).

Tenofovir/FTC was associated with a greater drop in hip BMD at 96 weeks compared to abacavir/3TC (-4.0% vs -2.6%, p=0.025) with no difference between atazanavir/r and efavirenz (p=0.59, each approx -3.0%). Early declines in hip BMD did not appear to reverse over time.

Fracture rates were similar in all groups, with an incidence of 1.7 per 100 patient years, all of which were reported as traumatic (ie expected in general life). No difference by regimen was seen in the main study (where 12% of fractures were without trauma).

Changes in fat distribution was complicated by the study decision to select a relatively marginal 10% cut-off for fat loss as the endpoint. No differences were seen between arms using this criteria (approximately -16%), with a post-hoc analysis using >20% reported in <5% patients with no clear RTI or third drug association.

Absolute mean values increased in both RTI arms (approximately +1 kg gain, no statistical difference) but this was higher in the atazanavir/r vs efavirenz groups (approximately +2 kg vs +1 kg; +30% vs +15%, both p=0.008).

Trunk fat increases were similar in each RTI group, but atazanavir/r had greater increases at 96 weeks compared to efavirenz (approximately +2.4 kg vs +1.2 kg, p=0.023).

COMMENT

The clearest outcome from these complicated results is likely to be a stronger recommendation for atazanavir/ritonavir as a clinical option in for first-line therapy.

Absolute differences in side effects, tolerability and metabolic differences are more complicated to interpret in clinical terms, even when they are statistically significant, but would be a factor to consider in individual patients at higher risk.

The reductions in bone mineral density in all groups are concerning, especially given the high percentage of patients with low levels at baseline. While fracture rates in this study were low, other studies at CROI suggested that the concern that ageing will uncover reduced BMD as a greater complication in HIV-positive people compared to the general population, may, unfortunately, be well founded.

Fat changes are difficult to interpret given the choice of endpoint for fat loss, although ~5% patients lost >20% fat across all arms. The significant increases in trunk fat, largely interpreted as a return to health effect, were based on DEXA results. The analysis of CT results, not included in the CROI presentation, is needed to determine whether this is an accumulation of visceral or subcutaneous fat.

References

Unless stated otherwise, all references are to the Programme and Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections, 16-19 February 2010, San Francisco.

All oral abstracts are available as webcasts.

http://www.retroconference.org

1. Daar E et al. ACTG 5202: Final results of ABC/3TC or TDF/FTC with either EFV or ATV/r in treatment-naive HIV-infected patients. 17th CROI 2010. Oral abstract 59LB.
   http://www.retroconference.org/2010/Abstracts/39789.htm
2. Webcast: Advances in ART. Wednesday 9.30am.
   http://www.retroconference.org/2010/data/files/webcast_2010.htm
3. US study changes use of abacavir/3TC in naïve patients with viral load >100,000 copies/mL based on DSMB recommendation. HIV Treatment Bulletin, April 2008.
   http://i-base.info/htb/1811
4. Sax P et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. N Engl J Med. 2009;361. DOI: 10.1056/NEJMoa0906768.
   http://www.ncbi.nlm.nih.gov/pubmed/19952143
5. 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. 17th CROI 2010. Oral abstract 106LB.
   http://www.retroconference.org/2010/Abstracts/39788.htm
6. Webcast: Complications of HIV and ART. Thursday 9.30am.
   http://www.retroconference.org/2010/data/files/webcast_2010.htm

Pipeline compounds and new approaches to treatment

Simon Collins, HIV i-Base

There were fewer presentations at this years meeting on either new drugs or comparative studies between existing drugs. While the missing studies were very noticeable, this is probably more due to the recent approval of several new drugs over the last two years.

It may be significant though that most of the notable studies were nearly all included in one oral abstract session. [1]

QUAD, elvitegravir and cobicistat

New clinical data was presented on the integrase inhibitor elvitegravir, in combination with a new pharmacokinetic booster from Gilead called cobicistat (previously GS-9350), both coformulated with tenofovir/FTC in a four-in-one tablet called Quad. [2]

When Quad was compared to Atripla (efavirenz + tenofovir + FTC), over 80% of patients in each group had undetectable viral load (less than 50 copies/mL) after 24 weeks. However, mean baseline viral load was <40,000 copies/mL, and it was only >100,000 copies/mL in 25% of patients. In this Phase 2 study, patients in the Quad group (n=48) became undetectable more quickly than those on Atripla (n=23), as was seen with raltegravir. For example, after 8 weeks, about 80% people were undetectable with Quad compared to about 50% with Atripla.

While Quad was better tolerated in terms of not having efavirenz-related side effects, a caution due to the impact of cobicistat on reducing estimated glomerular filtration rate (eGFR) - but not actual GFR - suggests that management of renal toxicity may have to be handled differently.

Results from a second Phase 2 study were presented in the same oral presentation, this time comparing the new booster (n=50) to ritonavir (n=29), each in combination with atazanavir, tenofovir and FTC. [2]

No differences were seen in efficacy or tolerability between the two boosters. Unlike ritonavir, cobicistat has no antiretroviral activity.

In summary, results were sufficiently encouraging for both QUAD and cobicistat to be taken into larger Phase 3 studies.

Compounds in earlier development

A dose-finding Phase 1 study of a CCR5-inhibitor in development with Tobira Pharmaceuticals under the compound name TBR-652. The compound has a plasma half-life of 35-40 hours allowing once-daily dosing and although metabolised by CYP and non-CYP pathways is neither and inducer or inhibitor of CYP P450. [3]

These first results in 54 HIV-positive patients produced median viral load reductions of 1.7 log with the 50, 75 and 150mg doses after 10 days monotherapy. Although baseline viral load was lower in the 150mg group (median 4.0 logs, compared to 4.5 and 4.6 logs in the 50mg and 75mg groups), all patients using the 75mg dose had >1.0 log reductions. Patients were treatment-experienced (off treatment for at least 6 weeks), CCR5-naïve and CCR5-postive. No dose-related or serious side effects were reported, though the study was only in about 50 people.

Side effects were mild (none reported at the 75mg dose) and included nausea, diarrhoea, headache and fatigue in greater frequency at the 100 and 150mg - although many of these were reported as being associated with one patient with a concomitant infection.

Very little new information was available for the new integrase inhibitor in development with Shionogi and GSK called S/GSK1349572. [4] Although included in the oral session, this was more a product overview, adding no new in vivo data to that presented at the IAS meeting in Cape Town last year. [5]

Results from a pooled analysis of 721 treatment experienced patients in the unfortunately named Victor-E 3 and 4 Phase studies, presented by Joe Gathe, disappointingly found to too little difference compared to placebo for the troubled CCR5-inhibitor vicriviroc to continue to be taken forward for further development. In a modified ITT analysis the percentage of patients with undetectable viral load (<50 copies/mL) at 48 weeks was 64% and 61% in the vicriviroc and placebo groups respectively (p=0.6). [6]

The presentation suggested this was because of more effective background drugs were available for patients to construct optimum background therapy (approximately 65% had ≥3 active drugs), for the third agent to show significant advantages. A prespecified sub analysis showed that 70% of people randomised to the vicriviroc arms who had ≤2 active drugs achieved <50 copies/mL compared to 55% of the placebo group, and an indication that this was significant. As the vicriviroc group had fewer active drugs at baseline, this potentially obscured a difference in activity between the two arms.

While safety was apparently similar, during the questions, we learned that there were 7 vs 0 deaths in the vicriviroc and placebo arms respectively, not apparently significant after adjusting for time on treatment.

Despite the early promise, it looks likely that the development of this compound will now be put on hold. [6]

Preliminary studies looking at a handful of other targets and approaches, including attempts to target latently infected cells were presented as posters.

Frauke Christ and colleagues from University of Leuven, Belgium, detailed potential compounds from a new class of integrase inhibitor, called LEDGINS, that would not bind at the active site, and therefore not be cross-resistance to raltegravir or elvitegravir. These potential molecules, 2-(quinolin-3-yl)acetic acid derivatives, were designed by rational drug design, and identified after screening 200,000 molecules. [7]

Stephen Mason presented preclinical results on two early compounds that could interfere with the assembly and stability of the capsid core, that are in development at Boehringer Ingleheim. These compounds interrupt the process for assembling new virus and were shown to have activity against resistant HIV from other classes.

Many presentations reiterated that eradication with current drugs is not possible, due to the inability to recognise latently infected resting cells. Even after many years of maximally suppressive therapy, it is well established that viral load rapidly rebounds to pretreatment levels, potentially within weeks of discontinuing treatment.

At least five new types of treatment are the focus of research on how to target latently infected cells. These include cellular restriction factors – human proteins that reduce HIV replication and that can help or block infections – such as tetherin, a protein

that blocks HIV release, APOBEC3, an immunity gene that has anti-HIV activity, and TRIM5-alpha, a protein that in some monkeys protects against HIV infection, and that gene therapy could perhaps be modified to adapt the related human protein. Zinc finger inhibitors that can knock out CCR5 were included in other presentations, although this potential target that has been on the outer radar of investigative treatment for at least 15 years.

References

Unless stated otherwise, all references are to the Programme and Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections, 16-19 February 2010, San Francisco.

1. Webcast: Advances in ART. Wednesday 9.30am. http://www.retroconference.org/2010/data/files/webcast_2010.htm
2. Cohen C et al. Single-tablet, fixed-dose regimen of elvitegravir/emtricitabine/tenofovir disoproxil fumarate/GS-9350 achieves a high rate of virologic suppression and GS-9350 is an effective booster. 17th CROI 2010. Oral abstract 58LB. http://www.retroconference.org/2010/Abstracts/39864.htm
3. Palleja S et al. Safety and efficacy of TBR 652, a CCR5 antagonist, in HIV-1-infected, ART-experienced, CCR5 antagonist-naïve patients. 17th CROI 2010. Oral abstract 53. http://www.retroconference.org/2010/Abstracts/37579.htm
4. Johns B et al. The discovery of S/GSK1349572: a once-daily next generation integrase inhibitor with a superior resistance profile. 17th CROI 2010. Oral abstract 55. http://www.retroconference.org/2010/Abstracts/37960.htm
5. First results of new integrase compound: GSK1349572. HTB October 2009. http://i-base.info/htb/5976
6. Gathe J et al. Phase 3 trials of vicriviroc in treatment-experienced subjects demonstrate safety but not significantly superior efficacy over potent background regimens alone. 17th CROI 2010. Oral abstract 54LB. http://www.retroconference.org/2010/Abstracts/39832.htm
7. Christ F et al. First-in-class inhibitors of LEDGF/p75-integrase interaction and HIV replication. 17th CROI 2010. Oral abstract 49. http://www.retroconference.org/2010/Abstracts/37630.htm
8. Titolo S et al. Discovery of potent HIV-1 capsid assembly inhibitors. 17th CROI 2010. Oral abstract 50. http://www.retroconference.org/2010/Abstracts/38238.htm

Clinical benefits of stopping smoking: CVD and CHD risk returns to that of 'previous smoker' in HIV-positive people within three years

Simon Collins, HIV i-Base

An analysis from the D:A:D study, presented as an oral session, reported that HIV-positive people who stop smoking can expert similar direct health benefits to HIV-negative people.

Kathy Petoumenos from the University of New South Wales, Sydney, looked at rates of cardiovascular disease before and after stopping smoking in over 27,500 HIV-positive patients from Europe, the US and Australia, who had smoking status recorded in the prospective D:A:D cohort study.

The group looked at four endpoints: fatal and non-fatal myocardial infarction (MI), a broader definition of coronary heart disease (CHD), cardiovascular disease (CVD) combining CHD and stroke, and all cause mortality. Event rates were calculated for never smokers (n=8,920), ex-smokers at D:A:D study entry (n=6,265), current smokers (n=11,951), and smokers who stopped during D:A:D follow-up (n=8,197).

Current smokers were more likely to be male (77%), white (70%), infected through IV drug use (32%) and HCV-positive (34%), but CD4, viral load, BP, lipids and ARV-exposure were broadly similar between groups.

Incidence rate ratios (IRR) were determined adjusting for age, sex, cohort, calendar year, antiretroviral treatment, family history of CVD, diabetes (men and women), and time updated lipids and blood pressure assessments. Mortality endpoint also adjusted for HCV, HBV, mode of HIV exposure, ethnicity and incidence of CVD during follow-up.

Up to February 2008, there were 432 (MI), 600 (CHD), 746 (CVD) and 1902 (mortality events) endpoints. Crude event rates were 2.85, 3.96, 4.94, and 12.45 per 1000 person years respectively.

With never-smoked as the reference, increased risks rates were 1.73 and 3.40 for previous- and current-smokers respectively. Rate ratios for patients who had stopped smoking for <1, 1-2, 2-3 and >3 years follow-up since quitting, were 3.73, 3.00, 2.62 and 2.07 respectively, compared to never-smokers. This showed significant reductions within a year of stopping that continued to reduce over subsequent years. A similar pattern was seen for CHD and CVD, and although these were not significant at all timepoints, this is likely to be related to the lower number of events in some groups and the lower number of people who stopped smoking more than two years ago. The protective trend here is clear and important (see Table 1).

Although current smokers were at 28% higher risk of mortality, with no difference between never- and former-smokers, no clear reductions were seen during follow-up since stopping, with all confidence intervals crossing 1.0, even in a sub-group at higher risk of CVD-related mortality (in patients older than 50 years).

An explanation for the higher rates seen in the most recent (< 1 year) quitters was explained by the likelihood that a medical incident could have been the prompt needed to stop smoking. This group would therefore be at higher risk compared to current smokers (who would have been symptomatic). This was supported by the cause of mortality being more likely to be HIV/

Table 1: Incidence rate ratios by baseline smoking status and time since quitting

	Never	Previous	Current	<1 year	1-2 years ago	2-3 years ago	>3 years ago
MI	1.0	1.73	3.40	3.73	3.00	2.62	2.07
CHD	1.0	1.60	2.48	2.93	2.48	1.90	1.83
CVD	1.0	1.38	2.19	2.32	1.84	1.60*	1.49*
Mortality	1.0	0.99*	1.28	1.67	1.02*	1.34*	1.30*
Mortality >50yo	1.0	1.21*	1.31	1.68	1.02*	1.43*	1.16*

* Non significant (CI crossed 1.0)

AIDS in the never smoked group with higher rates of non-AIDS malignancies seen in the previous and stopped groups.

The study has limitations in the amount and type of data that were collected on smoking (e.g. no start/stop dates or pack-year data). However, the significant reductions on CHD with each year after stopping smoking should support cessation programme for HIV-positive people, a greater percentage of whom smoke than the general population.

COMMENT

This is the first time that the clinical benefits of stopping smoking has been reported in HIV-positive people and these findings should not be taken for granted.

Each year, HIV-positive people are advised on the importance of modification of lifestyle for 'healthy options' related to the complicated etiology of cardiovascular health and any study that can show tangible benefits is important.

This is particularly important given the higher rates of lung cancers reported in other studies. Keith Sigel and colleagues reported that HIV is an independent risk factor for lung cancer after adjusting for smoking (IRR 1.80; 95%CI 1.28 2.15). [2]

Edgar Simard from the US National Cancer Institute, reported a 3-fold observed incidence of lung cancer in HIV-positive patients within 3-5 years of an AIDS diagnosis compared to the general population (and increasing cumulative incidence). [3]

Meredith Shiels and colleagues reported that lung cancer was one of the cancers that was being diagnosed at an earlier age in HIV-positive compared to HIV-negative people, and that this 3-4 year difference was statistically significant after adjustment for multiple comparisons (p<0.001). [4]

References

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http://www.retroconference.org

1. Petoumenos K et al. Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study. 17th CROI, 2010. Oral abstract 124.
2. Sigel K et al. HIV infection is an independent risk factor for lung cancer. 17th CROI, 2010. Oral Abstract 30. http://www.retroconference.org/2010/Abstracts/38365.htm
3. Simard E et al. Cancer incidence and cancer-attributable mortality among persons with AIDS in the US. 17th CROI, 2010. Oral abstract 27. http://www.retroconference.org/2010/Abstracts/38173.htm
4. Shiels M et al. Do people with AIDS develop cancer at younger ages than the general population? 17th CROI, 2010. Poster 757. http://www.retroconference.org/2010/Abstracts/37914.htm

HIV increases the risk of lung cancer, independent of smoking status

Simon Collins, HIV i-Base

Keith Sigel and colleagues presented an analysis from the US Veterans Ageing Cohort Study Virtual Cohort (VC) on the relationship between HIV and lung cancer. [1]

The advantages of this database included size, smoking status data from a related health survey and a matched HIV-negative control group, although this was an almost exclusively (98%) male study. Median age was 47 years and ethnicity was approximately 40% white, 40% black. 10% Hispanic and 10% other. Approximately 30% were current smokers, 15% recently quit (< 1 year), 25-50% distantly quit (> 1 year) and 20% of HIV-positive compared to 25% of HIV-negative had never smoked.

The analysis compared over 3,700 HIV-positive and nearly 10,000 HIV-negative patients (contributing 28,500 and 76,800 person-years of follow-up respectively).

Lung cancer was defined using International Classification of Diseases (ICD-9) codes and Incidence Rate Ratios (IRR) were adjusted for age, race, smoking exposure, and Chronic Obstructive Pulmonary Disease (COPD).

The overall incidence of lung cancer per 100 person years was 0.26 compared to 0.16 in the HIV-positive vs HIV-negative groups (unadjusted IRR 1.5, 95%CI 1.2–2.0). Results from the adjusted analysis are detailed in Table 1.

Table 1: Adjusted IRR for lung cancer multivariate model including all covariates

Variable	IRR	95% CI
HIV infection	1.8	1.3–2.4
Age	1.1	1.1–1.1
Race/ethnicity: *		
African-American	0.9	0.7–1.2
Hispanic	0.4	0.2–0.8
Other	0.9	0.5–1.6
COPD	1.5	1.1–2.1
Smoking exposure: **		
Current daily smoker	9.8	4.4–21.4
Current occasional smoker	3.4	1.0–11.6
Recently quit smoking (<1 yr)	9.9	4.4–22.3
Distantly quit smoking (>1 yr)	5.1	2.4–11.2

* Reference = white race; ** Reference = never smoked.

The authors concluded that the incidence of lung cancer was significantly increased in HIV-positive men in their group, even after adjusting for smoking exposure.

COMMENT

This study reported slightly lower rates of increased risk of lung cancers in HIV-positive individuals compared to rates that were 2- to 6-fold higher in earlier studies, that also adjusted for smoking status. [2, 3, 4]

While the approximate 2-fold increased risk associated with HIV was significant and is important, the presenter emphasised the 10-fold higher risk for current smokers (that was halved to around 5-fold for former smokers who had quit more than one year earlier).

References

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http://www.retroconference.org

1. Sigel K et al. HIV infection is an independent risk factor for lung cancer. 17th CROI, 2010. Oral Abstract 30.
http://www.retroconference.org/2010/Abstracts/38365.htm
2. Cadranel J et al. Lung cancer in HIV infected patients: facts, questions and challenges. Thorax 2006; 61:1000-1008.
http://thorax.bmj.com/content/61/11/1000.abstract
3. Engels EA et al. Elevated incidence of lung cancer among HIV-infected individuals. J Clin Oncol 2006; 24 (9); 1383-1388. (March 2006).
http://jco.ascopubs.org/cgi/content/abstract/24/9/1383
4. Kirk GD et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Inf Dis 2007; 45:103-110.
http://www.journals.uchicago.edu/doi/abs/10.1086/518606

HIV-positive people in the HOPS cohort have 4-fold risk of fracture compared to general population in the US

Simon Collins, HIV i-Base

Over the last ten years HTB has reported numerous studies of lower bone mineral density and higher rates of osteopenia and osteoporosis in HIV-positive people compared to rates in age- and gender-matched general population.

While some research groups cautioned that their findings might not translate into higher fracture rates, most others suggested that ageing was likely to compound this risk and that it would be only a matter of time before the additional impact of HIV might be seen.

Two studies at CROI unfortunately suggest that these concerns are likely to be real.

Christine Dao from the US CDC in Atlanta and colleagues presented an analysis of fracture rates from 1994-2008 in over 8,400 HIV-positive patients followed in the HIV Outpatients (HOPS) Cohort and compared this to rates from non-HIV US inpatient (NHDS) and outpatient (NHAMCS) surveys that were weighted to make inferences to the US general population.

Only first fractures were included from HOPS and adjusted Hazard Ratios (AHR) were calculated controlling for age and gender. As fracture data were not comprehensively collected in HOPS prior to 2000, the presentation focused on fractures from around 5800 patients seen at least annually over the last eight years.

Baseline characteristics at first visit included: 79% male; 52% non-Hispanic white, 38% non-Hispanic Black; median (IQR) age 40 years (34-46), median BMI 24.4 (22.3-27.4); median time since diagnosis 5.3 years (1.3-9.9). Three-quarters of patients were treatment-experienced with median viral load (for the cohort) of 1,300 (<400-35,560) copies/mL.

Approximately 4% patients (236/5826) experienced a fracture at median age 45 years (38-51), roughly in proportion to baseline characteristic of race and gender, although only 51% of fractures were in treatment-experienced patients.

Gender-adjusted rates were restricted to patients aged 25-54, representing most HIV-positive individuals and showed not only an increase in fracture rates over time from about 55 to 85/10,000 PY, p=0.01 (compared to stable rates at around 30/10,000 PY in general population outpatient data). The rate in HIV-positive people was stable from 2002-2008 (and was approximately 4-fold higher).

Fractures at fragility sites (wrist, vertebra, femoral head) occurred at higher rate in both HIV-positive men and women compared to the general population, and are detailed in Table 1.

Factors independently associated with increased risk of fracture (adjusted HR: 95%CI) included: age >47 years (1.6; 1.0–2.5, p<0.05); nadir CD4 <200 cells/mm3 (1.6; 1.1–2.3, p=0.04); HCV coinfection (1.6; 1.1–2.3, p=0.01); diabetes (1.6; 1.0–2.6, p<0.05); and history of substance use (1.5; 1.0–2.3, p<0.05).

Limitations of the study included the use of different data collection systems for the HIV-positive and general population groups, no data linking bone mineral density to fracture risk, and whether this increase was due to an increase in events or a potential improved reporting.

Table 1: Percentage of fractures by anatomic site in adults 25-54 years old (HOPS 2000-2008)

	HOPS	NHAMCS-OP	P (vs HOPS)
Men	n=146	n=1,705,433	
Wrist	9%	3%	<0.05
Vertebra	10%	1%	<0.05
Femoral head	3%	2%	NS
Non-fragility site	78%	94%	<0.05
Women	n=45	n=1,136,788	
Wrist	4%	8%	NS
Vertebra	18%	4%	<0.05
Femoral head	7%	1%	<0.05
Non-fragility site	71%	86%	<0.05

Importantly, they also stressed that the actual event rate remained low, even though the relative rate was significantly higher.

Nevertheless, the researchers concluded that HOPS patients experienced higher rates of fracture compared to the general US population, that this rate increased over time and included a higher percentage of fragility fractures; and that in addition to known risk factors, low CD4 nadir was also associated with increased fracture risk.

Julie Womack and colleagues from the Veterans Ageing Cohort Study (VACS) presented results from men in the largely male VA cohort, focusing on the prevalence and incidence of fragility fractures (ie associated with minimal or no trauma, and with low bone mineral density). [2]

The VACS is a prospective observational cohort of about 40,000 HIV-positive veterans matched 1:2 by age, sex and site to around 80,000 HIV-negative controls. This analysis only included first fracture. Wrist fractures and compound fractures were excluded because of the higher likelihood of being related to trauma.

Multivariable models were adjusted for HIV status, race, enrollment date, age, coinfection, BMI and corticosteroid use, with additional adjustment for baseline CD4 and ARV use in HIV-positive patients.

During a median follow-up of 8 years (range 4-11), 952 fractures (644 hip and 308 vertebral) fractures were recorded, with an unadjusted incidence of 16 vs 11/10,000 PYFU in the HIV-positive vs HIV-negative groups. Fractures occurred at a mean age of 55 years (SD±11).

Prevalence results showed that across all ages only hip fractures occurred at a significantly higher rate in the HIV-positive vs HIV-negative groups (p<0.0001), with a difference developing and widening from age 40 onwards. Although vertebra fractures were generally similar in both groups, the rate in HIV-positive men increased significantly in men over 70 years who were HIV-positive.

After adjustment for cofactors (AHR; 95%CI), including Caucasian race (1.79; 1.57–2.03), BMI <19 (2.50; 1.54–4.05), alcohol use (H1.79; 1.47–2.18), pulmonary disease (1.38; 1.10–1.73), cerebrovascular disease (2.16; 1.54–3.02), and peripheral vascular disease (1.64; 1.10–2.44), the HIV effect was reduced, though still significant (1.38; 1.18–1.60). Similar ratios applied for the full model and HIV-positive only model.

The presentation also discussed management and this was picked up in the question session afterwards. Prevention is stressed for all patients. Clinical assessment for fracture risk was recommended for patients aged 40-50 and DEXA indicated when HIV is not the only risk factor.

Several members of the audience commented that they would encourage broader use of DEXA scans, especially given the high rates of other risk factors, including higher rates of smoking, alcohol use and low testosterone.

Although ARV use was not found to be significant in this study, another question from the audience suggested that this was unlikely to be a reliable conclusion, as the study defined exposure by baseline use of d4T, tenofovir, PIs or NNRTIs, rather than looking at cumulative exposure more commonly adopted in most studies.

Finally, a third presentation in the same oral session reported fracture incidence in a retrospective analysis in about 2400 women (approxiamtely 1700 HIV-positive, 700 HIV-negative) in the Women's Interagency HIV Study (WIHS). Of note, this study also collected data on smoking, opiate/cocaine use and vitamin D/calcium supplementation.

Fractures occurred in 148 (9%) HIV-positive women vs 47 (7%) HIV-negative women producing incidence rates of 1.79 vs 1.41/100 PY, respectively (p=0.13 NS). Analysis by fracture site also showed no significant difference in rates by HIV status. In the multivariate analysis, HIV status remained non-significant, with only age, race (being Caucasian), HCV coinfection and serum creatinine only showing positive relationship to increased fracture rate. The only determinants of time to fracture in HIV-positive women were age (per 10 years older HR 1.2; 95%CI 1.0–1.5, p=0.047) and previous AIDS defining illness (HR 1.9; 95%CI 1.3–2.7, p=0.0008), but not CD4 count or ARV use.

Although no impact of HIV was seen over five years of follow-up the limitations of this study was that this was broadly a pre-menopausal patient group and in a modest sample size. Also, approximately 50% women had high BMI which is associated with protecting bone density and strength.

The conclusion included recognition that fracture risk could increase in HIV-positive post-menopausal women, given that oestrogen has a protective effect and other studies have already highlighted the lower levels of bone mineral density in HIV-positive women.

References

Unless stated otherwise, all references are to the Programme and Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. 16-10 February 2010, San Francisco. All oral abstracts are available as webcasts.

http://www.retroconference.org

1. Dao C et al. Higher and increasing rates of fracture among HIV-infected persons in the HIV Outpatient Study compared to the general US population, 1994 to 2008. 17th CROI 2010. Oral abstract 128. http://www.retroconference.org/2010/Abstracts/37582.htm
2. Womack J et al. HIV-infection and fragility fracture risk among male veterans. 17th CROI 2010. Oral abstract 129. http://www.retroconference.org/2010/Abstracts/39138.htm
3. Yin M et al. Fracture rates are not increased in younger HIV+women. 17th CROI 2010. Oral abstract 130. http://www.retroconference.org/2010/Abstracts/38338.htm

OCTANE 2: nevirapine and lopinavir/r are similar when used with tenofovir and FTC in treatment-naïve women

Polly Clayden, HIV i-Base

In an oral presentation, James McIntyre showed data from the OCTANE/A5208 trial. This trial, conducted in seven African countries, was designed to evaluate which of two antiretroviral regimens is more effective in women previously exposed to single dose NVP and whether single dose NVP compromises subsequent NVP-containing HAART. [1]

OCTANE was composed of Trial 1 and Trial 2. Trial 1 women (n=243) were NVP exposed at least six months prior to the study and those in Trial 2 (n=502) were unexposed. Women in each trial were randomised to receive either NVP or lopinavir/ritonavir (LPV/r) in regimens with tenofovir (TDF) and emtricitabine (FTC). Women with CD4 <200 cells/mm3 were eligible.

The time from randomisation to death or virologic failure (defined as plasma viral load <1 log copies/mL below baseline 12 weeks after treatment initiation, or ≥400 copies/mL at or after 24 weeks) was the primary endpoint in both studies.

Trial 1 was stopped by the DSMB in October 2008 at a median of 66 weeks, after an interim analysis, which found LPV/r to be significantly more effective than NVP and associated with fewer side effects. We reported this data in previously in HTB. [2, 3]

It is notable that in this study the LPV/r arm performed extremely well with only 8% of women meeting an endpoint vs 26% in the NVP arm (adjusted HR 3.6; 95% CI 1.7–7.5).

Trial 2 was designed to assess equivalence (defined as 95% CI for the HR: 0.5–2.0) between the two treatment arms. As in Trial 1, women were followed for ≥48 weeks. This was an intent-to-treat analysis of 500 women (2 excluded): 249 in the NVP arm and 251 in the LPV arm.

Baseline characteristics were similar in both arms, median: age 34 years, CD4 121 cells/mm3 and viral load 5.15 log copies/mL. One woman in the LPV/r arm had received single dose NVP but was included in the analysis. In a random sample of 119 women, baseline NVP resistance was detected in 1% of women. The median duration of follow-up was 118 weeks; 14 women in the NVP and 6 in the LPV/r arms were lost to follow-up.

Dr McIntyre reported that 42 (17%) women in the NVP arm and 50 (20%) in the LPV/r arm reached the primary endpoint (HR 0.85; 95%CI 0.56–1.29). These results met the criteria for equivalence. The as-treated analysis results were similar (HR 0.71; 95%CI 0.45–1.13).

When the investigators broke down the composite endpoint to look at virologic failure and death separately, they found 15% vs 17% experienced virologic failure and 2% vs 3% died in the NVP and LPV/r arms respectively.

Overall, 93 women discontinued NVP or LPV/r permanently, 70 (28%) in the NVP arm and 23 (9%) in the LPV/r arm, HR 3.4 (95% CI 2.2-5.5). Of these, 35 (14%) in the NVP arm and 0 in the LPV/r arm discontinued due to adverse events, p<0.0001.

Grade 3 or 4 signs/symptoms while receiving NVP or LPV/r were reported in 75 (15%) women (14% in NVP, 16% in LPV/r arm), and 26% and 22% (respectively) had grade 3/4 laboratory test abnormalities. Dr McIntyre noted that the protocol took a conservative approach to adverse events for women receiving NVP but events in the LPV/r arm could be managed without a protocol-mandated switch in therapy.

In conclusion, the study reported that NVP+TDF+FTC and LPV/r+TDF+FTC were equivalent in treatment-naïve women. This suggests that the previously reported inferiority of NVP in Trial 1 was related to NVP resistance from single dose NVP exposure.

COMMENT

James McIntyre remarked that these data are reassuring for programmes using nevirapine, particularly in Africa where it is a mainstay of antiretroviral regimens.

What remains unexplained is why the LPV/r arm in Trial 1 performed so well whereas in Trial 2 what we are seeing is similar to general experience.

When this was questioned after the presentation Dr McIntyre remarked that this raises "intriguing possibilities" and there may be some plausibility that nevirapine-induced mutations could have some effect on gag/pol cleavage causing conformational changes which may make protease enzymes less effective. If so, protease inhibitors would have less to inhibit, so would work better. He added that he knew of no evidence to support this!

It is perhaps worth noting that equivalence in this study is powered with an equivalence range from 0.5 to 2 - ie requiring a doubling or halving of the risk is still defined as 'equivalent'.

When looking at absolute rates at other studies that use a tighter range, differences of up to 12% are typically viewed as being 'non-inferior'. Using a doubling/halving in risk is stretching this even further.

References

Unless stated otherwise, all references are to the Programme and Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. 16-10 February 2010, San Francisco. All oral abstracts are available as webcasts.
http://www.retroconference.org

1. McIntyre J et al. Efficacy of ART with NVP+TDF/FTC vs LPV/r+TDF/FTC among antiretroviral-naïve women in Africa: OCTANE Trial 2/ACTG A5208. 17th CROI, 2010. Oral abstract 153 LB.
http://www.retroconference.org/2010/Abstracts/39798.htm
Webcast: Treatment outcomes in women and children. Friday 9.30am.
http://www.retroconference.org/2010/data/files/webcast_2010.htm
2. OCTANE Trial DSMB finds ritonavir-boosted lopinavir superior to nevirapine in HIV-positive women previously exposed to single dose nevirapine. HTB, December 2008.
http://i-base.info/htb/261
3. Lopinavir/r containing regimen superior to nevirapine containing regimen in women previously exposed to single dose nevirapine. HTB, April 2009.
http://i-base.info/htb/1449

HIV incidence and retesting in pregnancy

Polly Clayden, HIV i-Base

Several groups have documented high rates of HIV acquisition during pregnancy and breastfeeding.

Two oral presentations at CROI showed findings from investigations into HIV incidence and retesting among women in high prevalence settings in Africa.

John Kinuthia from the University of Nairobi, Kenya presented data from a study looking at HIV incidence among mothers accompanying their infants for routine 6-week immunisation at 6 maternal–child health clinics in Nairobi and Nyanza Province of Western Kenya. [1]

In this study, mothers completed a questionnaire, before their HIV test, that assessed sociodemographic characteristics, obstetric history, HIV risk perception, and participation in PMTCT programmes during their last pregnancy. The investigators compared characteristics of HIV-negative women who seroconverted during pregnancy and immediately post partum to those who did not.

Dr Kinuthia reported that 2035 out of 2135 (95.3%), mothers who had tested HIV-negative in pregnancy, accepted a repeat HIV test at the immunisation visit. Of these, 53 (2.6%) were HIV-positive, giving an overall estimated HIV incidence of 6.8 (95%CI 5.1–8.8) per 100 woman-years.

The mean age of the mothers was 23.7 years. Of these 86.8% were married, 7.1% in polygamous marriages and 29.4% were employed.

Mothers who seroconverted were more likely to be employed (45.3% vs 29.0%, p=0.01), married (96.2 vs 86.6%, p=0.04) and from a higher HIV prevalence region (60.4% in Nyanza vs 28.8% in Nairobi, p<0.001).

Married women, in a polygamous relationship were significantly more likely to seroconvert (19.6% vs 6.7%, p<0.001). Age, educational level, HIV risk perception, history of physical assault,

and economic status were not associated with seroconversion. In multivariate analysis, region (OR 3.6; 95%CI 2.1–6.4, p<0.001) and employment (OR 1.9; 95%CI 1.1–3.3, p=0.03) were independent predictors of seroconversion.

Dr Kinuthia suggested that the limitations of the study included no data on the timing of the mothers' initial HIV test, nor their partners' status.

He concluded that repeat HIV testing in early postpartum was highly acceptable and resulted in detection of substantial HIV incidence. He noted that the incidence in pregnancy and early postpartum in this study compared to that among cohorts of sex workers and women in discordant relationships. He stressed the need for an urgent review of services for negative pregnant women in regions with high HIV seroprevalence and interventions such as couple counselling and testing, the promotion of safer sex in pregnancy and awareness of the risk of infection and in turn MTCT.

Following on from this was a presentation from Mary Pat Kieffer from the Elizabeth Glaser Pediatric AIDS Foundation, showing data from a study in which retesting in maternity facilities was used to provide interventions for women who became infected late in pregnancy. [2]

Swaziland has a very high rate of HIV prevalence among pregnant women (42%) and a high uptake of PMTCT.

The primary objective of the study was to evaluate the effectiveness of a provider focused intervention in increasing ARV coverage at time of delivery. As secondary objectives the investigators sought to determine HIV incidence in late pregnancy and the number of newly-indentified HIV-positive women in maternity. They also looked at whether provision of nevirapine to women who refused testing increases coverage.

Maternity staff received an extra one-day training based on the women's status on arrival. This included:

- Testing women with unknown status and offering nevirapine (NVP) to those who declined.
- Routine HIV retesting as standard of care for women who tested negative three months or more earlier (Swazi guidelines).
- Ensuring all newly identified women receive ARV treatment or prophylaxis.

Women received antiretrovirals in accordance with Swazi national guidelines (NVP+3TC+AZT for women meeting criteria for treatment or short course AZT plus single dose NVP and AZT+3TC "tail" prophylaxis for healthier women).

Sampling used 6 public maternity sites, matched as pairs and randomised within the pair to intervention or control.

Data on testing and ARV prophylaxis were collected through questionnaires and MoH registers.

Cord blood samples were collected as dried blood spots (DBS) and tested for HIV. All positive DBS were tested for NVP. Coverage was defined as number of cord bloods with detectable NVP.

The investigators found 1398/2444 (62.3%) women enrolled in the study had previously tested negative in pregnancy.

Overall NVP was detected in 75% cord bloods, this was significantly higher in the intervention than the control groups, 80% vs 69%, p=0.0001. Dr Kieffer noted that the only group of women for whom there was no significant improvement was those who already knew their status and had taken their ARV prophylaxis at home (p=0.23).

The most critical finding of this study was the high level of HIV incidence in pregnancy: 4.4% women who were HIV negative in ANC were positive at time of delivery giving a rate of 16.75 new infections per 100 person-years. Dr Kieffer suggested that, like the previous data from Nyanza, this rate is similar to cohorts of sex workers and IDU.

She compared these rates to earlier data from Rakai that showed 1.1 per 100 person years incidence in non-pregnant women vs 2.3 in pregnant women per 100 person years.

The second critical finding was that ARV provision almost doubled for women who seroconverted during pregnancy (n=58), 26% vs 54% in control vs intervention groups respectively (p=0.03).

Dr Kieffer explained that this was still only reaching about half those that seroconverted. Control sites had retested 14% (135/959) HIV-negative women, compared to 45% (528/1185) women at intervention sites p<0.0001; relative risk 3.17 (95%CI 2.67–3.74). The primary reason for this was the Swazi guidelines only recommend retesting after 3 months or more, but a significant proportion of women (38%) had been previously tested for HIV earlier than this so were not eligible for retesting.

"Reaching women who become infected late in pregnancy cannot be an afterthought for PMTCT programmes" she said.

Like the previous study these data highlight the need for interventions to identify and provide ARV prophylaxis to women who seroconvert in pregnancy and prevention strategies to enable HIV-negative women to remain negative.

COMMENT

This issue is important and was also raised by Lu et al at CROI last year. [3]

The question of poor test performance discussed by Black et al in AIDS was also discussed following the presentation. [4]

Whether these transmissions can be attributed to HIV incidence in pregnancy or poor test performance, unidentified HIV positive women in pregnancy remain a barrier to the eradication of paediatric HIV.

References

Unless stated otherwise, all references are to the Programme and Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. 16-10 February 2010, San Francisco. All oral abstracts are available as webcasts.
http://www.retroconference.org

1. Kinuthia J et al. Co-factors for HIV Incidence during Pregnancy and the Postpartum Period. 17th CROI, San Francisco, 2010. Oral abstract 155.
http://www.retroconference.org/2010/Abstracts/38372.htm
Webcast: Treatment outcomes in women and children. Friday 9.30am.
http://www.retroconference.org/2010/data/files/webcast_2010.htm
2. Kieffer MP et al. Repeat HIV testing in labor and delivery as a standard of care increases ARV provision for women Who Seroconvert during Pregnancy. 17th CROI, San Francisco, 2010. Oral abstract 156.
http://www.retroconference.org/2010/Abstracts/37241.htm

Webcast: Treatment outcomes in women and children. Friday 9.30am.
http://www.retroconference.org/2010/data/files/webcast_2010.htm

3. High rates of HIV acquisition in pregnancy and post partum in Francistown, Botswana. HTB April 2009.
http://i-base.info/htb/1425

4. Black V et al. High HIV incidence or poor test performance? AIDS, 23 October 2009. Vol 23; (16) p2234-2235.

Efavirenz use in pregnancy and birth outcomes

Polly Clayden, HIV i-Base

Of all the antiretrovirals, efavirenz attracts the most controversy with regard to use in pregnant women. Two posters at CROI looked at birth outcomes among mothers who received efavirenz in pregnancy. [1, 2]

Daniel Westreich and colleagues analysed prospective data from Themba Lethu Clinic in Johannesburg. They examined the risk factors for pregnancy after initiation of HAART using Cox proportional hazards regression and looked at birth outcomes in women receiving efavirenz.

The investigators reported that of 5011 women initiating HAART between April 1 2004 and March 31 2007, 351 (7%) became pregnant giving a rate of 4.1 pregnancies per 100 woman years (95% CI 3.7–4.5).

They found that this was less among older women (>35 years) and those with lower CD4 counts or employed.

The investigators noted that although women who initiated HAART with efavirenz based regimens were less likely to become pregnant that than those starting with nevirapine, HR 0.6 (95% CI 0.4–0.8), 68% (n=238) of pregnancies occurred in women receiving efavirenz.

The investigators looked at 136 of the women receiving efavirenz for pregnancy outcome. They reported three maternal deaths, 39 women lost to follow up and one who refused to be interviewed. In addition 12 women were still pregnant at the time of analysis.

Out of 81 pregnancies analysed, 8 were voluntarily terminated and 13 miscarried. Of the remaining 60 live births, 41 were examined using the Denver Development Screening Test. According to this scale, 30 infants were classified as "within normal limits" and 11 (>25%, 95% CI 14–43) were "suspect" for developmental delay. The investigators did not find any congenital abnormalities among the infants examined.

The investigators rightly suggested that further study including a comparison group is required to evaluate whether suspected neurodevelopmental delays or miscarriages are associated with efavirenz use. And they wrote, "These results suggest that the risk of efavirenz in pregnancy may be less catastrophic than feared".

A related poster authored by Daniel Conway and colleagues reported findings from an analysis of prevalence of congenital abnormalities among antiretroviral-exposed infants in IMPAACT P1025. This US cohort study enrolled all women and infants in P1025 born between 2002 and 2007 (n=1306) during pregnancy or up to two weeks post-partum. No information was provided regarding prospective or retrospective enrollment, that is, whether any women/infants could be enrolled after an anomaly had already been diagnosed.

A total of 1112 infants were eligible for analysis. Infants were examined for congenital anomalies and reviewers were blinded to in utero antiretroviral (individual drugs and classes) exposure. In utero exposure was classified as 1st, 2nd/3rd trimester and unexposed. The investigators used logistic regression to estimate the relationship between congenital anomalies and antiretroviral exposure.

The investigators reported 80 congenital anomalies among 61 infants, a rate of 5.49/100 live births (95%CI 4.22–6.99). These were broken down into organ systems involved: cardiovascular (n=33), genitourinary (n=7), renal (n=8), musculoskeletal (n=15, including accessory digits of hand or foot, n=7), craniofacial (n=3), central nervous system (n=3), chromosomal (n=3), eye (n=3), gastrointestinal (n=5).

This study reports that first trimester exposure to efavirenz was associated with a significantly increased risk of congenital anomalies (OR 2.89; 95%CI 1.15–7.25) compared to 2nd/3rd trimester exposure. No information was provided regarding the types of anomalies associated with efavirenz exposure.

They did not find any other classes of antiretrovirals nor individual drugs (only data for efavirenz and AZT were shown) to be associated with increased risk of anomalies. Covariates including ethnicity, maternal age and substance use (tobacco, alcohol and recreational drugs) were not significantly associated with increased risk of congenital anomalies.

COMMENT

Because of the uncertainties about efavirenz use in pregnancy, all new information on this subject is worth reporting.

Unfortunately neither of the posters summarised here showed enough data to make their interpretation straightforward and both studies seem underpowered.

The Themba Lethu Clinic analysis does not report baseline data and has high loss to follow up. Only the abstract is on the conference website so it was not possible to double-check these data.

The P1025 numbers are also small, about 1/10 of the APR, including those with efavirenz first trimester exposure (47 vs 501). [3] They do not report what the 6 anomalies with first trimester efavirenz exposure were, which seems very important in view of the monkey data. The only other antiretroviral they report on individually is AZT.

Some of the P1025 data are already in the APR though it is not clear which, and not all women were enrolled into this study before pregnancy outcome was known which would make them ineligible for the APR. Retrospective observations of birth defects cannot be used to determine birth defect prevalence, because of differential reporting bias, that is, that a foetus or infant with a birth defect would be more likely to be enrolled than one with an unknown or normal outcome.

Good data to guide recommendations in this area are urgently needed including other important outcomes such as spontaneous abortion and termination of pregnancy.

References

Unless stated otherwise, all references are to the Programme and Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. 16-10 February 2010, San Francisco.

1. Westreich D et al. Pregnancy, efavirenz, and birth outcomes in Johannesburg. 17th CROI, San Francisco, 2010. Poster abstract 922.
http://www.retroconference.org/2010/Abstracts/38870.htm
2. Conway D et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals: IMPAACT P1025. 17th CROI, San Francisco, 2010. Poster abstract 923.
http://www.retroconference.org/2010/Abstracts/36925.htm
3. Antiretoviral pregnancy registry.
http://www.apregistry.com/forms/interim_report.pdf

Pregnancy outcomes in women using non-AZT HAART in Europe

Polly Clayden, HIV i-Base

AZT is the only antiretroviral licensed for use in pregnancy. In resource rich settings AZT-containing regimens are becoming less and less common and in turn increasing numbers of women are becoming pregnant while receiving non AZT-containing HAART, or initiating non-AZT-containing HAART in pregnancy.

A poster at authored by Shema Tariq and colleagues reported findings from an investigation into the risk of detectable maternal viral load (VL) at delivery, congenital abnormality and mother to child transmission (MTCT) in pregnancies among women receiving HAART containing and not containing AZT. [1]

This analysis combined data from the National study of HIV in Pregnancy and Childhood (NSHPC) and the European Collaborative Study (ECS).

All live singleton births from 2000 to 2009 with ≥14 days of HAART in pregnancy were included. The investigators used logistic regression to estimate adjusted odds ratios (AOR).

A total of 7353 (6310, NSHPC and 1263, ECS) pregnancies were included, of which 1199 (15.8%) were exposed to non-AZT HAART. Of this group, 23.2% and 71.3% were on HAART prior to conception in the AZT and non-AZT groups respectively. Exposure to non-AZT HAART increased over time: 2000–2002 19.6% vs 17.1%, 2006–2009 41.4 vs 58.7% women received AZT vs non-AZT HAART respectively, p<0.01.

Tenofovir and abacavir was the most commonly used non-AZT drug in this cohort; approx 45% and 35% respectively.

In multivariate analysis the investigators found no evidence of associations between non-AZT HAART and detectable viral load at delivery, risk of congenital abnormalities (including in a sub-analysis of pregnancies with 1st trimester exposure or rate of MTCT, see Table 1.

The investigators noted that information on maternal VL at delivery was missing for 45% of pregnancies however the proportions of missing data were similar for both groups. Additionally HIV status was not yet reported for 20% of infants, mainly those born recently. They suggested that this is unlikely to introduce bias.

The investigators described these results as reassuring and that continued monitoring of pregnancy outcomes and longer term consequences of in utero exposure to these antiretroviral drugs is required.

Ref: Tariq S et al. Pregnancy outcomes in HIV-infected women using non-zidovudine HAART in Europe: 2000 to 2009. 17th CROI, San Francisco, 2010. Poster abstract 895.
http://www.retroconference.org/2010/Abstracts/37281.htm

When should HAART be initiated in pregnancy to achieve an undetectable viral load?

Polly Clayden, HIV i-Base

Women who do not need treatment for their own HIV in resource-rich countries generally receive a short course of HAART in pregnancy to prevent mother to child transmission (MTCT).

It is considered a safe option for women with low or undetectable viral loads (VL) to choose vaginal delivery. BHIVA guidelines recommend a cut off of <50 copies/mL and the US guidelines <1000 copies/mL.

However the optimum timing to initiate short course HAART and achieve an undetectable viral load is uncertain.

A poster authored by Phillip Read and colleagues showed findings from a retrospective UK study across five centres in London and the South East, conducted to provide data for clinicians for the timing of short course HAART in pregnancy.

All available data were included for women commencing boosted PI, NNRTI or triple NRTI based HAART from 2000 onwards

In this study demographics, gestation, drug class, CD4 count, and VL results were collated. VL data were right-censored at delivery date and drug regimen analyses were intent-to-treat. Survival curves for reaching a viral load <50 copies/mL were stratified by VL at initiation of HAART. Cox's proportional hazards regression model adjusted for demographics and immuno-virological parameters.

In this study, 439 pregnancies met the inclusion criteria and 378 had sufficient data for analysis.

Table1. Maternal and infant outcomes AZT vs non-AZT HAART multivariate analysis, AOR (95% CI)

	Detectable maternal VL at delivery	Congenital abnormalities (all pregnancies)	Congenital abnormalities (1st trimester HAART exposure)	MTCT
n	4212	7353	1930	6111
AZT HAART (ref. group)	1	1	1	1
Non-AZT HAART	0.90 (0.73-1.11); p=0.33	0.95 (0.64–1.41); p=0.80	0.76 (0.46–1.25); p=0.28	1.81 (0.77–4.26); p=0.18

Of those evaluated, 70% of women were of black African origin and their mean age at conception was 29.9 (range 14.7–49.8) years. Median pre-treatment CD4 and viral load was 330 cells/mm3 (IQR 195–470) and 8243 copies/mL (IQR 2341-32,640).

For their regimen, 246 women (65%) started PI-, 129 (34%) NNRTI-, and 3 (1%) NRTI-based HAART, initiated at a median of 23.2 weeks gestation (IQR 20.4 to 26.3).

By their delivery date (mean 38 weeks), 292 (77%) women achieved VL <50 copies/mL after a median of 58 days. Pre-treatment VL was associated with both the time taken and the proportion achieving a VL <50 copies/mL at delivery, p<0.001.

A baseline viral load of <10,000, 10,000 to 50,000, 50,001 to 100,000, and >100,000 resulted in 91%, 73%, 54%, and 37% of women achieving <50 copies/mL at delivery, respectively.

In multivariate analysis, the hazard ratio (HR) for a NNRTI regimen achieving a viral load <50 copies/mL compared to a PI was 0.7 (95% CI 0.52 -0.94). If VL was >10,000, 58% of PI and 66% of NNRTI regimens achieved <50 copies/mL.

When baseline VL was <10,000 copies/mL, gestation at initiation of HAART did not significantly change the probability of a VL <50 copies/mL at delivery. With a baseline VL of 10,000–50,000 copies/mL, the HR for a VL <50 copies/mL declined to 0.51 if HAART was initiated after 23.3 weeks (p<0.01) while if viral load was >100,000, starting HAART before 20.4 weeks gave a HR of 0.2 (p <0.01) compared with 0.1 if started after 20.4 weeks (p <0.01).

The investigators concluded with four key messages:

- Women with a VL >10,000 copies/mL should commence HAART by 20.4 weeks
- Women with a VL >100,000 copies/mL should commence HAART without delay
- If the VL is <10,000 copies/mL, HAART may be deferred to 26 weeks
- If the VL is >10,000 copies/mL NNRTI-based HAART, where appropriate, may be more successful

And they noted: "Final decisions on mode of delivery often depend on the VL at 36 weeks gestation and this needs to be taken into account when starting HAART based on these data".

COMMENT

This analysis provides useful data to guide when to commence short course HAART in pregnancy.

Presumably, a larger proportion of women would commence long term treatment if they were starting according to current guidelines, as the median baseline CD4 count in this data set was 330 cells/mm3 (IQR 195–470), and previous guidance used a 200 CD4 cells/mm3 threshold at which to start HAART.

Ref: Read P et al. When Should HAART be initiated in pregnancy to achieve an undetectable viral load? 17th CROI, 16-19 February 2010, San Francisco. Poster abstract 896.

http://www.retroconference.org/2010/Abstracts/37418.htm

Pregnancy outcomes in infants exposed to maternal antiretrovirals in utero

Polly Clayden, HIV i-Base

Several posters at CROI 2010 showed findings from studies looking at outcomes in infants exposed to maternal antiretrovirals in utero.

Tenofovir exposure in DART

Enniie Chidziva and colleagues from the DART trial evaluated infants born to women mainly receiving tenofovir (TDF) based HAART in Uganda and Zimbabwe from 2004 to 2009. [1]

We have reported earlier results from the DART trial and pregnancy outcomes in previous issues of HTB. [2, 3]

During DART there were 223 live births with 6 infant deaths; 217 infants were alive two weeks after birth. Of these 129 (59%) were exposed to TDF in utero. Infants were evaluated in DART and in a separate follow up study.

The investigators reported that congenital abnormalities occurred in 7/217 (3%) of infants overall and 4/129 (3%) with TDF exposure. The abnormalities were: talipes 3 (2 with TDF exposure), cardiac 1, hydrocephalus 1(with TDF exposure), skin tag 1 (with TDF exposure) and undescended testes 1.

The majority 182/217 (84%) of infants were enrolled in the infant follow up study. At their last visit they were a median age of 26 months (IQR 13–39); 69% were <12 months of age. The investigators noted that infants who were not enrolled in the follow up study were likely to have been born during the earlier part of the trial.

Prophylaxis was given to 152/182 (84%) of infants (single-dose nevirapine 44%, AZT 18%, sd NVP+AZT 23%, other 15%)

Of the 182 infants, 73 were ever breastfed for median 92 days (range 5-1186 days). Unadjusted HR for currently BF vs never BF 0.45 (95% CI 0.05–3.62) and for stopped vs never BF 0.7 (95% CI 0.19–2.57, p=0.59).

Of the 171 children tested, all were HIV-negative, 3 were lost to follow up and 8 died before testing. Fourteen children died at a median age of 9.4 months, giving 6% 12-month mortality. Of these, 8 had in utero TDF exposure, 6 were HIV-negative and 8 untested.

Only 4/386 creatinine and 7/310 phosphate measurements were abnormal, all were grade 1 and confined to 7 children of which 4 were exposed to TDF in utero (3 throughout pregnancy and one 61% of time in utero). There was no evidence of an effect of TDF in utero on growth after 48 weeks (p=0.31) and there were no bone fractures.

Additionally, an Italian cohort study reported by Alessandra Vigano and colleagues showed that exposure to TDF during the second and third trimesters of gestation, when bone formation occurs, does not impair bone mass and bone metabolism in HIV-negative children born to HIV-positive women. [2]

Mashi and Mma Bana

Two studies with data combined from the Mashi and Mma Bana PMTCT trials in Botswana looked at infant anaemia and birthweight respectively. [5, 6]

We have reported on both trials in previous issues of HTB. [7, 8, 9, 10, 11]

Scott Dryden-Peterson and colleagues compared the incidence of severe and life-threatening (grade 3 or 4, DAIDS 2004 toxicity tables) anaemia in breastfed (BF) infants exposed to HAART in utero with BF and formula fed (FF) infants exposed to AZT in utero in these trials.

Endpoints were incidence of first severe anaemia from birth to 7 months and the analyses used scheduled measurements of first born uninfected infants.

A total of 1788 infants met the inclusion criteria (1096 Mashi, 692 Mma Bana). Of this group, 743 were exposed to maternal HAART (AZT+3TC+LPV/r or AZT+3TC+NVP), one month of post natal AZT and BF (categorised as HAART+BF; 517 to in utero AZT, 6 months of post-natal AZT, and breastfeeding (AZT+BF); and 528 infants to in utero AZT, 1 month of post-natal AZT, and formula feeding (AZT+FF).

The investigators reported there were 126 infants with severe anaemia by 7 months with a cumulative incidence of 12.6 % (n=89) in HAART+BF, 5.4 % (n=26) in AZT+BF, and 2.3 % (n=110 in AZT+FF.

Severe anaemia occurred more frequently among HAART+BF infants than either AZT+BF infants (OR 2.51, 95% CI 1.59-3.95), or AZT+FF infants (OR 6.11, 95% CI 3.2-11.6), both p<0.0001.

In multivariate analysis, predictors of severe anaemia (AOR; 95%CI) were: HAART+BF (2.4; 95%CI 1.5–3.8 and 5.7; 95%CI 3.0–10.7) compared to AZT+BF and AZT+FF, respectively; low birth weight <2.5 kg (2.4; 95%CI 1.5–3.9); and male sex (1.5; 95%CI 1.0–2.2). Maternal CD4, VL, haemaglobin, education, income, study site and gestation at delivery were not significantly associated with severe anaemia.

Birthweight <2.5kg occurred in 103 (13.97%), 43 (8.4%) and 31 (5.9%) of infants in the HAART+BF, AZT+BF and AZT+FF groups respectively.

The investigators reported no differences in infant anaemia according to maternal HAART regimen. Microcytosis or hypochromia occurred in 39/89 (43.8%) infants in the HAART+BF group, with severe anaemia.

Patients with severe anaemia were treated with iron/multivitamin supplementation, and 10 infants (7.9%) received transfusions. Of those who improved to grade <3 with iron/multivitamin supplementation alone this occured in ≤30 days in 43 (34%), 31–90 days in 50 (39.7%) and >90 days in 18 (14.3%) infants. Three (2.4) infants died while grade 3–4 and 2 (1.6) were lost to follow up.

The investigators concluded: "The clinical implication of this finding requires further investigation to ensure that the established benefits of using HAART for MTCT prevention are maximised for all infants."

The same research group looked at the impact of HAART and short course AZT on longitudinal growth in a subset of Mashi and Mma Bana infants. They noted that HAART for PMTCT may lead to lower birth weight but longitudinal effects of in utero exposure on infant growth have not been previously reported.

In this analysis, Kathleen Powis and colleagues evaluated breastfed, HIV-uninfected infants born ≥37 weeks and exposed in utero to at least 2 weeks of either HAART or AZT. Infants in the HAART-exposed group received postnatal AZT for 1 month. Infants in the AZT-exposed group received 6 months of AZT-prophylaxis during breastfeeding.

The investigators calculated gender-based weight-for-age, length-for-age, and weight-for-length z-scores were using WHO Child Growth Standards. They compared mean z-scores using the Student's t- test and analysis of response profiles.

This analysis included 437 AZT-exposed infants from Mashi, and 592 HAART-exposed infants from Mma Bana.

Median maternal baseline CD4 counts were 393 and 337 cells/mm3 (p=<0.001) and median viral load 4.34 and 4.19 log copies/mL (p=0.04) for Mashi and Mma Bana women, respectively Demographics were similar between cohorts.

The median time of in utero AZT exposure was 5.7 weeks (range 2.0–10.9 weeks), and median in utero HAART exposure was 12.1 weeks (range 2.6–22.3 weeks).

Median birth weights were 3.1kg in AZT-exposed and 3.0kg in HAART-exposed (p<0.001). HAART exposed infants had significantly lower mean weight-for-age, length-for-age, and weight-for-length z-scores (p<0.001, p = 0.02, and p= 0.007, respectively).

However, the investigators reported that by 3 months of age the infants' median weight was no longer different by exposure group, and their weight remained similar to 6 months. Mean weight-for-age differed over time by exposure group (p <0.001). Length-for-age remained lower in the HAART-exposed group to 6 months of age, but weight-for-length improved significantly over time compared with AZT-exposed infants (p<0.001).

They noted that the proportions of infants with z-scores >2 standard deviations below the mean were not different between exposure groups.

These early developmental comparisons are useful and longer-term comparisons are planned. The investigators wrote: "The early correction of birth weight differences among HAART exposed infants is reassuring for programmes utilising maternal HAART for treatment and PMTCT."

COMMENT

Both DART and the Botswana group continue to provide urgently needed and excellent data on maternal /infant health and outcomes.

References

Unless stated otherwise, all references are to the Programme and Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections, 16-19 February 2010, San Francisco.

1. Chidziva E et al. Outcomes in infants born to HIV-infected mothers receiving long-term ART in the DART trial, 2004 to 2009. Poster abstract 924.
http://www.retroconference.org/2010/Abstracts/38485.htm
2. Pregnancy outcomes in the DART trial. HTB, April 2007.
http://i-base.info/htb/2667
3. Pregnancy rates and outcomes among women in the DART trial. HTB, October 2009.
http://i-base.info/htb/5945
4. Vigano A et al. Exposure during gestation to HAART, including tenofovir, does not impair bone status and metabolism in HIV-positive children born to HIV-positive mothers. Poster abstract 926.
http://www.retroconference.org/2010/Abstracts/38485.htm

5. Dryden-Peterson S et al. Increased risk of severe but reversible anemia following perinatal exposure to maternal HAART in infants in Botswana. Poster abstract 927.
http://www.retroconference.org/2010/Abstracts/37152.htm
6. Powis K et al. Impact of HAART and short-course zidovudine on longitudinal growth of HIV-exposed uninfected breastfed infants, Botswana. Poster abstract 928.
7. Mashi study – late breakers on breastfeeding. HTB, April 2005.
http://i-base.info/htb/7450
8. Risk factors for breastfeeding transmission, HTB, April 2008.
http://i-base.info/htb/1831
9. Breast milk, HIV suppression and decreased mother to child transmission. HTB, October 2005.
http://i-base.info/htb/7036
10. Response to nevirapine containing HAART following single dose nevirapine for PMTCT. HTB, February 2007.
http://i-base.info/htb/2745
11. Reducing HIV transmission during breastfeeding. HTB, August 09.
http://i-base.info/htb/4466

Maternal TB, HIV and pregnancy

Polly Clayden, HIV i-Base

Two posters looked at maternal TB in HIV-positive pregnant women.

Amita Gupta and colleagues from the SWEN India Study Group assessed the effect of maternal TB (prevalent or incident) between pregnancy to 12 months post-partum on risk of HIV MTCT. [1]

The SWEN trial compared the use of extended NVP to single dose NVP among breastfed infants to reduce MTCT of HIV. [2] A secondary objective of the trial was to look at maternal and infant morbidity and risk factors for MTCT.

Maternal VL, CD4, duration of breastfeeding, type of ART intervention and maternal hepatitis coinfection are well known to be factors associated with HIV MTCT. The role of maternal TB however has not been well characterised.

The investigators used multivariable logistic regression to determine the impact of maternal TB on HIV MTCT. They used WHO criteria to define TB cases and manual methods for AFB smear and culture.

They found, out of 783 mothers, with a median duration of follow up of 365 days (IQR 346-368), median CD4 472 cells/mm3 (IQR 317-667; 7% <200 cells/mm3), 3 had prevalent TB diagnosed in pregnancy and 30 had incident TB by 12 months post partum.

When they looked at maternal TB and HIV transmission, they found among mothers with any TB the HIV transmission rate was 30.3% (10/33) compared to 11.6% (87/750) among mothers without TB (OR 3.3 95%CI 1.5–7.2, p=0.02). When they restricted the analysis to maternal TB diagnosed before HIV transmission this gave a transmission rate of 20.7% (6/29) among mothers with TB compared to 12.3% (91/754) among mothers without, (OR 1.9 95% CI 0.8–4.8, p=0.17).

Mothers with TB had a higher baseline viral load than mothers who did not (85,651 copies/mL vs 37,639 copies/mL, p<0.01).

In multivariate analysis, maternal TB was associated with an OR 2.4 (95%CI 1.0–5.98), for HIV transmission adjusting for maternal factors (viral load, CD4, AZT, NVP, HAART) and infant factors (breastfeeding duration, infant NVP, gestational age, birth weight) associated with MTCT of HIV.

The investigators acknowledged that this analysis had limitations including that as a secondary trial endpoint it was likely to be underpowered, not all TB diagnoses were culture confirmed so some misclassification bias was possible and unmeasured confounders could possibly explain this finding.

However they concluded that maternal TB appears to be an important risk factor associated with HIV MTCT but that, "larger studies are needed to confirm this and to understand the pathogenesis since this appears to be independent of maternal viral load and CD4".

Celine Gounder and colleagues from the Perinatal HIV Research Unit performed a cross sectional study across six antenatal clinics in Soweto to look at provider initiated screening for TB among pregnant women.

The study included all pregnant women >18 years of age presenting to the clinics, who gave verbal consent to participate. Women presenting with obstetric complications or medical emergencies, who declined or were unable to provide verbal consent, and prisoners were excluded.

Regardless of their HIV status, women were screened for symptoms of active pulmonary TB ie, cough for ≥2 weeks, sputum production, fevers, night sweats or weight loss.

Information on their demographics, HIV status, CD4 count, and prior TB and HIV history was also collected at the time of symptom screening.

Any woman with any symptom of active TB was then asked to provide a single sputum specimen, which was sent for sputum smear microscopy, mycobacterial culture and identification, and INH/RIF drug-susceptibility testing.

The investigators reported that 3970 pregnant women were enrolled in the study between December 2008 and August 2009 who had a median age of 26 years (range 18-49).

Of these women, 1492 (36%) were HIV-positive. The percentages of women with CD4 count in the following strata at diagnosis were: 2% (0–50), 17% (51–00), 30% (201–350), 22% (351–500), 19% (>500), and 9% unknown (the investigator noted that 49% had a CD4 count of ≤350 cells/mm3). Additionally, 5% had a prior history of TB disease, and 21% had previously been exposed to someone with active pulmonary TB.

The investigators reported that the prevalence of active pulmonary TB was 696/100,000 among HIV-positive pregnant women (10/1492 cases), and 200/100,000 among HIV-negative pregnant women (5/2478 cases). They did not identify any cases of MDR-TB.

The investigators wrote: "Provider-initiated TB screening among HIV-infected pregnant women is a high yield intervention, and should be integrated with PMTCT services."

They added: "Given that 49% of the women had $CD4^+$ T cell counts ≤350 cells/mm3, both ART and IPT should be considered in high TB/HIV prevalence settings."

References

1. Gupta A et al. Maternal TB is associated with increased risk of HIV mother-to-child transmission. 17th Conference on Retroviruses and Opportunistic Infections (CROI), 16-19 February 2010, San Francisco. Poster abstract 899.
http://www.retroconference.org/2010/Abstracts/37899.htm

2. Gounder C et al. Provider-initiated screening for TB among pregnant women in antenatal clinics in Soweto, South Africa. 17th Conference on Retroviruses and Opportunistic Infections (CROI), 16-19 February 2010, San Francisco. Poster abstract 900. http://www.retroconference.org/2010/Abstracts/37899.htm

Botswana IPT trial: Continuous isoniazid superior to 6 months short course

Nathan Geffen, TAC

Taraz Samandari of the CDC presented the results of a randomised double-blind placebo-controlled Isoniazid Preventative Therapy (IPT) trial at CROI. This trial took place in Botswana and randomised HIV-positive patients to either six months of IPT, the standard of care, or continuous therapy, ie the 36 month duration of the trial. [1]

Botswana began implementing a country-wide IPT programme in 2001. The protocol provided for six months of IPT and no Tuberculin skin testing. The rationale for this trial was that evidence has been emerging that the effects of 6-month IPT decrease with time.

For the first six months, the entire cohort --after screening-- of 1,995 patients was initiated on open-label 300mg once-daily isoniazid. After six months patients were randomised to either receive placebo or continue receiving isoniazid. There were 989 in the six-month arm (6H) and 1,006 in the continuous one (36H). Patients also received 25mg vitamin B6 daily.

Patients were excluded from the trial if they had current weight loss or an AIDS-defining illness, a history of IPT, TB in the last three years, an abnormal chest x-ray, signs of TB based on a physical examination or the following laboratory criteria: Hgb<6.6gm/dl, neutrophil count <1,000 cells/mm3, platelets <75,000/mm3, AST(SGOT) >2.5 times the upper limit of normal, ALT (SGPT) >2.5 times upper limit of normal, total bilurubin >1.5 times the upper limit of normal, creatinine >1.5mg/dl and negative beta-HCG.

There were no significant differences between the 6H and 36H arms at baseline. Females comprised 72% of the cohort. Median age was 32. Median CD4 count was approximately 300 cells/mm3. Just under 4% had a history of TB. In 6H, 23% of participants were TST-positive (>=5mm) and in 36H, this was 26%. By six months about 45% of the cohort had initiated ART.

Only 11 people were lost to follow-up. There were 176 withdrawals and 36 deaths. Adherence was good: at 36 months, 78% of participants had attended more than 80% of their visits (where pills were provided). In a random sample of 200 people on 36H, 74% had detectable INH in urine at 25-30 months.

In intention-to-treat analysis, there were 34 incident TB cases in the 6H arm and 20 in the 36H arm (HR: 0.57, p=0.047). In a modified intention-to-treat of 1,655 people who were enrolled after six months there were 25 TB cases in the 6H arm and 12 on the IPT arm (HR: 0.47, p=0.033). In a per protocol analysis of people who had attended least 5 out of 6 clinic visits (ie >=80% adherent), there were 19 and 8 TB cases in 6H and 36H respectively (HR=0.043, p=0.045).

In an analysis of TST-positive patients, the results were even more compelling. There were 13 incident TB cases in 6H and 4 in 36H (HR:0.26, p=0.019). In the modified intention-to-treat it was 11 cases in 6H and 1 case in 36H (HR: 0.08, p=0.015) and in the per-protocol analysis 8 and zero cases respectively (HR: 0.0, p=0.007). However, in TST-negative patients the reduction was slight and not significant (incidence rate of 0.98 versus 0.78 per 100 patient years; HR: 0.86; p=0.69).

The effect of 6 months IPT remained the same as the 36H arm for nearly six months after the completion of the open-label part of the study, but then TB cases escalated in the 6H arm.

ART initiation was evenly distributed between the two arms. Increasing ART use decreased TB incidence for all participants. By one year, the risk was reduced by half.

Compared to 6H patients not on ART:

- 6H TST-negative patients on ART had a TB hazard ratio of 0.5 (95%CI: 0.26-0.97).
- This was identical for 6H TST-positive patients.
- 36H TST-negative patients not on ART had a TB hazard ratio of 0.92 (95%CI: 0.4-2.1).
- 36H TST-positive patients not on ART had a TB hazard ratio of 0.08 (95%CI: 0.01-0.06).
- 36H TST-negative patients on ART had a TB hazard ratio of 0.46 (95%CI: 0.16-1.3).
- 36H TST-positive patients on ART had a TB hazard ratio of 0.04 (95%CI: 0.01-0.36).

After month 6, there were seven possibly drug-related adverse events in the 6H arm and 12 in the 36H arm. The difference was not significant. There was one death possibly due to isoniazid in the 36H arm (hepatic encephalopathy), though the patient also had severe herpes. There were 20 cases of severe hepatitis in the first six months (across both arms) and 15 subsequently (6 on 6H and 9 on 36H).

DST was available for 24 samples in the 6H arm and 14 in the 36H arm. There were three cases of INH mono-resistance in 6H and 1 in 36H. One patient on each arm had MDR TB.

Mortality was 1.4% per annum. Interestingly it was non-significantly higher in the 36H arm (HR: 1.55; p=0.17). However, for TST-positives, the HR was 0.28 (p=0.06) and for TST-negatives, the HR was 2.99 and this was significant (p=0.01).

Samandari concluded that:

- The benefit of 6 months of IPT was lost in less than 6 months after treatment completion.
- Continuous IPT reduced TB incidence by 43% compared to 6 months of IPT.
- TST-positive patients were at high risk of TB after six months of IPT, even on ART.
- Continuous IPT was 92% effective in reducing TB in TST-positive patients.
- ART's effect was smaller than continuous IPT in reducing TB, but additive.
- However, only ART reduced TB in TST-negative people.
- Provision of IPT did not increase isoniazid resistance.
- TST-negative patients may be unduly exposed to harm by IPT.

COMMENT

This is one of the largest and best-conducted IPT studies to date. The finding that the benefit of IPT can only be maintained with continuous therapy is important. This study makes a strong case for scaled up IPT rollout. The new South African treatment guidelines provide 6 months IPT in all patients who are not indicated for ART.

However, the significantly higher mortality in TST-negative patients in the intervention arm is cause for concern. It suggests that Tuberculin skin testing must be done before initiating patients on IPT.

Ref: Samandari T et al. Randomized, placebo-controlled trial of 6 vs 36 months isoniazid TB preventive therapy for HIV-infected adults in Botswana. Oral abstract 104LB. 17th Conference on Retroviruses and Opportunistic Infections, 16-19 February 2010, San Francisco.

http://retroconference.org/2010/Abstracts/39555.htm

http://retroconference.org/2010/Sessions/027.htm

40th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease

3-7 December 2009, Cancun, Mexico

Introduction

Several presentations at this conference indicated that there is progress in TB drug development and diagnostics. For example, at least three drugs for the treatment of TB and drug-resistant TB are in advanced clinical trials, including moxifloxacin, TMC207 and OPC-67683. We include reports on:

- Cepheid Gene Xpert diagnostic technology for TB
- Adherence of TB patients on self-administered treatment
- High mortality and poor record-keeping for in-patients in Kwazulu-Natal Hospital
- Factors affecting survival of XDR TB patients

Many delegates from African countries struggled to get visas for the conference, because the only Mexican consulate in Southern Africa is in Pretoria. Cancun is primarily known as a holiday resort and it was not an appropriate venue for this conference. Hopefully in future years it will be held in venues easily reached by people most affected by TB.

Cepheid Gene Xpert diagnostic technology for TB

Nathan Geffen, TAC

Current State of TB Testing

Current diagnostics for active TB are limited by cost, complexity, long diagnostic time, poor sensitivity or poor specificity. A point of care, affordable, easy-to-use, highly sensitive and specific test for active TB, analogous to HIV rapid tests, is urgently needed. Sputum microscopy is the standard technique used to diagnose TB in many developing country health facilities but has poor sensitivity especially in immune-compromised patients. It also requires a skilled health worker or technician.

The closest to a current gold standard for an active TB diagnosis is to perform both a liquid and solid culture test. These, however, have median turnaround times measurable in weeks.

Nucleic acid amplification techniques such as the FAST Plaque TB assay and PCR give results much faster but still take days and are much less sensitive and specific. They are also expensive. All these methods are compromised by the fact that some patients struggle to provide quality sputum samples.

Cepheid Gene Xpert

Mark Perkins of FIND presented data at the International TB conference in Cancun on a new nucleic acid amplification diagnostic technology for TB, the Cepheid Gene Xpert. The key data he presented has subsequently been published in the Journal of Clinical Microbiology by a group of researchers from FIND; New Jersey Medical School; Cepheid; Pham Ngoc Thach Hospital, Ho Chi Minh City and Makerere University, Kampala. [1, 2]

The Clinical Microbiology paper describes the Cepheid Gene Xpert as an integrated hands-free sputum-processing and real-time PCR system with rapid on-demand, near-patient technology, to simultaneously detect M. tuberculosis and rifampicin resistance. The device consists of a computer installed with Cepheid's proprietary software and a machine --the smallest of which is about the size of a desktop computer-- that takes cartridges loaded with sputum and reagents. The cartridges consist of a syringe barrel, a sonicator dome, a reverse-transcriptase PCR tube and a rotary valve.

The molecular beacon-based PCR assay that the system uses was shown to have high sensitivity and specificity on MDR isolates from the US, Spain, Mexico and India but without the machine is complex and labour-intensive to carry out. Rifampicin resistance is detected by mutations in the 81-base pair rifampicin resistance-determining region of the rpoB gene, which according to research cited by the authors occurs in 95 to 98% of rifampicin-resistant strains and are usually absent in rifampicin-susceptible ones. The authors indicate that rifampicin resistance is a good proxy for isoniazid resistance (and consequently MDR-TB, which is defined as resistance to both drugs).

The cartridges contain liquid sample-processing, PCR buffers and freeze-dried (lyophilized) PCR reagents. To prepare a cartridge, (1) PCR buffer is added to the sputum sample (ratio of 2 to 1), (2) the mixture is shaken for 5 seconds, (3) then allowed to stand for ten to 15 minutes, (4) 2 to 3 ml are transferred to the cartridge and (5) the cartridge is loaded into the machine, at which point the test can begin. It takes approximately two hours to give a result. Up to four cartridges can be loaded into the smallest machine.

Validation tests

The researchers report results of several tests to measure the machine's accuracy. Only some are described here. They found that the device has a limit of detection (LOD, defined as the number at which there is a 95% probability of a positive result) in clinical samples of 131.0 colony forming units (CFU) per ml of sputum (95% CI: 106.2-176.4). By way of comparison, the gold standard BACTEC 960 MGIT culture test has a LOD of 10-100 CFU/ml and fluorescent microscopy has a LOD of 10,000 CFU/ml. [3]

Sputum samples from Vietnamese patients were used to validate the clinical efficacy of the device. The assay detected TB bacteria in all 29 smear-positive samples (95% CI: 85.4-100%) and 38 of 53 smear-negative samples that were culture-positive (71.7%; 95% CI: 57.4-82.8%).

To validate rifampicin resistance detection, 64 Ugandan cases were studied, in which the patients were being retreated for TB and therefore had a higher probability of rifampicin resistance. The device detected resistance in all nine known rifampicin resistance cases, giving a sensitivity of 100% (95% CI: 63.0-100%) and in 1/55 rifampicin-susceptible cases giving a specificity of 98.2%. (95% CI: 89.0-99.9%). The authors sequenced the rpoB gene of this discordant isolate and found a mutation commonly associated with rifampicin resistance. They therefore suggest that the Gene Xpert gave the correct result and the current standard rifampicin resistance test gave the wrong one. They point out that similar errors have been reported in other studies and furthermore that in this case the isolate was known to be resistant to both isoniazid and ethambutol, increasing the likelihood of rifampicin resistance. Furthermore, the device detected M. tuberculosis in 63 of the 64 sputum samples from culture-positive Ugandan patients (98.4%; 95% CI: 90.5 to 99.9%). Twenty laboratory control sputum samples from patients not suspected of having tuberculosis were negative.

The researchers measured the time required to analyse one and eight sputum samples, beginning at the moment that a sputum sample was given to a laboratory technician. The time-to-result for one sputum sample processed alone was just under two hours. The time-to-result for eight samples processed together was two hours. Total hands-on time was about five minutes.

Perkins indicated that sensitivity and specificity are greatly improved if more than one cartridge is used per patient instead of one, but this is not discussed in the Clinical Microbiology article.

Cost

Cepheid has not responded to a question about the cost of the device and its reagents. Based on informal discussions it appears the cheapest complete machine costs between US$25,000 and US$30,000 and handles four cartridges. The cartridges are $22 each. If three cartridges are needed per patient, then the cost per test is $66. This all needs to be confirmed, however. Cepheid's website indicates that developing country public health systems will qualify for substantial discounts.

COMMENT

A largely hands-off automated test that produces highly sensitive and specific results in less than two hours would greatly improve patient-care. However it remains unclear that the Gene Xpert can be widely used in resource-poor settings, including most of Southern Africa.

Opinion about the device is cautious, with concern about its cost and lack of validation.

The machine is being tested in a National Health Laboratory Systems laboratory at the Site B Community Health Centre in Khayelitsha, Cape Town, with the assistance of Medecins Sans Frontieres. While this is a resource-poor setting, the health centre is relatively well resourced compared to the kinds of health facilities usually found in this kind of neigbourhood. The staff at this facility found the device convenient and easy to use, especially compared to smear microscopy. It is conceivable that at facilities with this kind of infrastructure, the machine will have a useful place.

There are several caveats about the machine:

- **Unless the prices of both the machine and the cartridges come down dramatically, this device will not be rolled out beyond advanced laboratories and academic hospitals. If the machine proves useful in practice, there is potential for an activist-driven campaign to drive prices down, with the argument for price reductions perhaps strengthened by the fact that substantial public money was used to develop the device. The authors of the Clinical Microbiology article indicate that cost and cost-effectiveness studies are planned.**
- **It is unclear how complex the process of preparing the cartridge is and how much training is required for health workers to operate it, though the Khayelitsha technician operating the machine found it easy and quick to use. It will be important**

to validate the specificity and sensitivity of the device in pilot operational settings before it is made generally available.

- **The authors point out that freezing may alter sputum viscosity and improve nucleic acid recovery from mycobacteria. They therefore state that the results need to be confirmed in larger prospective studies with fresh samples. (They did however document similar LODs regardless of whether the assay was performed with fresh or frozen sputum samples in analytic studies using spiked sputum.)**
- **The clinical test sample sizes are quite small with consequent large confidence intervals. Further validation, preferably from an operational setting such as Khayelitsha, is needed.**
- **It is unclear if Cepheid is or has obtained CE mark (demonstrating that it has met European Union consumer safety, health or environmental requirements) or FDA approval for the device.**

If the device does prove itself in practice a further question that will arise is to what extent rifampicin resistance should be used as a proxy for assuming isoniazid resistance and consequently MDR TB. Should isoniazid-resistance testing still be done if rifampicin resistance is detected? If so, what clinical decisions must be taken while waiting for results?

Even in the best-case scenario, ie the Gene Xpert proves itself to be a robust highly specific and sensitive TB diagnostic tool in operational settings and its price is made affordable, we remain short of the holy grail point-of-care test for active TB. Nevertheless, it is possible that this device will have a useful place in the current TB diagnostic arsenal.

Thank you to Julian Duncan, Helen Lee, Gregg Gonsalves, Cheryl McDermid, Helen Cox and the Khayelitsha NHLS staff.

References

1. Perkins M. Xpert MTB/RIF: Automated molecular detection of TB and MDR at point of treatment. Presentation at 40th Union World Conference on Lung Health, December 2010.
http://www.finddiagnostics.org/export/sites/default/resource-centre/presentations/iualtd_40th_union_conf_cancun_2009_FIND_Forum/XpertMTB_MarkPerkins.pdf
2. Helb D et al. Rapid Detection of Mycobacterium tuberculosis and rifampin Resistance by Use of On-Demand, Near-Patient Technology. Journal of Clinical Microbiology, Jan. 2010, p. 229–237.
http://jcm.asm.org/cgi/content/full/48/1/229
3. Roscigno G. Drug resistant TB and new diagnostics for people living with HIV: emerging results from FIND. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 19-22 July, Cape Town.
http://www.stoptb.org/wg/tb_hiv/assets/documents/DRUGRE~1.PDF

Adherence of TB patients on self-administered treatment

Nathan Geffen, TAC

In the October 2009 issue of HTB South, we described a pilot study by Atkins and colleagues in which TB patients self-administered treatment. [1] At the World Lung Conference, a poster by MSF examined self-administered treatment at a site in Homa Bay, Kenya. [2] This is in contrast to direct observation of treatment recommended by the World Health Organisation (WHO).

This cross-sectional study consisted of a survey of 279 potentially eligible patients taken from the TB register in November 2008 and June 2009. Of these, 67 (24%) did not participate because five never started treatment, 20 defaulted before the survey, 11 were dead, four were hospitalised, 13 refused to consent to the home visits necessary to carry out the survey and 14 were not found. Patients received education on TB treatment. They had to collect their medicines weekly during the intensive phase and monthly during the continuation phase.

The survey consisted of four measurements: an interviewer-administered questionaire, visual analogue scale in which the patient estimated adherence in the last month, pill counts and an isoniazid urine strip test. For those who participated the median age was 35 years, 46% were female, 79% had pulmonary TB and 69% were HIV-positive. Of those who were HIV-positive, 73% were on ART.

The interviewer-administered questionaire asked questions about pill intake over the past four days. If patients responded that they had taken all their pills, their adherence was described as exact. If they took 75% of their pills, their adherence was described as satisfactory, else their adherence was described as unsatisfactory. 95% were exact, 3% satisfactory and 2% unsatisfactory.

On the Visual Analogue Scale assessment, patients were asked: "How much of your prescribed TB medications have you taken in the last month?" 93% answered 90-100%. 7% answered 80-90% and only one patient answered less than 80%.

Overall, 98% of patients tested positive for isoniazid. Pill counts results were described as exact if 100% of pills were taken, satisfactory if at least 80% of pills were taken and unsatisfactory otherwise. 84% were exact, 10% satisfactory and 6% unsatisfactory. However pill count data was unavailable for 64 patients.

There was no significant difference observed between the intensive and continuation phases for any of the four measures of adherence nor were there significant differences between HIV-positive and HIV-negative people, nor between people on ARVs and people not on ARVs.

Reasons given for non-adherence varied with 17 patients giving 36 reasons, the most common being "ran out of pills" (8 patients), followed by "away from home" (7 patients), followed by, "forgot to take medication" (6 patients).

The Kappa coefficient measures agreement between qualitative assessments. A Kappa < 0.4 is moderate or poor agreement, $0.4 - < 0.75$ is fair to good agreement and ≥ 0.75 is excellent agreement. The only combination of assessments that had fair to good agreement was INH positivity and the questionaire (Kappa = 0.43). All other binary comparisons of the assessments had poor to moderate agreement.

The authors pointed out that the INH test was expensive and needed a cold chain and that pill counts had poor reliability and inconsistent data. Therefore they state that in routine settings, the questionaire and visual analogue scale should be the preferred adherence measurement tools. They also state that adherence measurements should not be based on just one tool.

The authors concluded that adherence was high among surveyed patients but acknowledged that the study was limited by several factors including that only patients who consented to home visits were surveyed, the adherence visit was sometimes too close to the last visit and patients who defaulted before the survey were not included.

COMMENT

At the time of the conference, data was not yet available to adequately compare patient outcomes and adherence. Hopefully the researchers will publish this soon.

While this study has some serious limitations–particularly that it does not examine patients who were not adherent before the survey started–observational data is accumulating that self-administered treatment for TB can compete with the directly observed treatment model promoted by the WHO. A randomised open-label trial to compare these methods is warranted. Such a trial should compare health outcomes and adherence, but also perceptions of patient dignity, travel costs incurred by patients and cost to the health system.

References
1. Geffen N. 2009. Overview of TB-related studies at IAS. http://i-base.info/htb/5919
2. Huerga H et al. 2009. Adherence to self-administrated tuberculosis treatment in Homa Bay, Kenya. 40th World Lung Conference, Cancun, December 2009.

High mortality and poor record keeping for TB in-patients in Kwazulu-Natal Hospital

Nathan Geffen, TAC

A poster by Cudahy and colleagues examined mortality and record-keeping of TB in-patients in Edendale Hospital in Kwazulu-Natal. [1]

The researchers conducted a cross-sectional audit of patient charts in medical wards for a 4 week period in early 2009. These records were compared with the hospital TB register. Patients who were prescribed TB treatment and lived longer than 24 hours from admission were included for analysis. They identified 79 such patients. All were on first-line TB medication, but some were retreatment cases (ie they also received streptomycin). There were 40 pulmonary and 39 extra-pulmonary TB cases. HIV status was known for 68 (86%) of patients, of whom 58 were HIV-positive and 43 had CD4 counts < 200 cells/mm3, but only 13 patients were on ART. The mean CD4 count for HIV-positive patients was 95.

Of the 79 TB patients, 24 died as inpatients. None were recorded as deaths in the hospital register submitted to the district TB control programme. Five were recorded as transferred to a local clinic for follow-up in the hospital register. The remaining 19 were unrecorded. 16 had TB as the recorded cause of death on their death certificates.

Two of the 79 left hospital against medical advice, but they were unrecorded in the TB register.

Five of the 79 were transferred to a TB hospital. Four of them were unrecorded in the TB register and one was recorded, incorrectly, as transferred to a local clinic for follow-up.

The remaining 48 were discharged to home to be followed up at their local clinics. Only 66% of them reported to their local clinic within 30 days. The register recorded only 36 patients transferred to local clinic for follow-up. The other 12 were unrecorded.

The authors note that a similar audit was conducted seven years ago with similar results. However, the poor recording of deaths is a new finding. One positive finding is that in the previous audit 30% of patients did not have an HIV test result, while now it was only 14%.

The authors conclude that "these results add to the conclusion reached elsewhere that patients, often HIV-positive, present late for care directly to hospitals and sick enough to require admission. This has left medical wards overcrowded and overworked leading to the poor outcomes seen in this audit. More resources need to be directed to TB care at hospital sites and better systems need to be implemented to track patient outcomes once discharged."

COMMENTS

These are disturbing findings and action by the Kwazulu-Natal Provincial Department of Health is necessary to rectify the discord between hospital and patient records. While the authors' conclusion is accurate, the death reporting system worked better seven years ago. It is possible that years of mismanagement of health in Kwazulu-Natal, has led to worsening systems.

Nevertheless, it is unlikely that the findings about record keeping of TB mortality at Edendale are exceptional. Nor are the problems likely to be peculiar to South Africa. This has implications not only for the accuracy of statistics kept for the Millenium Development Goals as pointed out by the study's authors, but also for Statistics South Africa's mortality data.

The accuracy of TB and HIV data supplied by the National Department of Health are ultimately dependent on the quality of data at health facility level. Given these findings about TB statistics at one of the larger Kwazulu-Natal health facilities, it raises questions about the quality of data of HIV patients generally and consequently the quality of the statistics provided by the National Department of Health on numbers of people on ART.

Elsewhere in this issue and in several previous HTB-South issues we have described high mortality in cohorts of drug-resistant patients. But this small study demonstrates very high mortality in HIV-positive hospitalised TB patients generally. It underscores the importance of early TB screening and ensuring HIV-positive people with TB are prioritised for ART. It is disturbing that only 13 out of 43 patients with AIDS were on ART, though it is possible that all or some of those were still in the intensive phase of TB treatment and consequently not eligible for ART if their CD4 counts were about 50 cells/mm3.

Ref: Cudahy P et al. 2009. TB Case Outcomes at a Large Public Sector Hospital in Kwa-Zulu Natal, South Africa. 40th World Lung Conference, Cancun, December 2009.

Factors affecting survival of XDR TB patients

Nathan Geffen, TAC

A poster by Shenoi and colleagues at the World Lung Conference examined survival characteristics of people with XDR TB in Tugela Ferry, Kwazulu-Natal. [1]

This was a case controlled study. It included patients registered at Tugela Ferry with new active TB. Patients also had had culture and drug susceptibility testing demonstrating resistance to isoniazid, rifampin, ciprofloxacin, and kanamycin. Survivors were defined as patients who were alive at least six months from sputum collection. Non-survivors were defined as patients who died within six months from sputum collection. Non-survivors were matched to survivors by year of XDR TB diagnosis.

The researchers found records of 460 patients with XDR TB from 2005 to 2008. Of these 122 were confirmed alive at time of receipt of DST results and referred for XDR TB treatment. Of these, 68 met the definition of survivors and 74 met the definition of non-survivors. Remarkably, only one patient in each arm was HIV-negative.

The XDR TB regimen used in Tugela Ferry was ethambutol, pyrazinamide, ethionamide cycloserine or Terizidone, Para-aminosalicylic acid (since 2007) and capreomycin for at least six months followed by an 18 month continuation phase that excluded capreomycin. Amoxicillin/clavulanate and clarithromycin were added to the regimen if one of the above was discontinued due to toxicity or if patients were still TB-culture positive after 12 months of treatment. Patients were also treated with antiretrovirals if there CD4 count was lower than 200 cells/mm3.

Survival was associated with several factors. The most significant and intuitively sensible of the treatment characteristics associated with survival were having started XDR TB treatment (97% v 28%, p<0.0001), having ever received ART (82% v 42%, p<0.0001) and having a higher baseline CD4 count at XDR diagnosis (162[IQR:72-260] v 84 [IQR:40-157] cells/mm3, p=0.004). Being smear negative also predicted survival (37% v 79%, p<0.0001). The majority of patients on ART initiated therapy prior to diagnosis of XDR TB. The authors indicate that ART may have unmasked XDR TB IRIS in some patients.

The authors emphasise that laboratory diagnostic delay is a major impediment to detecting XDR TB. They also suggest that smear negativity and better multi-organ functioning suggested less disease severity at baseline. They state that concurrent therapy for both XDR TB and HIV coinfection is feasible and associated with successful XDR TB outcomes.

COMMENT

Although this is a small case controlled study, this research is important for understanding how to improve survival in XDR TB patients. The new South African HIV treatment guidelines, in line with these findings, now provide for ART for all HIV-positive patients with drug-resistant TB, irrespective of CD4 count. The new guidelines are described in this issue of HTB South.

Notable is the apparent extremely high mortality rate. From the 460 patients identified, only 128 were confirmed alive. While this does not mean that all of the remainder died, it is very probable that most of them did. Furthermore, of the confirmed survivors, less than half lived six months. The likely availability of new TB drugs in the next few years will probably help reduce the drug-resistant mortality rate. But, even more important is finding ways to diagnose drug-resistant TB quicker, primarily by getting DST results back to clinics and hospitals faster. This will probably have the greatest short to medium-term impact on reducing drug-resistant TB mortality.

It would be useful if the authors clarified some of their findings in greater detail (some of the data on their poster is unclear or counterintuitive) and published this valuable study in a journal.

As the authors recommend, prospective studies to examine their findings in greater detail are needed.

Ref: Shenoi SV et al. 2009. Comparison of characteristics of XDR TB survivors with those of non-survivors in rural Kwa-Zulu Natal, South Africa. 40th World Lung Conference, Cancun 2009.

TREATMENT ACCESS

FDA approval of generic ARVs

Since the last issue of HTB, the US Food and Drug Administration (FDA) has granted tentative approval for the following new generic ARV products.

Drug and formulation	Manufacturer, Country	Approval date
Abacavir, 300mg tablets	Strides Arcolab, India	12 May 2010
ddI (didanosine) 125, 200, 250 and 400mg. Delayed-release Capsules All four of the strengths will be packaged in HDPE bottles in 30's and 500's	Mstrix, India	08 April 2010
Tenofovir DF, 300mg tabs	Hetero, India	06 April 2010
Nevirapine tablets for oral suspension, 50 mg, for children weighing ≥5 kg	Aurobindo, India	24 February 2010
Efavirenz cross-scored tablets, 200 mg (to be broken into two 100 mg or four 50 mg doses for pediatric dosing.	Strides Arcolab, India	12 February 2010

"Tentative Approval" means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, but because of existing patents and/or exclusivity rights, it cannot yet be marketed in the United States. Tentative approval does, however make the product eligible for consideration for purchase under the PEPFAR program for use outside the United States.

Effective patent dates are listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

COMMENT

This brings the total of FDA approved generic drugs and formulations to 111 since the programme started. An updated list of generic tentative approvals is available on the FDA website:

http://www.fda.gov/oia/pepfar.htm

Source: FDA list serve:

http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm122951.htm

Waiting lists grow in the US

Due to the poor economy and increased HIV testing efforts, the US public assistance programme called ADAP (AIDS Drug Assistance Programmes) across are facing unprecedented growth and severe funding shortages and placing people on waiting lists, cutting eligibility and removing drugs from their formulary. The HIV/AIDS community is asking for a $126 million emergency appropriation from President Obama and the Congress.

On 10 April 2010, the 859 individuals currently on ADAP waiting lists by state were: Idaho (25), Iowa (62), Kentucky (191), Montana (17), North Carolina (356), South Carolina (33), South Dakota (32), Tennessee (55), Utah (74) and Wyoming (14).

Cost-containment strategies instituted over the last years included reducing formularies, lowering the level of financial eligibility, using a CD4 threshold of <350 cells/mm3, initiating waiting lists, capping enrollment and capping use of T-20.

For an update on the states with waiting lists and other cost containment measures go to the ADAP Watch update at:

http://www.nastad.org/

MSF criticise Abbott over new ritonavir formulation

MSF press statement

Both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration have recently approved the long-awaited heat-stable 100mg tablet version of ritonavir, the antiretroviral booster drug produced by Abbott Laboratories.

The market authorisation of a heat-stable version of ritonavir as a separate pill finally ends both the stranglehold by Abbott on the treatment options available to people living with HIV/AIDS and the medical double standards the company has promoted by failing to prioritise the development of safer versions of its medicines. Protease inhibitors (PIs) are the cornerstones of second-line AIDS therapy, as set out in World Health Organization (WHO) guidelines.

PI-based regimens recommended in the guidelines include a booster drug, to be taken in conjunction with the PI, in order to make the regimen more effective. Ritonavir is still the only approved booster in existence.

Although Abbott has been marketing the heat-stable version of ritonavir since 2005, this has only been as a fixed-dose combination with its own protease inhibitor, lopinavir - not as a separate heat-stable pill. Until now, 'standalone' 100mg ritonavir was only available in a soft-gel formulation that requires refrigeration, making it extremely ill-suited for use in developing countries. This in turn severely restricted the choice of protease inhibitors for people on antiretroviral treatment, particularly in the developing world, as the use of all PIs other than Abbott's own lopinavir came with refrigeration constraints.

By failing to move faster on creating a separate ritonavir tablet, the company therefore built a market advantage for its own PI lopinavir, and made the use of other life-saving protease inhibitors less practical.

Abbott's delay extends to promoting medical double standards. The soft-gel version of ritonavir comes with more side effects and more dietary restrictions than the heat-stable version. In fact in 2007, the EMA raised this as a public health concern with Abbott. The absence of a heat-stable ritonavir also restricted the possible use of second-line AIDS drugs for patients co-infected with tuberculosis.

As a result of Abbott's inaction, many people living with HIV have therefore been deprived of additional, improved and vital treatment options.

Looking ahead, one particular area of need is the development of a heat-stable combination of atazanavir and ritonavir, one of the two PIs (with lopinavir/ritonavir) recommended by WHO for second-line treatment. A fixed-dose combination of atazanavir/ritonavir would in fact present considerable advantages over lopinavir/ritonavir, as it will reduce the pill burden from four to one pill a day.

Other PIs that require boosting with ritonavir are darunavir (which WHO indicates may form part of a future third-line antiretroviral therapy), and nearly all other PIs are more effective when used with a ritonavir booster. But to date, Abbott has not allowed manufacturers to produce any of these PIs in a fixed-dose combination with ritonavir.

It is hoped that generic manufacturers in developing countries will move forward with the development and registration of such boosted heat-stable PIs as fixed-dose combinations. Where there are potential patent barriers that prevent them from doing so, use should be made of safeguards in patent laws to ensure these are overcome.

MSF calls on Abbott to:

- Register heat-stable ritonavir tablet widely in developing countries.
- Ensure that the price is affordable to patients in all developing countries (Abbott's discounted price of US$83 per person per year for the heat-stable and soft-gel versions of ritonavir is only available for the absolute poorest countries).
- Develop a more adapted heat-stable paediatric formulation of lopinavir/ritonavir (such as soluble granules or sprinkles) for young children who can not swallow the existing tablet.
- Facilitate access to more affordable versions of ritonavir and fixed-dose combinations containing ritonavir by putting the patents on ritonavir into the Patent Pool for HIV medicines currently being set up by UNITAID.

Source: Médecins Sans Frontières - Campaign for Access to Essential Medicines press statement. MSF press statement "Approval of heat-stable ritonavir ends years of neglect by Abbott: years of medical double standards and stranglehold by Abbott come to an end". (12 February 2010).

http://www.msfaccess.org

TB TREATMENT AND PREVENTION

TB screening algorithm to determine who can safely go onto IPT and who needs to be treated

Nathan Geffen, TAC

A simple, reliable and affordable algorithm to identify if a patient can safely be initiated onto isoniazid preventative therapy (IPT) would be very useful. It is important to reduce the risk of initiating patients with active TB on IPT so that they are not effectively given monotherapy with the prospect of developing resistance to isoniazid. Furthermore, it is important that patients with active TB are initiated onto TB treatment. Research published by Cain and colleagues in the NEJM examines this problem. Their large prospective study of HIV-positive antiretroviral-naive patients in Cambodia, Thailand and Vietnam examined 80 million unique combinations of one to five predictors of TB in order to identify the most effective TB screening algorithm. They also identified the most effective TB diagnostic algorithm for patients who were received positive screening results. [1]

Cohort

A total of 1,836 HIV-positive antiretroviral-naive people from eight out patient facilities were screened for eligibility for the study. Of these, 1,768 were eventually enrolled. Three samples of sputum and one each of urine, stool, blood, and lymph node aspirate for patients with lymphadenopathy were obtained for TB culture testing. Patients who were culture-positive for TB were assumed to have TB. Twenty patients could not have their TB status classified and were excluded from the analysis. TB was diagnosed in 267 (15%) of patients.

The sensitivity of screening and diagnostic algorithms was determined based on the results of the culture tests. Sputum smears from and chest radiographs of patients were also taken.

At baseline, the median CD4 count was 242 cells/mm3 (IQR: 82 to 396). Median age was 31 years (IQR: 7 to 72) and just over half were male.

Screening

The challenge for a screening algorithm is to find the best combination of signs, symptoms and history of exposure, easily determined at any level health facility, that maximises the number of negative patients correctly diagnosed as negative but also minimises the number of patients who are suspected of being positive and consequently require microscopy and culture. For example, an algorithm that simply assumes everyone does not have TB might result in too many patients with active TB being inadvertently prescribed isoniazid monotherapy resulting in unnecessarily high isoniazid resistance, as well as many patients with active TB going untreated. On the other hand an algorithm that assumes everyone needs diagnostic testing might be impractical and too expensive in most settings.

The study found that requiring more than one symptom present for a positive diagnosis resulted in too low sensitivity. Also, considering only one or two symptoms was too insensitive. On the other hand, considering four or more symptoms conferred no substantial additional benefit over

three symptoms but added complexity to the algorithm. The best screening algorithms therefore were ones, which required the presence of one or more of three symptoms. These were:

- Cough or fever of any duration or drenching night sweats for three weeks out of the previous four weeks: This algorithm has a sensitivity of 93%, specificity of 36% and negative predictive value of 97%.
- Cough, drenching night sweats, or loss of appetite of any duration in previous four weeks: This has the same sensitivity and negative predictive value as above, and a specificity of 35%.
- Cough in previous 24 hours or fever of any duration or drenching night sweats for three weeks in previous 4 weeks: This has a sensitivity, specificity and negative predictive value of 90%, 43% and 96% respectively.
- Cough in previous 24 hours or drenching night sweats or loss of appetite of any duration in previous 4 weeks: This has a sensitivity, specificity and negative predictive value of 89%, 44% and 96% respectively.

The authors show the benefit of three symptoms over two by giving this example: As compared with two symptoms (cough or fever of any duration in the previous four weeks) a combination of three symptoms (the addition of night sweats for three weeks or more) reduced by five the number of patients with false negative screens but increased by 18 the number of patients who needed diagnostic evaluation.

Using the recommended three criteria screening algorithm, 1,199 of the 1,748 participants would have needed diagnostics, but there would have been 18 patients with false negatives not referred for diagnostics. By comparison, the WHO screening approach of only referring patients for diagnostics if they have had a cough for more than two or three weeks would have resulted in only 355 patients being referred for further diagnostics, but 179 false negatives.

Diagnostics

For patients who receive a positive screen, the researchers recommend the following algorithm:

- Start with AFB microscopy of two sputum smears. Patients with at least one positive sputum result should be initiated on TB therapy in most cases.
- For patients with two smear negative results, conduct a chest x-ray. If the x-ray is abnormal, clinical judgment should be used to determine if the patient should be treated, followed by confirmatory mycobacterial culture.
- For patients with a normal x-ray but a CD4 count below 350 cells/mm3, clinical judgment should be used to determine if the patient should be treated, followed by confirmatory mycobacterial culture.
- The authors state that for patients with a CD4 count ≥ 350 cells/mm3 it is unclear what to do. Remember, these are patients with at least one symptom associated with TB.

Applying the screening/diagnostics algorithm to this cohort, the results were as follows:

- Of the 1,199 patients with a positive screen for TB using the screening algorithm described by the authors, 113 had at least one sputum positive result from two sputum smear microscopy examinations. Of these, 98 (87%) had culture-confirmed TB.
- Of the 1,086 with two sputum-negative results, 250 had an abnormal chest x-ray, of whom 83 (33%) had TB.
- Of the 836 with normal chest x-rays, 558 had a CD4 count < 350 cells/mm3. Of these, 55 (10%) had TB.
- Of the 278 with a CD4 count ≥ 350 cells/mm3, 13 (5%) had TB.
- A total of 808 culture tests would need to be done (comprised of the 250 patients with abnormal chest x-rays and the 558 patients with CD4 counts below 350 cells/mm3)

Using this algorithm, the number of false negative results in the screening and diagnostic steps combined was 31, far fewer than the WHO methodology. The authors also compared their combined screening/diagnostic algorithm to one in which all patients underwent chest x-rays and microscopy of two sputum smears, without symptom screening or culture confirmation. This method would have yielded 75 false negatives; ie patients who had tuberculosis but nevertheless had normal x-rays and two negative smears.

The study also found that patients who had false negative results with the screening/diagnostic algorithm tended to have higher CD4+ cell counts than patients who had false negative results with the other two approaches.

The authors conclude by recommending validation of the algorithm in Africa and other parts of the world. They also argue that policy changes should be considered based on their findings.

COMMENT

This excellent paper is the most detailed analysis of how to diagnose TB in HIV-positive antiretroviral-naive patients, a critically important challenge. The sample size is large and the methodology sound. Furthermore, although the cohort is Asian, the high rate of TB in this cohort means it has some applicability to southern African settings. However, the authors are right that validation of the algorithm is needed. This study could and should be carried out in southern Africa.

Even for well-resourced settings, this study is important. It takes a few weeks for the gold-standard TB diagnostic, a liquid medium culture test, to return a result. In the meanwhile clinicians need to decide whether or not to commence treatment or isoniazid preventative therapy.

However, the study also shows how costly, slow and difficult TB diagnosis is. Even the authors' algorithm, albeit an improvement on the WHO's current one, has a large number of false negatives (cf HIV testing). It is also more expensive to carry out than the WHO one. Many health facilities do not have the resources to carry out the diagnostic part of the algorithm, which involves far more sputum smears and chest x-rays than the WHO one. Indeed, the shortcomings of all current TB screening and diagnostic algorithms makes it difficult to implement isoniazid preventative therapy in many health facilities.

The findings of this study remind us again of the need for faster, cheaper and more sensitive and specific TB diagnostics.

Ref: Cain K et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. NEJM 362;8 February 25, 2010.

http://content.nejm.org/cgi/content/full/362/8/707

Analysis of the emergence of drug resistant TB in a South African mine

Nathan Geffen, TAC

A prospective study of workers with TB in a South African gold mine that was published in Emerging Infectious Diseases provides useful data on the emergence of drug resistant TB. Calver and colleagues found that drug resistant TB was developing in this setting despite stringent treatment adherence. Much of this resistance was probably nosocomial, but also occurred in the work and living environments. The authors found that diagnosis delay and inappropriate therapy facilitated disease transmission and drug resistance. [1]

An over two-fold increase in drug-resistant TB cases at the mine was noted in 2003. The study was carried out at the mine from January 2003 to November 2005. Mine employees as well as any of their dependents who were diagnosed during the study period with drug-resistant TB were included in the study. The researchers found that 3,003 patients were diagnosed and notified with TB. Of these, 1,443 (48%) had new pulmonary TB cases, 755 (25%) were retreated for pulmonary TB and 805 (27%) patients had extrapulmonary TB.

Patients were identified either via an active screening programming that included biannual chest radiographic screening (30%) or because they sought care because they had TB symptoms (70%). The cure rate was high, 87%, and 12% of patients died. The remainder (less than 2%) defaulted or had an unsuccessful treatment outcome. Adherence was high, in the region of 95 to 98%.

Drug resistance

Drug-resistant TB was diagnosed in 128 mine workers, of whom 124 were male. All had worked at the mine for at least 6 months (median 15 years) and had passed a pre-employment physical examination that ruled out active TB. Of these 13 (10.2%) had isoniazid-resistance, 7 (5.6%) had poly–drug-resistant TB and 108 (84.4%) had MDR TB. Among patients with MDR TB, 26 had pre-XDR TB (ie resistance to either ofloxacin or kanamycin but not both) and 5 had XDR TB. HIV status was know for 91 drug-resistant patients, of whom 84 were HIV-positive and 7 were HIV-negative. 57 patients, including three with unknown HIV status, had CD4 counts below 200 cells/mm3. Most patients, 95 (74%) were smear-positive. This was 70% for HIV-positive patients, approximately consistent with other findings of 65%. Seven patients started ART before TB diagnosis and 22 after. Median time to initiation for the latter was 172 days (range 41 to 1,425 days).

Outcomes for drug-resistant patients were poor: 40 completed treatment or were cured; one patient failed treatment; 45 died; 32 were transferred out and 10 were lost to follow up. Median time to death was 5 months (range 1-24 months).

Clustering of drug-resistant isolates

The researchers conducted genetic clustering analysis of the drug-resistant TB isolates to try to determine patterns of infection. They analysed isolates from 124 of the 128 patients. Of these, 74 were clustered into 11 clusters ranging in size from 2 to 42. At least 63 isolates had primary drug resistance. Among the 50 unclustered isolates, 25 were from first-time TB patients at this facility, also suggesting primary infection. Clustering was more frequent amongst MDR than mono or poly-resistant TB strains (adjusted OR 14.13, p = 0.002 – unadjusted rate was almost identical). The same was true for XDR isolates compared to mono and poly-resistant ones (unadjusted OR 27.42, p<0.001). The pre-XDR and XDR isolates were strongly clustered with the MDR ones (24 of the 30 isolates were in MDR clusters). 59% of clustered patients had a previously documented TB episode.

The researchers analysed the types of contacts patients in the largest cluster had. They found most patients had multiple different contacts that put them at risk: 32 of the 42 had a non–MDR TB hospitalization at the same time another patient in the cluster was admitted for MDR TB, 39 worked in a shaft in which another MDR TB patient in the cluster had worked and 36 resided in the same residential unit where another MDR TB patient had lived.

Phylogenetic analysis indicated that resistant pyraziamide resistance occurred on two separate occasions. Then ethambutol resistance evolved independently. Ofloxacin resistance later evolved on six separate occasions, of which one of these isolates evolved into XDR causing disease in a single patient. The authors state that the "evolution of resistance to ethambutol and pyrazinamide represents the further amplification of drug resistance in the context of patients with undiagnosed MDR TB initially being given standard therapy". They further explain that, "an MDR TB case-patient with a strain resistant to isoniazid, rifampin, ethambutol, and pyrazinamide could then spread disease to persons who were cohospitalised for drug-susceptible TB or illnesses other than TB. Disease may develop in these persons, and they can then spread MDR TB to their contacts at their place of work or residence, thereby unintentionally perpetuating the drug- resistant TB outbreak. We believe that this observation is not unique to this setting."

The authors claim that although the mine's TB control programme was effective at preventing acquisition of resistance to first-line drugs, it was unable to prevent transmission of pre-existing MDR TB. Their study also confirms other findings that a prior TB episode increases the risk of a later episode through reinfection.

The authors concluded with several recommendations: integration of DOTS and HIV management programmes to ensure wider ARV availability, public awareness raising of TB symptoms to encourage earlier diagnosis, active screening of all patients making contact with the public health system, aggressive case finding, more frequent sputum smear examinations, more frequent culture-based diagnoses to identify cases before they become infectious, development and implementation of rapid drug susceptibility testing diagnostics, studies to optimise drug regimens and dosages and more rigorous control measures in health facilities to reduce nosocomial transmission.

COMMENT

This excellent study provides data that can be used for better modelling the development and spread of drug-resistant TB, at least within high-risk mine settings. Two other studies in community

settings referenced by the authors are worth noting. In a 1999 study by van Rie and colleagues they used genetic analysis to determine that two patients treated for drug-susceptible TB contracted MDR TB outside hospital, leading the researchers on that study to state that transmission of MDR TB is not limited to HIV-positive patients in institutional settings. [2] More recently, a 2007 study by Victor and colleagues found a cluster of 64 patients --out of 450 with drug-resistant TB-- that shared a rare mutation, indicating the spread of this drug-resistant strain within the cluster. They concluded that factors leading to the "development and spread of this drug-resistant genotype were inappropriate chemotherapy, poor adherence to treatment and prolonged periods of infectiousness due to delays in susceptibility testing." [3]

The conclusions and recommendations of Calver and colleagues must be supported. In particular, that 12 patients with drug-resistant TB died while receiving first-line therapy indicates the need for investigating how to optimise the process of diagnosing drug-resistant TB, including analysis of the National Health Laboratory Service's systems. Methods to reduce delays in health-seeking behaviour by people with symptoms of TB also need investigation. To implement all of Calver and colleagues' recommendations will require a massive investment of state, corporate and donor funds into TB. This is clearly necessary.

The authors also state that the "incidence of drug-susceptible TB has continued to rise, an increase that reflects both the rising HIV prevalence in this community and the occupational risks specific to the mine setting such as silicosis, congregate living, and working conditions." Pressure should be put on mining companies both by unions, civil society organisations and government to address these unacceptable living and working conditions in order to reduce the spread of TB, especially drug-resistant strains.

Much of the Department of Health's messaging aimed at promoting the reduction of drug-resistant TB emphasises patient adherence. This study adds to the body of evidence showing that this is only one part of the problems. Despite excellent adherence, drug-resistant TB continued to emerge because of poor technology and sub-optimal systems as well as working and living conditions conducive to the spread of TB.

References

1. Calver et al. 2010. Emergence of increased resistance and extensively drug-resistant tuberculosis despite treatment adherence, South Africa. Emerging Infectious Diseases Vol. 16, No. 2, February 2010.
http://www.cdc.gov/eid/content/16/2/264.htm
2. Van Rie A et al. Transmission of a multidrug-resistant Mycobacterium tuberculosis strain resembling "strain W" among noninstitutionalized, human immunodeficiency virus-seronegative patients. J Infect Dis. 1999;180:1608–15. DOI: 10.1086/315054
http://www.jstor.org/pss/30110459
3. Victor TC et al. Spread of an emerging Mycobacterium tuberculosis drug-resistant strain in the western Cape of South Africa. Int J Tuberc Lung Dis. 2007;11:195–201.
http://www.ncbi.nlm.nih.gov/pubmed/17263291

Systematic review of rifamycin studies shows eight months might be beneficial

Nathan Geffen, TAC

Khan and colleagues published a systematic review and meta-analysis in Clinical Infectious Diseases that evaluated the impact of three factors on failure, relapse and death during treatment of TB/HIV co-infected people. These were duration of rifampicin or rifabutin treatment, (2) daily versus intermittent dosing and (3) ART during TB treatment. [1]

Out of 5,128 titles identified by a literature search, 30 articles were ultimately included in the review. These described 26 studies, of which only six were randomised trials. All reported failure and death during TB treatment and 17 reported relapse rates. Only one study examined rifabutin, so the authors considered all rifamycins together.

The authors compared the findings of three trials with internal head-to-head comparisons of rifamycin treatment strategies, but pooling the results was impossible because all three used different durations of rifampicin treatment. In one of the trials, relapse and failure were similar in patients receiving 6- versus 9-month regimens. In another relapse rates were significantly lower after 12 months of rifampicin versus 6 months. In the third, patients who received rifampicin for 6 months of an eight month regimen had lower failure and relapse rates than those receiving it for only two months of an eight month regimen.

A pooled analysis of all 27 studies found that longer duration of rifamycin (≥ 8 months v 6 months v 2 months) was associated with less failure (1.9% v 2.6% v 2.9%), less relapse (3.3% v 9.8% v 10.8%) and less death during treatment (11.7 v 10.5 v 16.6), but the confidence intervals are very wide on all of these data and none reached significance because there were too few studies with too few participants. There were approximately 2,500 subjects in the studies that considered treatment failure, 1,300 in the studies that considered relapse and 3,000 in the studies that considered death during treatment.

However, in an analysis adjusted for a range of potentially confounding factors, rates of relapse and death were significantly higher among patients who received rifamycin for only two months compared to patients who received it for at least 8 months (relapse RR for two month rifamycin: 3.6 95%CI 1.1-11.7; death RR: 1.8 95%CI 1.0-3.1).

In studies where some patients were on ART during TB treatment there were significantly lower rates of failure (3.2% [95%CI 2.0-4.5] v 0.8% [95%CI 0-1.8]) and relapse (15.5% [95%CI 4.5-25.5] v 0.5% [95%CI 0-1.7]). But after adjustment this was non-significant.

Daily treatment was non-significantly better than three times weekly. However in adjusted analysis it resulted in significantly better relapse and failure rates during the intensive (or initial) phase of treatment (failure RR of intermittent treatment: 4.0 95%CI 1.5-10.4; relapse RR: 4.8 95%CI 1.8-12.8).

The authors describe several limitations of their analysis: there was only one randomised trial that assessed the schedule of treatment administration and only three trials that compared rifamycin duration. Because the pooled analysis mainly used observational data it was subject to confounding and selection bias. There was substantial variability in settings, patient characteristics, interventions and outcomes assessed.

COMMENT

This study suggests the need for a clinical trial to determine the optimal duration of rifamycin during TB treatment. It also underscores the lack of compelling data on how to optimise TB treatment, contrasted with the large number of trials that have been done on ART. As the authors say, "the most important and striking finding of this review is the paucity of well-designed and adequately powered randomised trials of HIV-TB co-infection treatment."

Reference

Khan F et al. 2010. Clin Infect Dis 2010:50 (1 May)

GUIDELINES

South African antiretroviral treatment guidelines updated

Polly Clayden, HIV i-Base

The South African Antiretroviral Treatment guidelines have finally been updated. [1]

These have been long-awaited as the last full edition was in 2004.

Important revisions include the use of tenofovir (TDF) in first line treatment (replacing d4T), more complex prophylaxis regimens and earlier treatment for pregnant women and universal treatment for infants <12 months of age.

The treatment guidelines are also summarised in an abridged version with a series of tables incorporating key recommendations from all three documents.

Management of adults and adolescents

When to start?

Antiretrovirals should be started in all HIV-positive patients with CD4 ≤200 cells/mm3 irrespective of clinical stage.

People with TB/HIV and pregnant women should start antiretroviral treatment at CD4 ≤350 cells/mm3. People with WHO stage 4 or DR TB should start treatment irrespective of their CD4 count.

What to start?

The recommended first line regimens for all new patients are:

- TDF+3TC or FTC+EFV
- TDF+3TC or FTC+NVP

Already receiving d4T-based regimen

If d4T is well tolerated patients should remain on this regimen. An early switch is recommended for any toxicity. People at high risk for toxicity (high BMI, low Hb, older female) should switch d4T for TDF.

Fast track

Pregnant women indicated for treatment, people with very low CD4 (<100 cells/mm3) and stage 4 with CD4 count not yet available and those with MDR/XDR TB, should be fast tracked ie start ART within two weeks of being eligible.

When to switch

Virlogical failure (>1000 copies/mL) over 3 months despite adherence interventions.

Second-line ART

Failing on d4T-based regimen:

- TDF+3TC or FTC +LPV/r

Failing on a TDF-based regimen:

- AZT+3TC+LPV/r

Third-line ART

Specialist referral where possible, but maintain on a failing regimen.

COMMENT

That these guidelines did not adopt <350 cells/mm3 as the threshold for starting treatment for all, in line with the WHO, the Southern African Clinicians Society and many national guidelines, has raised much discussion. [2] Arguably this consideration may be largely academic in a country where the median CD4 count at initiation is still about 100 cells/mm3 despite a massive scaling up of testing. [3]

However, now that the SA Ministry of Health is about to launch a campaign to test 15 million people by June next year, this situation is likely to change. Earlier treatment for select groups and fast track for those most at risk however are very welcome.

An important change is the replacement of d4T with TDF for first-line regimens. As well as following guidance to avoid the more dramatic effects of lactic acidosis, hopefully "well tolerated" and "early switch" will be interpreted in the very best interests of patients who have endured peripheral neuropathy or lipoatrophy associated with this drug. Equally dropping ddI from second-line regimens, though not affecting such large numbers of people, is a vast improvement.

Prevention of mother to child transmission

These guidelines make recommendations for pregnant women both eligible and ineligible for treatment and for infant feeding.

When to start?

As above, CD4 <350 cells/mm3.

What to start?

TDF+3TC or FTC +NVP

Women already receiving ART should substitute EFV with NVP if in first 12 weeks of pregnancy. Women contraindicated to TDF should receive AZT+3TC+NVP.

Prophylaxis for women CD4 >350 cells/mm3

AZT from 14 weeks + single dose NVP + AZT three hourly during labour; TDF+FTC single dose post delivery.

Infant regimens

Breast fed or formula fed infants of mothers on HAART: NVP at birth and daily for 6 weeks.

Breast fed or formula fed infants of mothers receiving prophylaxis: NVP at birth and daily for 6 weeks if formula fed or until cessation of breast feeding.

COMMENT

Guidance for pregnant women is broadly similar to WHO recommendations. However, the approach to use of efavirenz is far more cautious. Whereas the WHO interpreted the low quality, conflicting evidence for the risks of in utero exposure to confine the contraindication to the first trimester, these guidelines do not recommend its inclusion at all in pregnancy. From an operational point of view this will make treatment of pregnant women a bit more complicated and inconsistent with general adult recommendations. Efavirenz has a number advantages where simplification is important, it can be taken once daily in a fixed dose combination with TDF and FTC, unlike nevirapine there is no extra monitoring for rash and/or hepatoxicity risk and it can be used in conjunction with TB treatment.

The choice of a single dose of TDF/FTC "tail" coverage is an interesting one, whereas the WHO recommend 7 days of 3TC/AZT and this has been adopted by several national programmes, some have suggested that this may be too complicated to implement.

Chi et al showed a reduction in resistance using a single dose of TDF/FTC from approx 30% to 14% among women with CD4 cell counts of about 475 cells/mm3 receiving single dose nevirapine (women with CD4 <200 cells/mm3 were excluded and received HAART), of which approximately 80% received antepartum AZT for a median of about 37 days, and 30% had undetectable viral load at delivery. [4]

It is likely that a treatment threshold of <350 CD4 cells/mm3 will further exclude women most at risk for NNRTI resistance and this approach may offer a reasonable compromise between reduction of resistance risk and ease of implementation.

Management of HIV in children

When to start?

- Universal treatment for infants <12 months old.
- Clinical stage 3 or 4 or CD4 ≤25% or absolute CD4 <750 cells/mm3 for children age 1-5 years.
- Clinical stage 3 or 4 or CD4 ≤ 350 cells/mm3 for children ≥5 years to 15 years.

What to start?

- Infants and children <3 years old: ABC+3TC+LPV/r.
- Children >3 years old: ABC+3TC+EFV.

Second line

Children >3 years old failing ABC+3TC+EFV: AZT+ddI+LPV/r

Children >3 years old failing an AZT- or ddI-based regimen: ABC+3TC+LPV

Children failing a LPV/r-based regimen and/or <3 years old who are failing first-line require specialist referral.

COMMENT

Universal treatment for infants <12 months old and initiation at CD4 350 cells/mm3 for children >5 years old reflects current international consensus. Treatment for children between 1 and 5 years has little data to guide us, and WHO and national guidelines all give slightly different recommendations.

The threshold for initiation for children and adolescents between 5 and 15 years old is 350 cells/mm3 for all differs from adult recommendations, where a considerable number of people will not be eligible for treatment until CD4 drops to 200 cells/mm3.

References

1. SA Dept of Health. The South African Antiretroviral Treatment Guidelines, 2010. http://www.sanac.org.za/resources/art-guidelines
2. WHO. New HIV recommendations to improve health, reduce infections and save lives. (01 December 2009). http://www.who.int/mediacentre/news/releases/2009/world_aids_20091130/en/index.html
3. Geffen N. Guidelines on when to start treatment in resource poor settings. HTB, October 2009. http://i-base.info/htb-south/190

4. Chi BH et al. Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. Lancet. 2007 Nov 17;370(9600):1698-705. Epub 2007 November.
http://www.ncbi.nlm.nih.gov/pubmed/17997151

BHIVA draft guidelines for the treatment of opportunistic infections: online for comment

The 2010 British HIV Association guidelines for the treatment of opportunistic infection in HIV-positive individuals are now posted to the BHIVA website for comment.

Advances in the treatment of HIV infection with antiretroviral therapy have led to dramatic reductions in opportunistic infections and death. However, late presentation of HIV remains a problem and is a significant contributory cause to death in HIV-positive persons in the UK. Furthermore, a recent UK Health Protection Agency (HPA) analysis showed that of 46,700 patients with diagnosed HIV, 19% had CD4 counts <200 cells/mm3 and therefore remain at significant risk of opportunistic infection.

These guidelines have been drawn up to help physicians investigate and manage HIV-positive patients suspected of, or having an opportunistic infection (OI). The early chapters consider the most common presentations of OI disease such as respiratory, gastrointestinal and neurological disease. Then follow specific organisms such as Candida spp, herpes simplex virus and varicella zoster virus. Finally, special circumstances including pregnancy, the use of the intensive care unit, fever of undetermined origin and management of imported infections, are also addressed.

Each section contains information on the background, epidemiology, presentation, treatment and prophylaxis of OIs. Further information on the role of antiretroviral therapy is also discussed (see below).

The Guidelines Writing Group is grateful for all comments, which will be reviewed before publication.

http://www.bhiva.org

WHO TB guidelines

The 4th edition of the WHO guidelines includes 6 months of rifampicin in the initial phase of treatment as opposed to just 2 months. Wherever feasible, daily dosing is recommended throughout the course of therapy.

Other recommendations include provider initiated TB testing, and drug susceptibility testing (DST) for all previously treated TB patients at or before the start of treatment.

All HIV-positive patients with active TB should receive antiretrovirals.

World Health Organisation. Treatment of tuberculosis guidelines. Forth edition:

http://www.who.int/tb/publications/tb_treatmentguidelines/en/index.html

BASIC SCIENCE

Early predictors of disease progression

Richard Jefferys, TAG

Recent research involving SIV-infected macaques has suggested that the early loss of a particular type of memory CD4 T cell (known as a "central memory" T cell or Tcm) may be a key predictor of the subsequent pace of disease progression. Tcm are a long-lived subset of memory T cells that can proliferate robustly in response to antigen. Tcm proliferation generates a fleet of T cells belonging to a shorter-lived subset called "effector memory" (Tem) cells. Tem are generally viewed as first-responders that can rapidly execute anti-pathogen functions, while Tcm provide a stem-cell like renewal source for new Tem if their numbers need to be bolstered. Studies in HIV-infected people have consistently shown a loss of Tcm and increase in Tem (which equates to a decrease in long-lived resting T cells and an increase in short-lived activated T cells), but whether changes in the numbers of different T cell subsets during early infection can predict disease progression has not been thoroughly evaluated.

A new study published in the Journal of Infectious Diseases set out to answer the question of whether quantifying Tcm in early infection provides prognostic information. To provide sufficient statistical power to ensure confidence in the findings, a total of 466 individuals were studied, among whom 101 progression events occurred.

It turned out that the proportion or absolute number of Tcm did not correlate with subsequent disease progression (defined as the time to AIDS or death), but several other parameters did. These included the proportion of naïve CD8 T cells, with a greater proportion being strongly associated with slower disease progression ($p<0.001$); this correlation remained significant after adjustment for CD4 T cell count. The numbers of CD8 T cells expressing the IL-7 receptor (CD127) were also linked to the rate of progression; having fewer of these cells correlated with a faster disease course.

Immune activation was assessed by measuring the proportion of CD4 and CD8 T cells expressing the proliferation marker Ki67. In both subsets, higher proportions of Ki67-expressing cells equated to faster progression, and for CD8 T cells this relationship held up after adjustment for baseline CD4 T cell count, age, and viral load. The median time to AIDS or death among subjects with the highest levels of Ki67-expressing CD8 T cells (based on dividing participants into quartiles) was 4 years for those in the top quartile compared to 10 years for those in the lowest.

Finally, measures of cell-associated viral load (CAVL: the proportion of CD4 T cells containing HIV DNA) were correlated significantly with progression in those participants sampled within 225 days of their estimated date of seroconversion (225 days was the median time after the estimated date of seroconversion that samples were obtained). Among participants sampled later, CAVL was not significantly correlated with rate of progression, suggesting an important impact of the early spread of HIV among CD4 T cells on subsequent disease course. The researchers also evaluated CAVL in different CD4 T cell subsets: naïve, central memory, transitional memory and effector memory. To their surprise, naïve CD4 T cells showed relatively high rates of infection, albeit around 10-fold lower than the memory subsets.

Because resting naïve CD4 T cells are known to be very resistant to HIV, the researchers speculate that the infected naïve cells may have been rendered susceptible by immune activation (naïve CD4 T cells have been shown to become susceptible to R5-using HIV after they receive activation signals).

The authors conclude by stating: "we find that quantification of Tcm cells in early infection does not provide predictive power for progression. However, measures of homeostasis and activation, including CD127 expression and Ki-67, do provide such information and should be studied further to determine their role in clinical monitoring of HIV-1 progression…Future efforts to identify markers of subsequent progression should focus on measures of activation and homeostasis during the earliest stages of infection."

Source: TAG Basic Science Blog. (13 Jan 2010).

Ref: Ganesa A et al. Immunologic and virologic events in early HIV infection predict subsequent rate of progression. J Infect Dis 2010;201:272–284. doi: 10.1086/649430.

http://www.journals.uchicago.edu/doi/abs/10.1086/649430

Sex and the single microbicide

Richard Jefferys, TAG

The levels and distribution of an anti-HIV microbicide in the genital tract are likely to be critical factors in determining potential efficacy. Up until now, research studies have typically assessed microbicide levels in sexually abstinent women, which neglects to consider the potential impact of sexual activity. A new study in PLoS One looks at whether the physical act of sex and the introduction of semen into the genital tract affects the microbcide candidate 0.5% PRO 2000 gel. The study was conducted and completed before the recent announcement that 0.5% PRO 2000 gel had failed to show efficacy in preventing HIV infection in a large randomized clinical trial.

The results showed that 0.5% PRO 2000 gel levels were significantly lower after sex, and this correlated with a reduced ability of cervicovaginal lavage (CVL) from gel-treated women to inhibit HIV and HSV-2 in vitro. It was noted, however, that lower gel concentrations did not fully explain the reduction in antiretroviral activity; additional experiments revealed that seminal plasma also had an independent effect.

The researchers acknowledge that their study has limitations, including a small sample size and a single-dose approach that may underestimate microbicide levels compared to repeat dosing. Nevertheless, they suggest that "the current paradigm of microbicide development should be modified to include postcoital sampling following single and repeated dosing with both active and placebo products and should be expanded to include both CVL and biopsies to more fully define the pharmacokinetics and pharmacodynamics of lead candidates prior to embarking on large-scale efficacy trials."

Source: TAG Basic Science Blog. (29 Jan 2010).

Ref: Keller MJ et al. Postcoital bioavailability and antiviral activity of 0.5% PRO 2000 gel: implications for future microbicide clinical trials. PLoS ONE 5(1): e8781. doi:10.1371/journal.pone.0008781.

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0008781

Baseline naïve CD4 T cell numbers predict the immunological response to ART

Richard Jefferys, TAG

The loss of naïveté that comes with getting older is familiar to just about everyone. Somewhat less familiar is the fact that this is also true immunologically; our repertoire of naïve T cells and B cells – vital to responding to pathogens that have not previously been encountered, and keeping up with evolving chronic infections – steadily diminishes. For T cells, the loss is associated with declining output from the thymus, which also shrinks in size over time. It has been appreciated for many years that chronic infections can accelerate the pace of naïve T cell decline, but the effects of HIV far exceed those of any other chronic virus; progression to AIDS is typically associated with an almost complete loss of naïve CD4 and CD8 T cells.

Recent studies of long-term immune reconstitution on antiretroviral therapy (ART) have identified the ratio of naïve T cells to memory T cells as an important factor predicting the extent of CD4 T cell repopulation after 7+ years of treatment. [1]

A study from Timothy Schacker at the University of Minnesota now addresses the question of whether baseline measures of naïve CD4 T cell numbers can predict the potential for immune reconstitution on ART. [2]

The results of an analysis of 348 participants in AIDS Clinical Trials Group (ACTG) trials show that, indeed, baseline naive but not total CD4 T cell counts strongly predicted the magnitude of CD4 T cell increases after ART initiation. Lower naïve CD4 T cell levels at baseline were also associated with greater time spent with low CD4 T cell counts on ART, which is known to be associated with a greater risk of clinical events. The study findings suggest that measurements of naïve CD4 T cells could help optimize timing of ART initiation and lessen the incidence of poor immune reconstitution despite HIV suppression.

Source: TAG Basic Science Blog (01 March 2010)

References:

1. Immune recovery on antiretroviral therapy. TAG Basic Science Blog (04 February 2009).
2. Schacker TW et al. Measurement of naive CD4 cells reliably predicts potential for immune reconstitution in HIV. J Acquir Immune Defic Syndr. 2010 Feb 24. [Epub ahead of print]

http://journals.lww.com/jaids/Abstract/publishahead/Measurement_of_Naive_CD4_Cells_Reliably_Predicts.99039.aspx

Has poor CD4 T cell reconstitution in the gut been exaggerated?

Richard Jefferys, TAG

In recent years, loss of CD4 T cells from the gut of HIV-positive people has become a major research focus. Gut CD4 T cell depletion happens rapidly after infection, and many studies have suggested that recovery of these cells is typically limited even after prolonged antiretroviral therapy (ART). However, the bleakest data has been obtained by measuring the percentage of CD4 T cells in the gut relative to other lymphocytes, and this can produce misleading results because CD8 T cell numbers are increased in the setting of HIV infection.

A new paper from Irini Sereti's laboratory at NIAID reports that the picture is far more encouraging when absolute numbers of CD4 T cells are measured. Taking samples from both the colon and terminal ileum, the researchers show that absolute CD4 T cell numbers among people on long-term (>5 years) ART with viral loads less than 50 copies are comparable to uninfected

controls. The numbers are expressed as CD4 T cells per gram of tissue and the results for the ART-treated vs. control group were as follows: $3.9x10^6$ vs. $3.6x10^6$ (colon) and $1.0x10^6$ vs. $1.6x10^6$ (terminal ileum). The researchers note that in some prior papers, "the persistence of a high proportion of CD8 T cells in HIV-infected patients appeared to result in an underestimation of CD4 T cell reconstitution…our findings are in agreement with recent studies using both immunohistochemistry and flow cytometric analyses; some of these have suggested that gut CD4 T-cell reconstitution may even exceed what occurs in peripheral blood."

The researchers also write: "It has also been proposed that initiating ART therapy during acute infection may result in more rapid and complete reconstitution of the CD4 T-cell population in the gut. Three of the four patients in this study who reconstituted their CD4 T-cell counts in the colon to values higher than the median of the HIV-uninfected group had peripheral nadir CD4+ T-cell counts of less than 250 cells per microliter. This suggests that CD4 T-cell restoration may occur despite substantial disease progression before ART initiation."

Source: TAG basic science blog. Have Rumors of Poor Gut CD4 T Cell Reconstitution Been Greatly Exaggerated? (24 March 2010).

Ref: Ciccone EJ et al. Cycling of gut mucosal CD4+ T cells decreases after prolonged anti-retroviral therapy and is associated with plasma LPS levels. Mucosal Immunology (2010) 3, 172–181; doi:10.1038/mi.2009.129; published online 2 December 2009
http://www.nature.com/mi/journal/v3/n2/abs/mi2009129a.html

ON THE WEB

PLoS Medicine

http://www.plosmedicine.org

Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study - Myer L et al.

A multicountry cohort study in sub-Saharan Africa by Landon Myer and colleagues reveals higher pregnancy rates in HIV-infected women on antiretroviral therapy (ART).

Pretreatment CD4 cell slope and progression to AIDS or death in HIV-infected patients initiating Antiretroviral Therapy—The CASCADE Collaboration: A Collaboration of 23 Cohort Studies - Wolbers M et al.

Analysing data from several thousand cohort study participants, Marcel Wolbers and colleagues find that the rate of CD4 T cell decline is not useful in deciding when to start HIV treatment.

Effectiveness of Non-nucleoside Reverse-Transcriptase Inhibitor-Based Antiretroviral Therapy in Women Previously Exposed to a Single Intrapartum Dose of Nevirapine: A Multi-country, Prospective Cohort Study - Stringer JAS et al.

In a comparative cohort study, Jeffrey Stringer and colleagues investigate the risk of ART failure in women who received single-dose nevirapine for PMTCT, and assess the duration of increased risk.

Causes of Acute Hospitalization in Adolescence: Burden and Spectrum of HIV-Related Morbidity in a Country with an Early-Onset and Severe HIV Epidemic: A Prospective Survey - Ferrand RA et al.

Rashida Ferrand and colleagues show that HIV infection is the commonest cause of hospitalisation among adolescents in a high HIV prevalence setting.

FUTURE MEETINGS

2010 conference listing

The following listing covers some of the most important upcoming HIV-related meetings and workshops.

Registration details, including for community and community press are included on the relevant websites.

6th Intl Workshop on HIV and Hepatitis C Coinfection

31 May–2June 2010, Tel Aviv

http://www.virology-education.com

5th International Workshop on Clinical Pharmacology of Hepatitis Therapy *and* 5th International Workshop on Hepatitis C - Resistance and New Compounds

23–24 June and 24–25 2010, Boston

http://www.virology-education.com

5th International Workshop on HIV Transmission - Principles of Intervention

15-16 July 2010, Vienna

http://www.virology-education.com

2nd International Workshop on HIV Pediatrics

16-17 July 2010, Vienna

http://www.virology-education.com

XVIII International AIDS Conference (AIDS 2010)

18-23 July 2010, Vienna

http://www.aids2010.org

50th ICAAC

12–15 September 2010, Boston

http://www.icaac.org

3rd Intl Workshop on Clinical PK of TB Drugs

11 September 2010, Boston

http://www.virology-education.com

BHIVA Autumn Conference

7–8 October 2010, London

http://www.bhiva.org

3rd Botswana International HIV Conference

13-16 October 2010, Gaborone

http://www.botshiv.org.bw

12th Lipodystophy Workshop

4–6 November 2010, London

http://www.intmedpress.com/lipodystrophy

10th International Congress on Drug Therapy in HIV Infection

7-11 November 2010, Glasgow

http://www.hiv10.com

HIV i-BASE

HIV i-Base is an HIV-positive led treatment information service. We produce information both for clinicians and other health workers and for people with HIV.

Our publications are used and have been adapted in many countries and settings.

Our fully searchable website is designed to be fast to access, easy to use, and simple to navigate.

All i-Base publications are available online.

http://www.i-base.info

i-Base produce five non-technical treatment guides, which are available online as web pages and PDF files.

http://www.i-base.info/guides

- Introduction to combination therapy
- A guide to changing treatment
- Avoiding & managing side effects
- HIV, pregnancy & women's health
- Hepatitis C for People living with HIV

The site also includes a web-based Q&A section for people to ask questions about treatment:

http://www.i-base.info/questions

Recent questions include:

- Doubts when I'm told that my life expectancy is good…
- What is the prognosis if diagnosed with these symptoms?
- What is the risk of infecting my girlfriend with HIV?
- News reports of research that 'could' be a cure
- Does treatment work if you start with a low CD4 count?
- Can hepatitis B rea\ctivate?
- Does yohimbe interact with HIV meds?
- Pregnancy without viral load results
- Should I start treatment at CD4 320?
- How do I time my meds when travelling?
- Is a viral load result of 50 really a blip?
- Does skipping a dose have an immediate effect?
- Does masturbation have any effect on HIV-positive people?
- Personal results from a recent diagnosis…

We have also posted online a set of generic clinic forms, developed with the Royal Free Centre for HIV Medicine, which may be a useful resource for other hospitals.

http://www.i-base.info/clinicforms

HIV i-Base

www.i-Base.info

Southern African HIV Clinician's Society

www.sahivsoc.org

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