Notes on HIV and TB from CROI

There were many scientific studies on TB and HIV at the 16th Conference on Retroviruses and Opportunistic Infections (CROI). While the reports on TB diagnostics were bleak, there have been advances in TB treatment, particularly the use of prednisone in patients with Immune Reconstitution Syndrome related TB. There were also important scientific findings presented on how TB can be managed more effectively using existing technologies. Data on drug-resistant TB continues to be very concerning, with some studies reporting extremely high mortality rates.[1]

Integration of TB and HIV care

There is now unequivocal evidence that TB and HIV treatment must be integrated as the following studies show.

Salim Abdool Karim and his team at CAPRISA based at the University of Kwazulu-Natal conducted a randomised controlled trial that showed that initiating HAART in HIV/TB-co-infected patients, with CD4 counts <500 during TB treatment significantly improves survival. Over a three year period, 645 HIV-positive patients diagnosed with TB were given standard TB treatment and cotrimoxazole. Patients were randomised to either receive HAART while on TB treatment (integrated arm) or to defer HAART until the end of their TB treatment course (sequential arm).[2] The Drug Safety Monitoring Board (DSMB) recommended stopping the sequential arm because mortality was 55% lower in the integrated arm.[3] Clearly, the integrated strategy can only be implemented if clinics integrate TB and HIV care.(1)

A poster by **Geoffrey Fatti** and researchers with Absolute Return for Kids (ARK) showed an analysis of 109 facilities treating over 35,000 patients with TB, of which 98 facilities did not provide HAART. In the remaining 11 facilities, ARK introduced HAART. In facilities where ARK operated, TB cure rates averaged 79%, while at the non-HAART facilities, it was 71%.[4] Default rates at the former were 6% as opposed to 11% at the latter. Both results are statistically significant. The authors speculated that the reasons for this might be that "TB patients are screened for HIV and visa versa, resulting in earlier diagnosis, referral and management." They also explained that TB patients receiving HAART at ARK-supported sites "receive group education, individual counseling, adherence support tools and community adherence psychosocial support."(2)

Andrea Howard and her colleagues analysed 238 PEPFAR funded HIV sites that collectively treat 93,935 patients. They found that three key factors associated with patients being screened for TB. These were the availability of TB services, the site being located in a rural setting, a greater provider to patient ratio and a greater age of the TB screening programme. Certainly the first of these factors supports integration of TB and HIV treatment.(3)

As a corollary of the above studies, a poster by **Stephen Lawn** and researchers from the Desmond Tutu HIV Centre at the University of Cape Town showed the need for HAART programmes to screen more pro-actively for TB and to place people on HAART at higher CD4 counts to reduce the risk of TB. They examined their cohort of HAART patients and found, unsurprisingly, that TB rates were much higher at lower CD4 counts and in the first few months of HAART. Patients with CD4

1 I have put confidence intervals and other statistics in the footnotes so that it can be read by a wider audience.

2 "On average, participants in the integrated and sequential arms started ART 67 days and 261 days after starting TB treatment, respectively." (1)

3 95%CI 0.26 to 0.79; $p = 0.0049$. 5.1/100 person-years [24 deaths; n = 431] versus 11.6/100 person-years [26 deaths; n = 214]). Note the integrated arm is actually two arms, which is why n is double the size of the deferred arm. Two integration strategies are being tested and this part of the trial is ongoing.

4 This is a relative increase of 11.3% (95% CI: 9.1-13.6; $p < 0.0001$)

counts below 200 and in their first four months of HAART had a 1.7 times higher rate of TB.[5] They concluded "The excess adjusted risk of TB during early ART among those with baseline CD4 counts <200 cells/L was consistent with `unmasking' of disease missed at baseline screening. ... TB prevention would be improved by ART policies that minimized the time patients spend with CD4 cell counts below a threshold of 500 cells/L." In patients whose immune systems had recovered to CD4 counts above 500, TB rates were much lower, albeit still approximately twice the background population rate.(4)

Diagnostics

There was disappointing news on the diagnostics front. Several research groups showed that symptoms, such as coughing, differentiate poorly between patients with and without active TB. Smear tests, x-rays and PCR tests are also poor predictors of who has TB. The definitive TB culture test takes weeks to return a result (an average of 23 days according to a study conducted in Cape Town(5), but often much longer, ranging from 6 to 50 days), which is far too slow for determining if a patient should be treated. *(See footnote for simple explanation of TB diagnostics.[6])*

At a pre-conference meeting on TB, **Peter Godfrey-Fausett** and Helen Ayles of the London School of Hygiene and Tropical Medicine presented the results of TB diagnostics used in the ZAMSTAR community based prevalence studies. ZAMSTAR consists of four sites: one peri-urban and one rural in Zambia, and one medium density and one high density urban site in South Africa. This is a massive sample of 14,330 patients, both HIV-positive and HIV-negative. Alarmingly, they showed that coughing and other symptoms are a poor predictor of culture positive TB. The tables below show sensitivity and specificity percentages for various symptoms.

Sensitivity	*Total*	*SA*	*Zambia*	*HIV-ve*	*HIV+ve*
Number	14330	6297	8033	5666	2297
Any symptom	82.8	79.1	89.9	83.3	95.3
Any cough	61.7	58.8	67.1	66.7	67.4
Prolonged cough	33.5	28.4	43		
TB suspect	34.8	30.4	43	36.1	48.8
TB suspect or any 2 symptoms	67.8	64.1	74.7	69.4	79.1

Specificity	*Total*	*SA*	*Zambia*	*HIV-ve*	*HIV+ve*
Number	14330	6297	8033	5666	2297
Any symptom	37.9	42.6	34.1	35.8	29.4
Any cough	76.1	75.5	76.6	77.8	73.1
Prolonged Cough	93.4	92.2	94.2		
TB suspect	92.4	91.4	93.1	94	90.7
TB suspect or any other 2 symptoms	62.6	67.5	58.8	61	53

Tables from presentation titled *Sensitivity, specificity and predictive values of symptoms to detect tuberculosis in the ZAMSTAR community based prevalence studies* by Peter Godfrey-Faussett and Helen Ayles London School of Hygiene and Tropical Medicine, UK.

5 $p = 0.026$

6 TB is often diagnosed by taking sputum from suspected patients and applying an acid that stains the TB bacteria, thereby allowing them to be seen under a microscope. However the accuracy of this test, known as a smear test or sputum smear microscopy, is poor. It is specific (i.e. it does not usually diagnose TB in people who do not have TB), but it is not sensitive (i.e. it fails to diagnose TB in many people who have it, especially people with advanced HIV disease). A more accurate way to determine if someone has active TB is to try to see if TB in their sputum can be grown in a special culture in a laboratory. This however is very slow. Other ways to diagnose TB include the Tuberculin Skin Test, PCR tests, chest X-rays, blood tests and using clinical symptoms. All are problematic.

While using the presence of any symptom to diagnose TB is reasonably sensitive, it is very unspecific, resulting in many false positive diagnoses. However, using only a prolonged cough to screen TB is reasonably specific but highly insensitive, resulting in many cases of TB going undiagnosed.

Godfrey-Fausett considered the implications of this for Isoniozid Prophylaxis Therapy (IPT). A course of IPT reduces the risk of people with HIV getting active TB. However, in providing IPT it is preferable to not give it to people who have active TB because of the concern that they might develop resistance to isoniozid used as a monotherapy. However, because there is no accurate mechanism for diagnosing active TB other than the tardy culture test, it is difficult to determine which patients should receive IPT. Godfrey-Fausett discussed various algorithms for minimising the risk of placing someone with active TB onto IPT. He also suggested that it is not necessarily a serious problem to put someone with active TB on IPT.

Ingrid Bassett and her colleagues at McCord Hospital in Durban compared the cost of intensive TB screening for HIV-positive patients starting HAART against the World Health Organisation (WHO) standard of only doing a smear-test on patients who have had a cough for two to three weeks. The intensive TB screening procedure consisted of screening all patients regardless of cough and other symptoms of TB. This involved taking a chest x-ray, collecting a sputum sample, doing a smear test and doing a culture test. They calculated the additional costs incurred by this intervention versus what their costs would have been had they just done smear tests on patients with two to three week coughs. They found that just over 19% (159 cases) of their 824 patients tested positive for TB using a culture test. Using just a cough and smear test (i.e. the WHO recommendation) yielded very poor sensitivity and specificity (52% and 63% respectively). The most accurate predictor of culture-positive TB was to consider cough, other symptoms of TB and the chest X-ray combined, but even this was only 93% sensitive and a pathetic 15% specific. The cost per case identified using the WHO screening criteria was $240. The cost per case identified with intensive TB screening was $300. To identify all 159 cases of active TB cost an additional $360 per case. They concluded that "neither cough nor sputum smear alone were sensitive enough to serve as the trigger for screening HIV-infected patients for TB. Compared to screening based on cough, intensive screening doubles the TB cases identified with only a modest increase in the cost per case identified. Mycobacterial sputum cultures should be performed routinely in all patients prior to ART initiation in areas of high HIV/TB prevalence."(6)

Shaheen Hassim and her colleagues examined the sensitivity and specificity of PCR testing for multi-drug resistant TB. PCR testing is used to determine resistance to isoniazid and rifampicin, the two most important first-line TB drugs. Unfortunately, PCR testing's sensitivity and specificity, as with smear testing, was poor. A positive culture test matched a positive PCR result only 55.8% of the time. Specificity was better, but still poor. A negative culture test matched a negative PCR test in 88.3% of cases. This means that nearly half of TB cases are not found by the PCR test and it also incorrectly diagnoses 10% of patients as having TB when they do not.(7)

Similarly distressing results were found by **David Edwards** and his group from their cohort in a Cape Town township. They found that an "optimum screen using a combination of symptoms of cough, weight loss, fever and night sweats had a sensitivity of 78%, but specificity was very low (35%)." In other words 22% of their TB cases had no symptoms yet. They also found that Chest x-rays were normal in a third of cases. They reach the following poignant conclusion, "More than a quarter of patients had culture-positive TB. Symptom screening, sputum smears and chest radiology were poorly predictive for TB. Sputum culture was slow. New more rapid diagnostic tests are urgently needed."(5)[7]

7 The state of TB diagnostics is poor. Until it improves, it is worth considering offering, on a regular basis, a TB culture test to every patient with HIV and offering IPT to those whose culture test is negative. Smear-positive patients as well as smear-negative patients with symptoms of TB should be treated presumptively until their culture

Treatment

Matters look a little more promising for TB treatment.

Graeme Meintjes presented the results of a double-blind placebo controlled trial of prednisone for the treatment of patients who develop active TB as a consequence of Immune Reconstitution Syndrome (IRIS). This is a steroid that many clinicians have used to treat TB IRIS but this is the first clinical trial to determine its safety and efficacy. His team randomly assigned 55 patients to prednisone and 54 to placebo. The median CD4 count was 53 prior to HAART and 116 at the time they were enrolled on the trial. Average time in hospital spent by prednisone patients was shorter than those on placebo (1 versus 3)[8]. The cumulative number of hospital days of the prednisone group was 282 versus 463 days for the placebo group. There were also fewer hospital procedures in the prednisone arm (29 versus 38). Further evidence of prednisone's benefits are that during the four weeks of the study, five patients switched to open-label prednisone in the prednisone arm versus 19 in the placebo arm. Also, all six patients lost to follow-up were in the placebo arm.[9] Nine patients had potential drug-related side effects in the prednisone arm versus three in the placebo.[10] There was statistically significant symptom improvement in the prednisone arm too.[11](8)

This study showed that prednisone reduces hospitalisation and procedures. It also improved symptoms. There was no statistically significant difference in mortality (3 on prednisone versus 2 on placebo), but as Meintjes pointed out this was likely due to the exclusion of patients who were very ill from the study (they were given prednisone) and the switching of patients to open-label prednisone when their health deteriorated.

Elizbeth Corbett gave a summary of the state of TB research. She showed a slide of the TB drug development pipeline which looks more promising than a few years ago. There are six drugs in pre-clinical trial stages, two in phase one and three in phase two trials. Three existing drugs are being tested, either for new use or in higher dose, in phase III trials. The most promising new drug is TMC207. The interim results of a phase II trial comparing MDR TB treatment plus TMC207 versus MDR TB treatment plus placebo were presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy in October 2008. The study showed that the drug was safe and well-tolerated over eight weeks in patients with drug-resistant TB. 47.5% of patients in the TMC207 arm were culture-negative at the end of the eight weeks as opposed to 8.7% in the placebo arm.(9), (10)

In a pre-CROI presentation **Charles Flexner** of the Division of Pharmacology at John Hopkins University explained the pharmacology of TMC207. He concluded his talk by provocatively suggesting that it should be tested to see if it could eradicate latent TB with a single dose. Flexner's idea, albeit speculative, is exciting: a large percentage of people in Southern Africa are infected with latent TB with the potential to become active TB if their immune systems are weakened. If TMC207 worked against latent TB, this would be a major breakthrough against the disease. However, Flexner also pointed out the problem that pharmaceutical companies do not see TB drug development as a profitable endeavour. It is probable that were TMC207 an antiretroviral, it would have already been in a phase III clinical trial or even further. The slow progress on TB drug development is an example of how the current model of pharmaceutical drug development neglects diseases of the poor.

Given the promising early results of TMC207, it is worth asking if the drug should be made available to patients with drug-resistant TB on a compassionate care basis. (Though, as always, it is

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tests come back. (I would be interested in finding out what clinicians think of this, how regularly screening should take place and what the cost implications would be.)

8 $p = 0.05$

9 $p = 0.01$

10 $p = 0.07$

11 $p = 0.003$

important to be cautious about a drug whose safety and effectiveness testing is not yet complete.)

Prevention

The standard IPT regimen is 300mg of isoniazid daily for six months. A Cochrane Review has concluded that this reduces the risk of developing active TB in people with HIV, but the review also said that more research was needed to find the best regimen.(11) **Neil Martinson** and his colleagues conducted a randomised trial on 1,150 patients to determine if alternative regimens had advantages over standard IPT.

His team compared four regimens:

Regimen 1: 900mg of rifapentine plus 900 mg of isoniazid once weekly for 12 weeks
Regimen 2: 600mg of rifampicin plus 900 mg of isoniazid twice weekly for 12 weeks
Regimen 3: 300mg of isoniazid daily for the entire trial (an average of nearly 4 years for most patients on this arm)
Regimen 4: Standard IPT regimen

There were no statistically significant differences in TB incidence or death between the arms. There was a statistically significant greater number of adverse events in the continuous isoniazid arm (regimen 3). 54 patients were tested for resistance. One had rifampicin resistance (regimen 1), one had streptomycin resistance and three had MDR-TB (one in regimen 3 and and two in regimen 1). (12)

Since none of these regimens proved superior to the standard regimen, it should continue to be the TB prevention regimen of choice. However, the effectiveness of the other regimens was not inferior either and in some settings or with some patients it might make sense to use them.

Drug-resistant TB

News on drug-resistant TB in South Africa continues to be concerning.

Both as a poster and at a pre-conference meeting on TB, **Max 'O Donnell** presented data on XDR TB patients at King George V Hospital in Durban. In 2006-2007, 1,771 cases of MDR TB and 242 cases of XDR TB were referred to the hospital. O'Donnell and his team specified a six-month study period, in which they attempted to enrol 72 XDR TB patients. Four refused enrolment, six died prior to starting treatment and two had insufficient data, leaving a cohort of 60. The patients were transferred to the hospital from 26 different health facilities representing seven of the province's 11 districts. This implies that XDR TB is quite diffuse in Kwazulu-Natal. 25% of patients came from Tugela Ferry (the probable location of the original outbreak), 11% from Durban and 8% from Pietermaritzburg. 43 were HIV-positive, 12 negative and the remainder unkown. 21 were on HAART. At least 11 had never been treated previously for TB and at least 28 had never been treated for MDR TB. Three were health workers.

25 died and 6 defaulted, meaning that less than half were alive and accounted for by the end of the six month study period. Only 12 patients had converted to a negative culture. 17 were still in treatment. Interestingly, HIV disease increased the risk of death but this increase was not statistically significant, quite likely because the sample was too small to detect it.(13)

So while some treatment success was achieved, the outcomes for XDR TB remain very poor.

This was confirmed by a study from Tugela Ferry by **Neel Gandhi** and colleagues which found extremely high mortality rates in patients with MDR and XDR TB. They used the local TB register to identify drug resistant cases diagnosed from 2005 to 2007. They found 272 MDR TB cases and 382 XDR TB cases. One-year mortality was 82% and 69% for XDR and MDR cases respectively.

They noted that "40% of MDR and 54% of XDR TB cases died within the first 30 days."On a promising note, one-year mortality in MDR cases dropped from 87% in 2005 to 45% in 2007.[12] 30-day mortality also improved for MDR TB, from 57% to 32%. Unfortunately no statistically significant improvements in XDR TB occurred.(14)

Another study from Tugela Ferry by **Palav Babaria** and colleagues at Church of Scoland Hospital found alarmingly high rates of TB, including drug-resistant strains, among HIV-positive patients. They screened 263 HIV-positive patients. 52 (20%) were culture-positive for TB. Only 24 tested smear-positive, once more underlining the lack of reliability of this test in HIV-positive patients. Symptoms of TB were not a good predictor of disease, because most patients presented with coughs, night sweats, chest pains, weight loss and fever irrespective of their TB status. 13 patients had at least MDR TB (resistant to both isoniazid and rifampin), of whom 7 met the criteria for XDR TB as well.(15)

The study by Gandhi *et al.* made excellent recommendations on what is needed: a test that can diagnose MDR and XDR TB within one to two weeks, intensified case finding to identify patients at an earlier stage of disease, expansion and decentralisation of second-line TB treatment programmes, creation of integrated HAART and 2nd-line TB treatment programmes and infection control programmes in areas where TB patients congregate. The first of these, i.e. a better quicker diagnostic, is beyond the immediate control of the South African Department of Health, but the remaining recommendations are all achievable with current technologies. If we are to mitigate the effects of drug-resistant TB, the money and resources needed to implement these recommendations must be made available.

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