

HIV treatment bulletin

S O U T H

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To order copies send an email to: subscriptions@i-Base.org.uk

Editor: Polly Clayden

Contributing Editor: Simon Collins

Medical Consultants:

Dr Karen Beckerman, Albert Einstein College of Medicine. New York.

Dr Sanjay Bhagani, Royal Free Hospital, London.

Paul Blanchard, British School of Osteopathy, London.

Dr Martin Fisher, Brighton & Sussex University Hospitals.

Prof. Diana Gibb, Medical Research Council, London.

Dr Gareth Hardy, Case Western Reserve Univ. Cleveland.

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Dr Gareth Tudor-Williams, Imperial College, London.

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HIV i-Base

Fourth Floor, Thrale House

57 Great Suffolk Street, London SE1 0BB

T: +44 (0) 20 7407 8488 F: +44 (0) 20 7407 8489

<http://www.i-Base.info>

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EDITORIAL

This is the last issue of 2011. We include our final reports from IAS 2011 looking at the latest in cure research, ART and TB, and reassuring circumcision results from Orange Farm that dispel concerns about risk compensation.

We also include summaries of journal articles, focusing on pregnancy and paediatrics, a summary of the new drug resistant TB guidelines and report the stopping of the oral tenofovir arm of VOICE PrEP study.

May we take this opportunity to wish you a happy new year and happy reading.

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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Tel: + 27 (011) 341 0162

Fax: +27 (011) 341 0161

CONFERENCE REPORTS

6th IAS Conference on HIV Pathogenesis, Treatment and Prevention

17–20 July 2011, Rome

Introduction

This issue of HTB South includes further reports from IAS 2011.

The conference has an open-access searchable abstract database online.

<http://www.ias2011.org/>

The 'Programme at a glance' can be searched for key words but requires a free software upgrade Silverlight which is quick and easy to do. Then from this page you can search abstracts or presentations.

<http://pag.ias2011.org/>

Sessions with PowerPoint slides or webcasts have relevant icons next to them. As with previous years, the PowerPoint links on the left under the session time are not active, so to download PowerPoint files scroll down to the bottom of the session page.

Reports in this issue of HTB include:

- Cure research and viral reservoirs
- Orange Farm circumcision results dispel concerns about risk compensation
- Randomised trial of ART in TB patients with high CD4 counts

Unless stated otherwise, all references are the Programme and Abstracts of the 16th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 17–20 July 2011, Rome.

6th IAS: CURE RESEARCH

Cure research and viral reservoirs

Simon Collins, HIV i-Base

In addition to the prevention studies and the progress on pipeline drugs that made most headlines (see the previous issue of HTB), a third set of presentations through the meeting supported the IAS Conference Statement on the need for the cure. [1]

That 'the Cure' might again be seen as an achievable goal for research was resuscitated in keynote lectures from NIAID lead Anthony Fauci several years ago and several medical networks, including the IAS, already hold annual meetings to coordinate different approaches. US public funding now requires cure research as a key work stream for HIV treatment networks.

Whilst the scientific challenge of curing HIV has been the consistent focus for many committed researchers, the renewed level of funding is clearly driven by the financial challenge of providing lifelong global treatment. Even when the generic costs are reduced to less than \$100 per person per year, current treatment programmes need to more than double and then be sustained for coverage to meet the existing need. Perhaps increasing

the resources for cure research is therefore perhaps also the most ethical way to be able to withdraw from responsibility for funding global treatment.

However, these sessions in Rome were mostly held in the smaller rooms, filled to capacity. They were also frustratingly insular with few being available as webcasts or slides to download, including the plenary session by IAS President Elect, Françoise Barré-Sinoussi. [2]

Neither the IAS pre-conference workshop (New concepts in HIV Immunopathogenesis, Treatment and Vaccine Strategies) nor the rapid summary report from that workshop in the main IAS conference by Nicolas Chomont was webcast. However, slides are available from some of the workshop sessions and for the summary by Chomont. [3, 4]

A satellite meeting cosponsored by amfAR and IAS also was not webcast, although the slide presentations can be downloaded. [5] This meeting focused on whether:

- viral replication persists on HARRT;
- eradication research can progress in animal models or is dependent on human studies;
- eradication is most likely to come from targeting the viral reservoir or more recent approaches using gene therapy.

Several other presentations at the conferences looked at strategies to selectively reactivate the reservoir of latently infected resting CD4 cells, either at the pre- or post-integration step. This challenge is highlighted by the pool being estimated to be less than one in a million resting cells for someone on stable treatment with undetectable viral load.

Some researchers believe that success in this goal might eradicate HIV, though this is dependent on whether current treatment suppresses replication sufficiently to halt viral evolution. This might turn out to be possible, as it has been the conclusion from several intensification studies that have shown no further reduction on low level viraemia after increasing the potency of a three drug combination with a fourth drug, including an integrase inhibitor. [6] An oral presentation from Brunetta and colleagues reported no impact on CD4 reservoirs in gut-associated lymphoid tissue obtained from sigmoid colon biopsies at 48 weeks of follow up following intensification with raltegravir. [7]

A case reported by Chun and colleagues in an article in AIDS last year perhaps also supports this view. [8] This paper described one person - 'the Toronto patient' - who was enrolled and treated prior to seroconversion. Viral load was suppressed to <50 copies/mL on HAART for more than ten years, driving the pool of infected CD4 T cells down to less than one in 1.7 billion cells. Against advice, the person decided to stop treatment under research conditions. Viral rebound only occurred after 50 days with an increase to 1600 copies/mL followed by spontaneous suppression by day 95 back to undetectable. Subsequently, viral load steadily increased to approximately 8600 copies/mL on day 143 when treatment was restarted.

So one interpretation of this case could be to emphasise the difficulty of eradication - even with such an early, effective and sustained level of treatment. Another interpretation is that eradication might almost have been achieved. Perhaps another month, or year, or few years on treatment might have been sufficient to final exhaust the remaining pool on resting infected cells. This study is unlikely to be repeated.

Another more optimistic, but also unexplained, set of cases includes the 32 patients from the ANRS Visconti study reported at CROI this year. This group received antiretroviral therapy within ten weeks of seroconversion for a median of three years (1-7.5 years). Five of these people sustained virological control for a median of 6 years (range 4-10) after treatment discontinuation. [9] It is unclear why similar cohorts (Rosenberg, Walker et al.) have not had the same success.

However, over time, so long as treatment is maintained, the resting pool of infected cells might be able to be agitated to become active, most likely by using multiple approaches. This could reduce the time needed to eliminate this reservoir from decades down to years - with residual virus mopped up by antiretrovirals, allowing treatment to be stopped.

Importantly, research into activation of latently infected cells is already investigating a broad group of drugs that are already licensed. Studying HIV transcription at the molecular level is driving the understanding of differences between latent and productively infected CD4 cells including HDAC-1 and methylation sites in latent infection with the hope that these targets might switch cells away from latency.

A comprehensive review of potential molecules by Sharon Lewin and Christine Rouzioux in the 24 April edition of AIDS [10] was the basis of one of the presentations at the IAS cure workshop. [11]

These include histone deacetylase (HDAC) inhibitors (vorinostat, romidepsin, panabinstat, entinostat, belinostat, givinostat and at least nine others), a methylation inhibitor (5-azacytidine), cytokines (IL-7 - Eramune group, IL-15) and an antialcohol (disulfiram). Immune modulators with similar potential include antibiotics (minocycline), antirheumatics (auranofin), anti-PD-1 (MDX-1106) and protein kinase C modulators (bryostatins and others). Many of these compounds are already being studied in HIV-positive people.

An oral presentation by Claire Vandergeeten from the Vaccine and Gene Therapy Institute reported results from in vitro studies that suggest that IL-15 therapy may be used as a strategy to deplete the latent HIV reservoir while IL-7 maintains the reservoir both in vitro and in patients on stable HAART. [12]

This research is important and exciting. Many of these compounds have been studied for several years and for other studies are ongoing. A combination therapy approach is therefore likely to have a greater chance of success, for example, valproic acid or vorinostat plus prostratin. [13]

However, other researchers believe that an as yet unidentified sanctuary site would prevent the latent reservoir from being a slowly diminishing pool that theoretically might wear itself out, with or without stimulation to do so. This includes Steven Deeks at UCSF who co-chairs the IAS working group on cure research and was heads a recent \$4 million grant from the US NIH to develop a strategy to eradicate HIV. [14]

This raises the importance of finding out whether any compartments are actively replenishing the viral reservoir, currently untouched by the maximal suppression measured by plasma viral load.

If this is the case, then any strategy to activate latently infected cells would not be successful. In November 2010, Yuki and colleagues reported that ongoing replication (measured by

unspliced HIV RNA in CD4 T cells) is present in higher levels in gut sites (duodenum, terminal ileum, right colon and rectum) compared to that in PBMCs in patients on HAART with viral load suppressed to <40 copies/mL. [15]

The same group then showed that intensification with raltegravir in this group of patients produced a reduction in levels of unspliced RNA in the terminal ileum and a trend towards reduced T cell activation in other gut sites. [16]

For these researchers, looking for the impact of intensification studies in plasma viral load is searching in the wrong place. If tissue compartments are a source of ongoing viral replication, the spillover pool found in plasma may have limited relevance. Other cellular sites distinct from CD4 T cells contributing to the latent cellular reservoir include macrophages, hematopoietic stem cells, naive T cells, astrocytes, thymocytes and others.

Also, Maria Buzon and colleagues in Nature Medicine in 2010 reported increases in episomes following raltegravir intensification (shown by an increase in 2LTR in PMBCs) as evidence of de novo infection and reduced levels of activation. The extremely low level of replication is used to account for the non-development of resistance even over years. Also perhaps indicating that the chronic source for new virus drives a limited number of rounds of infection. [17]

Finally, in one of the few late breaker presentations with slides posted online, Hiroyu Hatano working with Deeks' group at UCSF reported that viral persistence was consistently associated with markers of immune activation and dysfunction (including PD-1 expressing cells) rather than plasma viral load. These measures were particularly elevated in people on treatment with low CD4 counts despite treatment (less than 350 cells/mm³ compared to higher), suggesting that patients below this cut-off present a more difficult and sobering challenge to any approach to a cure.

More optimistically, Hatano noted that the preferential expression of PD-1 by latently infected cells supports targeting this molecule as a strategy for depleting HIV reservoirs. The AIDS Clinical Trials Group (ACTG) in the US is planning an exploratory trial of Merck's experimental PD-1 inhibitor for this purpose. [18]

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6th IAS: PREVENTION

Orange Farm circumcision results dispel concerns about risk compensation

Nathan Geffen, TBonline

Amidst the excitement about HPTN052 at the Rome IAS meeting, the results of the ANRS Orange Farm circumcision programme received little publicity, despite stunning data.

Orange Farm was the site of the first of three randomised control trials that showed that circumcision reduces the risk of men contracting HIV in a predominantly heterosexual population. Following the trial, the researchers implemented a scaled up circumcision programme in Orange Farm. Bertran Auvert presented a late-breaker describing the results of this programme. [1]

There are several important findings from this study:

- Post-trial uptake was large. Orange Farm has now carried out approximately 25,000 circumcisions.
- No deaths or permanent injuries have occurred due to circumcision. There have been ten hospitalisations and in all these cases the adverse events were resolved.
- The benefit of circumcision on HIV incidence is durable.
- There was no evidence that incidence was affected by risk compensation.

Orange Farm is a township of about 110,000 adults about 45kms from Johannesburg. Since January 2008, free voluntary medical male circumcision to all boys and men older than 15 has been offered by the ANRS-sponsored project. The intervention includes community mobilisation and outreach, counselling, condom distribution, STI treatment, HIV voluntary counselling and testing and ART if eligible.

A baseline cross-sectional survey was done in 2007. This was a random sample of just under 1,200 males aged 15 to 49 years. The response rate was 74%. Male circumcision status was determined by genital examination. A second cross-sectional survey was done in 2010. It was almost the same size and the response rate was 88%. This survey included a background and sexual behaviour questionnaire. Again male circumcision status was determined by genital examination. Blood samples were tested for HIV, ARVs and for recent infection (within 6 months) using a population incidence detuned HIV test (Calypte EIABED).

Uptake

Male circumcision prevalence changed from 15.6% (95%CI: 13.6%-17.8%) of 15-49 year-olds in 2007 to 49.4% (95%CI: 46.5%-52.3%) in 2010. Using this data, the researchers calculated uptake, which increased across all age groups in the 2008-2010 period. In 15-49 year-olds it was 40% (95%CI: 38.0% to 43.5%) and 49.1% in 20 to 24 year-olds (95%CI: 42.1% to 52.4%). This substantial increase led Auvert to comment, "We are changing the social norms."

In a comparison of 590 circumcised versus 605 uncircumcised men, circumcised men were younger, more educated, less likely to be married and more often aware of their HIV status. No difference in sexual behaviour was detected. For example

reported condom usage was consistent (adjusted OR: 0.84; 95%CI: 0.63-1.1; $p=0.26$).

HIV prevalence and incidence

Among 586 uncircumcised men in the survey, 117 were HIV-positive (20%; 95%CI: 16.7%-23.2%). Among circumcised men, 36 out of 582 men were HIV-positive (6.2%; 95%CI: 4.3%-8.2%). This is a 55% reduction (95%CI: 39% to 70%).

In the 15-34 age group, the BED assay indicated that incidence in uncircumcised men was 3.7 per 100 person-years (95%CI: 2.2-6.1) and 0.6 per 100 person-years in circumcised men (0.19-1.9). The adjusted relative risk was 0.24 (95%CI: 0-0.66). Interestingly, this is equivalent to a 76% reduction that is exactly what the as-treated effect of the Orange Farm randomised control trial was.

Because of problems with the BED assay, a modelling exercise was also done in which HIV incidence was calculated from HIV prevalence data to determine the effect of circumcision on incidence. In this separate analysis the reduction in incidence was 83% (95%CI: 64%-98%) in 15-34 year-olds, consistent with the BED-based estimate.

It was estimated that without male circumcision, HIV prevalence would have been 25.1% higher in 15-49 year-olds in Orange Farm (95%CI: 13.1%-39.1%) and HIV incidence would have been 57.9% higher (95%CI: 17.0%-131%).

COMMENT

The key limitation to a study like this is that it is observational. But randomised controlled trials have already proven the efficacy of circumcision. This was the first prospective study to show the benefits of circumcision in a real-world operational setting.

A widely expressed concern about circumcision is that risk compensation would undo much of its benefit. The finding that the operational effect of circumcision matched the as-treated effect of the Orange Farm clinical trial addresses this concern. The lack of difference in reported condom usage also indicates that risk compensation is not a factor, but this must be discounted against the fact that survey participants give answers that they believe are consistent with societal expectations rather than what they actually do.

There should be no further objections to scaling up voluntary medical male circumcision in appropriately equipped facilities. The South African Department of Health has committed to scaling up circumcision and implementation is taking place in several provinces. PEPFAR and the Gates Foundation have both committed to funding circumcision programmes across sub-Saharan Africa. However South African guidelines have still not been published, albeit that a draft exists. These guidelines need to be finalised and published. An implementation plan also needs to be devised.

The Orange Farm researchers hope soon to be able to do an analysis of the effect of medical male circumcision on incidence in women.

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Thank you to Bertran Auvert, Dino Rech and Dirk Taljaard for assisting my understanding of this study.

Declaration of interest: Nathan Geffen am a member of the Orange Farm circumcision scientific committee.

6TH IAS: TB COINFECTION

Randomised trial of ART in TB patients with high CD4 counts

Nathan Geffen, TBonline

The benefits of initiating antiretroviral treatment (ART) in TB co-infected patients with CD4 counts below 350 cells/mm³ have been demonstrated in a number of recent studies. [1-2]

Now an open-label randomised controlled trial by Nanteza and colleagues has been published that looks at patients with higher CD4 counts. The trial, run in Uganda, compared 6 months of ART concurrent with TB treatment versus only TB treatment in patients with CD4 counts > 350 cells/mm³. The trial was small, but it provides some evidence that there is clinical benefit to placing patients with high CD4 counts on ART. [3]

From October 2004 through September 2008, 4,951 people were screened. Of these 250 patients co-infected with TB and HIV and with CD4 counts >350 cells/mm³ were enrolled. Of these 232 were randomised and 214 remained on the trial and eligible for analysis. The final control and intervention arms each had 107 patients. Patients in the intervention arm were given ART (abacavir, lamivudine and AZT) for six months. Participants were followed up for 24 months. The trial was designed and approved before several studies demonstrated that structured treatment interruptions are not a viable treatment option. The authors explained that the rationale of the study was that a punctuated course of antiretroviral therapy in patients with high CD4 cell counts would suppress viral replication during therapy for tuberculosis, block the effects of immune activation on T cells harboring HIV, slow the pace of HIV disease progression, and improve clinical outcomes.

The baseline characteristics of the patients were mostly well matched. There were slightly more men in the control arm (63% versus 52%). Nearly all patients had at least one TB symptom, especially cough. Median age was 31 years. Nearly 90% of patients were both smear and culture-positive. Interestingly 8% of patients were smear-positive and culture-negative, while only 3% were smear-negative and culture-positive. The intervention and control arms had similar median CD4 counts (between 500 and 550 cells/mm³) and median viral load (4.6 and 4.7 log₁₀ copies/mL).

The primary endpoint was a composite of CD4 cell count <250 cells/mm³, clinical AIDS, or death. In the intervention arm, 17 people reached this endpoint versus 25 in the control arm ($p=0.17$). Most people reached the endpoint on the basis of

CD4 count, 15 in the intervention arm and 18 in the control arm. They initiated lifelong ART. Although not statistically significant, there were consistently fewer endpoint events in the intervention arm throughout the trial. At 12 months of follow-up the difference between the arms reached significance (98% and 90%, respectively; $p=0.02$), but became non-significant by the end of the follow-up period.

There were two deaths in the ART arm and no clinical endpoints. There were three clinical endpoints and four deaths in the control arm. Despite the tiny numbers, this was significant ($p=0.048$).

In the intervention arm, 86% of participants achieved a viral load <400 copies/mL at three and six months. Viral load rebounded upon discontinuation of treatment to near baseline. The average viral load of the control group did not change significantly over the 24-month period.

There were 45 versus 28 adverse events in the control and intervention groups respectively. When considered individually, the risk of a grade 3 or 4 adverse event was 76% greater in the control arm than in the intervention arm (rate ratio, 1.76; 95% CI: 1.24–2.53). About half the adverse events took place during the six months treatment (ART or TB) stage of the study. Neutropenia was high and not significantly different in both arms (17 versus 25% in the intervention and control arms respectively). The authors therefore concluded that neutropenia is common in patients with tuberculosis, even when CD4 counts are >350 cells/mm³ and that treatment with concurrent antiretroviral therapy only partially mitigates the effect of HIV infection on bone marrow suppression. As would be expected in a trial of people with relatively high CD4 counts, no Immune Reconstitution Syndrome was detected.

No patients were culture-positive after six months of TB therapy. The average time to culture conversion was 37.5 days in the intervention group versus 29 in the control, but this was not significant ($p=0.37$).

The authors state that the trial provides limited further support for early initiation of treatment.

COMMENT

Although small and despite the outdated and short treatment intervention, this study does provide limited support for initiating all HIV-positive patients with TB on ART, even at high CD4 counts.

The World Health Organisation (WHO) recommends that treatment be provided to all patients with TB irrespective of CD4 count. The South African government has recently announced that it will treat all patients with CD4 counts <350 cells/mm³. This study offers some evidence, albeit not compelling, that South Africa should go further and implement the WHO recommendation. It seems likely that South Africa's new HIV and TB National Strategic Plan for 2012-2016 will provide for this.

Also interesting was that in this Ugandan setting 25% of the TB and HIV co-infected patients who screened for the trial had CD4 counts above 350 cells/mm³.

In Khayelitsha, Cape Town, nearly one in five HIV-positive patients presents with a CD4 count >500 cells/mm³ (communication with MSF). These statistics show that the question of determining the optimal starting point affects many people and is an important one.

We look forward to the results of the TEMPRANO and START trials that have been designed to answer this question.

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TREATMENT ACCESS

FDA approval of generic ARVs

Since the last issue of HTB South, 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
3TC/AZT 30 mg/60 mg for pediatric patients 3 months and older weighing at least 5 kg.	Cipla, India	22 September 2011
3TC/tenofovir 300 mg/300 mg FDC tablets co-package with nevirapine 200mg tablets	Matric laboratories, India	8 September 2011

FDC: Fixed Dose Combination

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>

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/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm>

Global Fund adopts restructuring recommendations and close to 50% funding shortfall for next round of grants

Simon Collins, HIV i-Base

A high level panel established six months ago by the Board of the Global Fund after widespread media publicity about corruption among some grant implementers released its report on 19 September 2011.

The panel, led by former President Mogae of Botswana and former US Secretary of Health and Human Services Michael Leavitt, was given a broad remit to look into the Global Fund's problems and what should be done about them. Much is riding on the report as several donors delayed making, or implementing, their funding commitments for 2011 and later until they the report was published and the Global Fund responded.

While identifying many areas for improvement, the Fund was recognised as a vital part of what makes health care function in many countries. Its failure would bring serious, dramatic and tragic consequences. Many of the recommendations related to changing the organisations role from providing an emergency response to sustainability with heightened public responsibility.

It is clearly important that the majority of recommendations, including major structural changes, were accepted by the Fund when the report was formally accepted the following week.

However, perhaps more significantly, the Global Fund looks likely to have significantly less funding for new grants in Round 11 - barely more than half - than the estimate published in May 2011. The Global Fund Observers reported that "the panel found this situation a cause for deep concern".

At the Global Fund Board meeting on 26 September 2011, the Fund revealed that its forecast of \$1.5 billion for Round 11 has been lowered to "not more than" \$0.8 billion, and that even this amount might not be available until the fourth quarter of 2013.

The previous forecast was based on the assumption that all donors would honour their pledges, and that donors that traditionally do not make pledges would provide funding at a level similar to what they had provided before. However, the global economic insecurity and other factors have shown these assumptions appear to be overly optimistic.

This has already resulted in an extended deadline for applications to at least March 2012 and a statement that given the financial restraints it will "consider options for reallocation of existing commitments" in order "to prioritize high-impact interventions."

The need to pressure donor countries to follow through and expand on their commitments has never been stronger or more important.

Source: Global Fund Observer. Issues 158 and 159

<http://www.aidspace.org/>

PREGNANCY & PMTCT

Increased risk of preterm delivery with protease inhibitor based HAART in Mma Bana

Polly Clayden HIV i-Base

The Mma Bana trial compared antiretroviral regimens to prevent mother-to-child transmission in pregnancy, with highly efficacious results and some of the lowest reported in Africa [1]

The investigators performed a secondary analysis to look at the occurrence of preterm delivery (PTD) among women in the trial with CD4 counts ≥ 200 cells/mm³ randomised to receive either ABC+AZT+3TC or LPV/r+AZT+3TC initiated at 26 to 34 weeks gestation. We reported the results from this analysis – presented at CROI 2011 – earlier this year [2]

Kathleen Powis and colleagues published the complete results of the PTD analysis in the August 15 2011 edition of the Journal of Infectious Diseases with an accompanying commentary from Athena P Kourtis and Mary Glenn Fowler. [3, 4]

There were 263 and 267 women in the NRTI and PI groups respectively in this study. Baseline characteristics were similar in the two groups, the women were a median age of 26.4 years with CD4 counts of about 400 cells/mm³ and approximately 67% were between 26 and 28 weeks gestation at enrollment. Overall 88 (16.7%) women had spontaneous PTDs.

Gestational age was calculated using an algorithm that combined maternal reported last monthly period and ultrasound.

In a multivariate analysis, adjusted for self reported maternal income ($p=0.02$ for 3 df), the investigators found PI-based HAART was associated with a two-fold higher rate of PTD compared to triple NRTI-based HAART, 21.4% vs 11.8%, AOR 2.02 (95% CI 1.25-3.27), $p=0.003$.

The investigators proposed that less weight gain in pregnancy due to possible gastrointestinal side effects of the PI might explain the increased PTD risk. However, although the mean change in BMI on HAART was lower in the PI group ($p<0.001$) this was not significantly associated with PTD.

Of the 464 women who initiated HAART before 32 weeks gestation, 12 (2.6%) had very PTDs (<32 weeks gestation). Of these, 8 (3.3%) were in the PI group and 4 (1.8%) in the NRTI group, $p=0.39$. The investigators noted that, only 3 of 12 women who had very PTDs completed 30 days of HAART prior to delivery limiting the interpretation of these findings.

By 6 months of age, preterm infants were significantly more likely to have a least one severe or life threatening respiratory tract infection than term infants, 9.1% vs 2.0%, $p=0.03$. Preterm infants were more likely to be hospitalised than term infants, 22.7 vs 12.7%, $p=0.02$. Their mortality was also higher in the first 6 months, 6.8% vs 1.4%, OR 5.3 (95% CI 1.7-16.9), $p=0.002$, compared to term infants.

When the investigators looked at infant morbidity and mortality by maternal treatment arm the only difference they found was infants born to mothers randomised to the NRTI arm were more likely to experience meningitis, 1.9% vs 0%, $p=0.03$.

In their commentary, Kourtis and Fowler explain that this is the first randomised clinical trial to demonstrate a difference between rates of PTD according to antiretroviral regimen. Although observational studies and analyses have suggested a risk with PI use others have not found this association.

They note that the Mma Bana trial was not designed to look at PTD specifically so the sample size may not be sufficiently powered to do so. Assuming a background PTD rate of 20%, in the general population in Botswana, a much larger sample would be needed to detect an increase in the risk of PTD of the size that was observed in the PI group. They point out that one unexplained finding is the lower rate of PTD seen in the NRTI group whereas the rate in the PI group does not appear to differ from the background rate in Botswana.

Their commentary suggests that the study by Powis et al may, “raise more questions than it answers”, despite providing interesting data, obtained in a randomised fashion from a resource limited setting, in a field where more is needed.

They raise the issue of the timing of treatment (ie the relatively late initiation), noting a third of women who delivered prematurely had only received less than 30 days of HAART, which is too short a period for there to have been an association with immune reconstitution and the resulting cytokine shift, which is one proposed mechanism for PTD. The design of the study also limits the investigation of very PTDs, which result in the most severe infant outcomes.

The only other randomised trial that may offer some more information is Kesho Bora, which did not show elevated PTD rates among women receiving PIs compared to AZT and single dose NVP (started between 28 and 36 weeks except the NVP), respectively 13% vs 11%.

They caution against the possible interpretation of these data and write, “it is too early to rush into recommendations without validation from further studies and careful consideration of the question at hand”.

COMMENT

Although not the primary study endpoint, these are the first RCT data showing an association between PI use in pregnancy and PTD. This is consistent with observational UK and European data, though not all from the US.

This association will be related to the PTD rate in the general population and other factors including timing of treatment.

References

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2. Clayden P. Preterm delivery and HAART. *HTB* April 2011.
3. Powis KM et al. Increased risk of preterm delivery among HIV-infected women randomised to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. *J Infect Dis* 2011, 204: 506-13
4. Kourtis P and Fowler MG. Antiretroviral use during pregnancy and risk of preterm delivery: more questions than answers. *J Infect Dis* 2011, 204: 493-4.

Efavirenz in pregnancy: update of systemic review and meta-analysis

Polly Clayden HIV i-Base

A systematic review and meta-analysis by Nathan Ford and colleagues, to February 2010, showed no increase in overall birth defects with efavirenz (EFV) use in the first trimester of pregnancy compared to other antiretrovirals or the general population. [1,2] But, the authors were unable to come to a definitive conclusion concerning the risk of rare outcomes such as neural tube defects due to the limited number of reports.

The same authors recently updated the meta-analysis to July 2011 and these findings were published ahead of print as a research letter in AIDS. [3]

This update found 181 additional live births with first trimester efavirenz exposure.

Across 21 studies, included in the analysis, 39 defects were reported among live births to 1437 women. The pooled prevalence of birth defects was 2% (95% CI, 0.82-3.18%) and ranged from 0% to 22.6%. There was one neural tube defect (myelomeningocele), an incidence proportion of 0.07% (95% CI, 0.002-0.39%). Prevalence appeared to be higher in developed countries compared to developing ones, $p=0.015$.

An analysis of the 11 studies that reported birth defects among women receiving EFV-containing regimens (38 defects from 1289 live births) vs non-EFV regimens (316 defects from 8122 live births) gave a relative risk of 0.85 (95% CI, 0.61-1.20).

There was variable reporting of secondary outcomes across the studies: 8 reported spontaneous abortion (prevalence range 0% to 16.05%); 8 stillbirth (prevalence range 0% to 13.3%), 5 preterm delivery (prevalence range 9.1% to 18.2%) and 10 termination of pregnancy (prevalence range 0% to 33.7%). From the three studies that reported termination of pregnancy for EFV-exposed vs non-exposed pregnancies, the relative risk for termination of pregnancy with EFV exposure was 2.81 (95% CI, 0.94-8.36).

The authors wrote that this expanded review confirms the findings from their previous meta-analysis. The pooled prevalence of defects for first trimester EFV-exposed births of 2% is similar to that reported for first trimester non-EFV exposed births in the Antiretroviral Pregnancy Registry of 2.9% and in the general population of 6%. They note that the incidence of neural tube defects of 0.07% remains low.

They add that the main limitation of the review is the small sample size, with over 80% of the data coming from just four studies where prospective reporting of birth outcomes has been established. With data for only 181 found for the update in the 18 months since the original review, "Prospective surveillance systems particularly in developing countries are needed to improve data reporting and inform the assessment of rare birth defects", they wrote.

COMMENT

That there were data for, what would work out as, an average of ten efavirenz-exposed pregnancies reported per month since the previous analysis definitely highlights the authors conclusion.

If more countries go down the same path as Malawi and recommend universal efavirenz-based HAART (lifelong from initiation) for

pregnant women, it is hoped that there will be good surveillance systems with these programmes to help to improve the numbers.

References

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AZT not equivalent to HAART to prevent mother-to-child transmission in a Botswana programme

Polly Clayden HIV i-Base

A study, first presented at CROI 2011, compared mother to child transmission rates for women receiving AZT (with or without single dose NVP) or HAART in pregnancy in the Botswana national programme. [1] We reported these data in the May issue of HTB. [2]

This prospective observational study conducted between February 2009 and April 2010, showed of 428 infants born to either 258 mothers receiving HAART or 170 mothers receiving AZT, those in the AZT group were significantly more likely to be HIV infected than those whose mothers received AZT, relative risk 13.9 (95% CI 1.8-108), $p=0.001$. There were nine transmissions in the AZT group and one in the HAART group.

Notably the women eligible for HAART had CD4 counts ≤ 250 cells/mm³ and those receiving AZT >250 cells/mm³.

Scott Dryden-Peterson and colleagues reported complete results in an online article published ahead of print in JAIDS. [3]

The overall findings are unchanged from those presented previously but the article includes some more details and discussion. The authors write: "Our findings do not support the equivalence of zidovudine and HAART for the prevention of MTCT." In the study over half (5/9) infections in the AZT group occurred in women with CD4 counts ≤ 350 cells/mm³.

The authors observed difficulties with the delivery of single dose NVP in this cohort (women receiving <4 weeks of AZT were eligible) with only 5 (22.7%) women receiving this. Preterm delivery rather than delayed initiation was the main reason in this cohort for short duration of antenatal antiretrovirals, with nearly one-third of infants born preterm or of low birth weight.

They add that the findings from this study indicate that a strategy to provide HAART for all HIV-positive pregnant women, as is being piloted in Botswana, could almost eliminate infant HIV infection.

COMMENT

Although better transmission results for women not indicated for treatment have been demonstrated in trials, programmers have often remarked that having a two-tiered approach to PMTCT is too complicated to implement.

References

1. Dryden-Peterson S et al. Effectiveness of Maternal HAART vs ZDV to Prevent MTCT in a Programmatic Setting: Botswana. 18th CROI. Boston. February 2011. Poster abstract 740.
2. Clayden P. HAART more effective than AZT monotherapy in the Botswana PMTCT programme. HTB May 2011.
3. Dryden-Peterson S et al. Highly active antiretroviral therapy versus zidovudine for prevention of mother to child transmission in a programmatic setting, Botswana. JAIDS. Publish ahead of print DOI: 10.1097/QAI.0b013e31822d4063.

Increased risk of HIV transmission to HIV-negative partners during pregnancy

Polly Clayden HIV i-Base

Physiological and behaviour changes during pregnancy may increase risk of HIV transmission. Results from previous studies looking at HIV acquisition in women in pregnancy have been inconsistent. No study has looked at transmission from HIV-positive pregnant women to men directly.

Investigators from the Partners in Prevention HIV/HSV Transmission study – a randomised controlled trial of acyclovir suppressive HSV treatment for the prevention of HIV transmission in serodiscordant African couples – evaluated the relationship between pregnancy and risk of HIV acquisition in women and transmission from women to men. Nelly Mugo and colleagues reported findings from this study in an article published ahead of print in August 2011 AIDS.

There were 3321 couples included in the overall analysis, of these, in 1085 (32.7%) and 2236 (67.3%) couples, the man and the woman were the HIV-positive partner respectively. The median follow up was about 20 months. Pregnancy testing was quarterly.

At enrollment, 94 (8.7%) HIV-negative and none of the HIV-positive women were pregnant (pregnancy was an exclusion criterion for HIV-positive women). Subsequently, there were 226 and 503 pregnancies among the HIV-positive and HIV-negative women respectively, during the study period. This gave an incidence of 15.3 pregnancies per 100 person years, with 1480 person-years of follow up at risk of pregnancy for the HIV-negative women and 16.0 per 100 person-years with 3147 person-years of follow up at risk of pregnancy for the HIV-positive women. A proportion of women (27 from each group) had two pregnancies during follow up and one HIV-positive woman was pregnant three times.

Out of a total of 61 seroconversions among women, 17 (27.9%) were during pregnancy. The incidence of HIV during pregnancy was 7.35 per 100 person years compared to 3.01 per 100 person years during times when the women were not pregnant, HR 2.34 (95% CI 1.33-4.09), $p=0.003$. In multivariate analysis, this effect of pregnancy on HIV acquisition was weakened and did not reach statistical significance, AHR 1.71 (95% CI 0.93-3.12), $p=0.08$.

Of the 58 HIV transmissions to men, 12 (20.7%) were during pregnancy. The incidence of female to male HIV transmission was 3.46 per 100 person years during pregnancy compared to 1.58 per 100 person years, HR 2.31 (95% CI 1.22-4.39), $p=0.01$. This effect remained statistically significant in multivariate analysis, AHR 2.47 (95% CI 1.26-4.85), $p=0.01$. A subgroup analysis suggested the risk may increase in early and late

pregnancy – AHR 2.64 (95% CI 1.02-6.84), $p=0.05$ and AHR 2.37 (95% CI 1.03-5.46) $p=0.04$ respectively - but the numbers in the subgroups were tiny (only 5 and 7)

The investigators also examined the use of antiretrovirals among women in pregnancy and the relationship to female to male transmission. Of the 503 pregnancies reported in HIV-positive women 216 (42.9%) resulted in live births, 143 (28.4%) in pregnancy losses, 14 (2.8%) had unknown outcomes and 128 (25.5%) were ongoing at study exit. The investigators noted that 119/143 (83.2%) of the pregnancy losses were before 20 weeks gestation, partly reflecting chemical pregnancies that were detected due to quarterly pregnancy testing in the study protocol.

Of the 216 pregnancies that ended in live births, 176 (81.5%) women received antiretrovirals but only 74 women received combination ART. The remainder received either short course or dual or single agent prophylaxis at the time of delivery. Of the 12 female to male transmissions during pregnancy, 9 (75%) women received antiretrovirals but this coincided with the time of transmission in only two couples. One woman was using short course AZT during labour and the second initiated ART in early pregnancy and her partner seroconverted shortly after. Adjustment for antiretroviral use in pregnancy did not alter the estimated risk of transmission, AHR 2.3 (95% CI 1.15-4.61), $p=0.02$.

The investigators wrote that this novel finding that pregnancy increases the risk of female to male HIV transmission has important public health implications and requires further studies to understand the possible biological mechanisms.

References

- Mugo N et al. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1 serodiscordant couples. AIDS published ahead of print August 2011.

PAEDIATRIC CARE

Pharmacokinetics of paediatric tenofovir based regimens

Polly Clayden HIV i-Base

In an article in the September 2011 edition of Antimicrobial Agents and Chemotherapy, Jennifer R King and colleagues from the P1058 protocol team reported pharmacokinetic (PK) data from children and adolescents treated with tenofovir (TDF) in combination with antiretrovirals with potential interactions.

PK results were shown for 47 participants aged 8 to 18 years, receiving a 300mg once daily TDF-based regimen. Participants received regimens that also contained an NTRI plus efavirenz (EFV) or darunavir/ritonavir (DRV/r) or atazanavir/ritonavir (ATV/r). The antiretrovirals and doses combined with TDF in are shown in Table 1.

Plasma samples were obtained pre-dose and over 24 hours. Statistical comparisons determined whether the 90% confidence intervals of the geometric mean (GM) AUC and Cmin for each antiretroviral were within 25% of those observed in previous studies demonstrating safety and efficacy. The AUC and Cmin target ranges and GMs (90% CI) are shown in Table 2.

In the presence of EFV only the GM for TDF Cmin was very slightly above the target upper limit of the 90% CI. In contrast the GM (90% CI) for EFV Cmin was above the target upper limit. The investigators noted that EFV exposure was high overall in this analysis although the participants were dosed according to FDA recommendations; six participants with high exposure were receiving the EFV-based triple fixed dose combination (Atripla) which they suggest may alter drug absorption in this population. They recommend a crossover study comparing Atripla to the individual formulations in children and adolescents to answer this question.

The GMs (90% CI) for TDF AUC and Cmin were within the target ranges when it was given with DRV/r, however they were

below the target ranges for DRV. The investigators wrote that these data suggest that higher than recommended doses of DRV may be necessary in paediatric patients in the presence of TDF, but the small sample size warrants a larger study to confirm these findings.

The GMs (90%CI) for TDF AUC and Cmin were only slightly higher in the presence of ATV/r, in contrast with that observed in healthy adults where these elevations are significant.

The investigators also observed that TDF PK did not differ between groups 1,2 and 3. This finding was unexpected as several PIs modestly alter TDF concentrations.

They concluded that none of the 90% CI AUC and Cmin values for the drugs tested were entirely outside the target range. So the recommended doses should provide exposure levels similar to that seen in adults. However they recommended that if individual patients experience adverse events or reduced clinical outcomes, while taking these agents in combination, monitoring exposure could be considered.

COMMENT

Gilead has now filed with the FDA and EMA for an indication for tenofovir for the 2-12 year age group. In Europe tenofovir is not approved for adolescents aged 12-18 (although there is considerable off label use), so we may be faced with the curious situation of approval for the younger but not older age group of children and adolescents.

The WHO expert paediatric group, consider a fixed dose combination dispersible tablet of EFV/TDF/3TC, scored once on one side and twice on the other to make dividing easy, to be an essential missing formulation for treating children. Modelling suggests that dosing delivered with divided tablets could work with weight band tables.

WHO is producing a white paper on tenofovir use in children.

Ref: King JR et al. Steady state pharmacokinetics of tenofovir-based regimens in HIV-infected paediatric patients. Antimicrob Agents Chemother 55: 4290-4.

Table 1: Antiretrovirals combined with TDF and doses

Group (n)	ARV	Doses (n)
1 (17)	efavirenz	200mg (1), 400mg (4), 600mg (12) QD
2 (13)	darunavir/r	300mg (2), 600mg (11) /100mg BD
3 (17)	atazanavir/r	150mg (3), 300mg (14)/100mg QD

BD: twice-daily; QD: once-daily.

Table 2: AUC and Cmin target range/GM (90% CI)

Parameter	Group 1		Group 2		Group 3	
	Tenofovir	Efavirenz	Tenofovir	Darunavir	Tenofovir	Atazanavir
AUC target range	2.3-3.6	32-124	2.3-3.6	51-80	2.3-3.6	15-75
GM (90% CI)	2.9 (2.5-3.4)	88.4 (65-120)	3.0 (2.5-3.6)	60.3 (48.7-74.7)	3.6 (3.1-4.2)	36.9 (33-42)
Cmin target range	0.05-0.08	0.9-3.6	0.05-0.08	3.1-4.2	0.05-0.08	0.3-1.0
GM (90% CI)	0.07 (0.05-0.09)	2.7 (1.8-4.0)	0.06 (0.05-0.08)	2.7 (2.0-3.6)	0.07 (0.06-0.09)	0.5 (0.4-0.7)

Values mg*h/liter (AUC) and mg/liter (Cmin)

Atazanavir pharmacokinetics in infants, children and adolescents

Polly Clayden HIV i-Base

An article in the July 31 2011 edition of AIDS describes atazanavir (ATV) pharmacokinetics (PK) in infants, children and adolescents given alone and boosted with ritonavir (ATV/r). Jennifer J Kiser and colleagues from the IMPAACT 1020A phase I/II study evaluated two formulations of ATV, capsules and a dispersible orange-vanilla flavoured powder across a range of age groups in treatment naïve and experienced participants from the United States and South Africa.

Participants were aged 91 days to 21 years and received unboosted or boosted (using ritonavir capsule or liquid formulations) ATV as part of a combination antiretroviral regimen. All participants underwent intensive 24-hour PK sampling on day 7; 195 enrolled and 172 had evaluable data.

All groups were started at a target dose of 310mg/m². To establish an acceptable ATV or ATV/r dose for an age group, 10 participants had to meet PK and safety criteria as defined by the protocol.

For PK these were: ATV AUC AUC_{0-24hr} of at least 30,000ng x h/mL and C₂₄ of at least 60ng/mL in at least 80% of participants; no AUC_{0-24hr} less than 15,000ng x h/mL and median AUC_{0-24hr} of 60,000ng x h/mL or less. And for safety: no life threatening toxicities; one or fewer participants with grade 3 or 4 toxicities (excluding bilirubin) linked to study treatment, and two or fewer participants with total bilirubin values greater than 5.1 times the upper limit of normal.

If these criteria were not met, the ATV starting dose was modified for the age group, either increased to 415, 520 then 620mg/m² or decreased to 205mg/m².

Nearly half (45%) of the participants were antiretroviral naïve at enrollment; 62% received ATV capsules and the remaining 38% ATV powder.

The investigators found unboosted ATV capsules met PK criteria at a dose of 520mg/m² for participants >2 to 13 years of age and 620mg/m² for those >13 to 21 years of age. Boosted ATV capsules met PK criteria at a dose of 205mg/m² for those >2 to 21 years of age. Boosted ATV powder met PK criteria at a dose of 310mg/m² for those >2 to 13 years of age.

Infants and young children aged 3 months to 2 years dosed with boosted ATV powder failed to meet PK criteria. There was a lot of intersubject variability in exposures this age group so that a dose escalation to 415mg/mL may have given ATV exposures in some young children greater than 90,000ng x h/mL.

The investigators wrote that additional studies are needed in this age group to determine if an appropriate ritonavir boosted dose can be identified.

Reference

Kiser JJ et al. Atazanavir and atazanavir/ritonavir pharmacokinetics in HIV infected infants, children and adolescents. AIDS 2011, 25:1489-96.

Crushing lopinavir/ritonavir tablets decreases exposure by almost half in children

Polly Clayden HIV i-Base

Crushing lopinavir/ritonavir (LPV/r; Kaletra) tablets is not recommended by the manufacturer as pre-clinical studies showed poor absorption with this method of administration compared to whole tablets with a single dose.

The liquid formulation of LPV/r is unpalatable and inconvenient so administering crushed tablets could potentially overcome this barrier to the paediatric use of this PI.

As single dose pharmacokinetics (PK) do not predict steady state LPV concentrations (due to the complex interaction with ritonavir [RTV]), investigators from the Children's National Medical Center (CMC) in Washington, DC, looked at LPV/r exposure in whole and crushed 200/50mg tablets in children. Results were published ahead of print in JAIDS.

Brookie M Best and colleagues conducted a prospective, open label, cross over PK study in 13 (6 boys, 7 girls) children and adolescents with a median age of 13 years (range 10-16) taking LPV/r tablets BID as part of their antiretroviral regimen with two NRTIs. The median LPV/r dose was 275/69mg/m² (range 193/48-372/93mg/m²). Two participants were excluded from the analysis, one refused to take the crushed tablets, and the other had very low or undetectable levels of LPV with both methods of administration. Data are from 11 participants.

The median LPV AUC, after receiving crushed and whole tablets respectively were, 92 (IQR 79-103) mg*hr/L and 144 (IQR 101-202) mg*hr/L; crushed/whole GM 0.55 (90% CI 0.45-0.69), p=0.003. The corresponding values for RTV were AUC 7 (IQR 4.5 -11.1) mg*hr/L and 13.3 (IQR 9.6-17.9) mg*hr/L; GM 0.53 (90% CI 0.4-0.71), p=0.006.

Oral CL/F (L/hr/m²) was significantly increased with crushed tablets for both drugs, respectively 1.4 and 1.6 times for LPV and RTV. The maximum post dose concentrations (C_{max}) were also reduced, (significantly for LPV, p=0.021) with crushed tablets.

The investigators wrote: "The reduced exposure with crushed Kaletra tablet dosing reinforces the need to discourage this practice."

COMMENT

This study was conducted prior to the introduction of the smaller tablet formulation (100/25 mg, LPV/RTV).

These data reinforce both the importance of following manufacturers instructions about dividing protease inhibitors and the need for an alternative formulation to the oral suspension. The sprinkle formulation, being developed by Cipla and studied in CHAPAS 2, is still eagerly awaited, particularly for the very young age group.

Reference

Best BM et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. JAIDS. Publish ahead of print. DOI: 10.1097/QAI.0b013e318232b057.

<http://217.160.60.64/2/medicine/art/jaids.htm>

TB COINFECTION

WHO Guidelines on guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update

Nathan Geffen, TBoonline

The World Health Organisation (WHO) has updated its guidelines for drug-resistant TB. [1]

The guidelines were last published in 2008. [2]

The guidelines make eleven recommendations. All of them were supported by very low quality evidence.

1. Rapid drug susceptibility testing of isoniazid and rifampicin or rifampicin alone is recommended if there are resources to do it and if rifampicin resistance is not rare in the patient group. Currently the line probe assay and the GeneXpert are the only diagnostic tools to meet the WHO criteria for rapid diagnosis (two days or less).
2. Sputum smear microscopy and sputum smear culture, rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDR TB during treatment.

This is a change from the 2008 guidelines that recommended monthly sputum smear microscopy and culture examination prior to culture conversion to negative and quarterly culture, with monthly smear examination after conversion.

Data pooled from 10 observational studies indicated that monthly sputum smear microscopy and culture performed best at identifying treatment failures early. This is conditional recommendation because of the resources required to implement it.

3. MDR TB patients should be treated with a fluoroquinolone. This is a strong recommendation.
4. MDR TB patients should be treated with a late-generation fluoroquinolone (levofloxacin, moxifloxacin, gatifloxacin and sparfloxacin) rather than an earlier-generation one. This is a conditional recommendation.
5. MDR TB patients should be treated with ethionamide or prothionamide. This is a strong recommendation.
6. In the treatment of MDR TB patients, four second-line drugs likely to be effective (including an injectable, kanamycin, amikacin or capreomycin) as well as pyrazinamide should be included in the intensive treatment phase. This is a conditional recommendation.
7. MDR TB patients should be treated with at least pyrazinamide, a fluoroquinolone, an injectable, ethionamide (or prothionamide) and cycloserine (or PAS if cycloserine cannot be used). This is a conditional recommendation.

Recommendations 3 to 7 were based on the results of three systematic reviews of observational data. Bias was likely substantial because some drugs may have been used for sicker patients. Nevertheless, this is the best available evidence.

Analysis showed that in the intensive phase a regimen with at least four drugs was likely to be effective. The analysis did not show any injectable to be superior to any other, so kanamycin

is recommended because of its lower cost.

Fluoroquinolones were significantly associated with cure and this association was greater with later-generation ones. The recommendations gave higher weight to interventions that increased the risk of cure and reduced the risk of failure, relapse and death. Consequently fluoroquinolones were strongly recommended despite potential long-term serious adverse events. The recommendation for later-generation fluoroquinolones was conditional because of the unknown long-term side effects of these drugs. Ciprofloxacin may have some anti-TB activity but it should not be used.

For oral bacteriostatic drugs the association with cure was higher for ethionamide than cycloserine which was higher than PAS. PAS is only recommended if there is no other effective drug available to make up the four-drug regimen. No significant association between cure and any of the following was found: amoxicillin/clavulanate, azithromycin, clarithromycin, clofazimine, roxithromycin and thiocetazone.

There were too little data on linezolid and high-dose isoniazid. Pyrazinamide showed slight benefit in one analysis.

Patients with XDR TB were excluded from this analysis so these recommendations do not necessarily apply to them. Nevertheless, the WHO recommends that the same principles used to design MDR TB regimens should be used for XDR TB regimens.

The regimen composition recommendations differ only in small nuances from the 2008 guidelines. Ethambutol has been removed as an alternative to pyrazinamide in the new guidelines, albeit that the new guidelines acknowledge that the decrease in efficacy associated with ethambutol in their analysis could be due to confounding.

8. The intensive phase of treatment for MDR TB patients should be at least eight months. This is a conditional recommendation.
9. A total treatment duration of at least 20 months is recommended.

The evidence base for recommendations 9 and 10 is the same as recommendations 3 to 7 and subject to confounding and bias. There was an association between treatment success and the length of treatment and the length of the intensive phase.

The 2008 guidelines recommended at least six months intensive phase treatment and at least 18 months of total treatment.

10. ART is recommended for all HIV-positive patients with MDR TB irrespective of CD4 count, starting within eight weeks after TB treatment. This was a strong recommendation.

Ten studies, none of them randomised controlled trials, informed this recommendation. The quality of evidence varied from low to very low quality. The recommendation is based in part on evidence from studies for any patients with TB and HIV (ie majority non DR patients).

11. Patients with MDR TB should be treated using mainly ambulatory care rather than models of care based on hospitalisation. This is a conditional recommendation. The data for this recommendation came from published and unpublished studies in Estonia, Peru, Philippines and Russia, but none of these were randomised controlled trials. Nor did these studies allow direct comparisons of effects between models of care. The key considerations informing this recommendation was that the cost per disability adjusted life-year was generally

lower in outpatient models and that these models appear to reduce exposure to infectious drug-resistant patients. However, the guidelines warn that ambulatory care can shift the burden of cost from the service provider to the patient (eg increased travel and food costs). Therefore implementation of ambulatory care models must be accompanied by provision of what the document calls “appropriate enablers”.

The guidelines state that important gaps in knowledge should be addressed in future research, particularly in the context of large-scale expansion of treatment for patients with drug-resistant TB. The document further calls for randomised controlled trials to determine the best combination of drugs and optimal treatment duration. Further research on (1) paediatric MDR TB treatment, (2) best regimens for patients with isoniazid resistance, (3) prophylaxis for contacts of MDR TB and (4) therapy for relief from adverse reactions due to second-line drugs is needed.

COMMENT

A common theme throughout these guidelines is the lack of evidence to support the recommendations.

The development of new TB drugs like TMC207 and OPC-67683 needs to be completed. The phase IIB trial results of TMC207 suggest that it is already better tested than many second-line TB drugs and therefore should be available to patients.

MSF has pioneered outpatient MDR TB care in South Africa. It would strengthen recommendation 11 if they published more data on this.

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IPT for adults: Should the Mantoux test have been removed from WHO guidelines?

Nathan Geffen, TBoNline

The 2011 edition of the World Health Organisation’s Guidelines for Intensified Tuberculosis Case-finding and Isoniazid Preventive Therapy for People Living with HIV in Resource-Constrained Settings has 12 recommendations. [1]

The fourth recommendation says that adults and adolescents living with HIV who have an unknown or positive tuberculin-skin-test (TST) status and who are unlikely to have active TB should receive at least 36 months of Isoniazid Preventive Therapy (IPT). Furthermore, IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women. The WHO says this is a strong recommendation with moderate quality of evidence to support it. The third recommendation is identical except that six months instead of 36 months of IPT is recommended and this is ranked as a strong recommendation with high quality of evidence.

The Guidelines for Tuberculosis Preventative Therapy Among HIV Infected Individuals in South Africa, published in 2010, are consistent with recommendation three. They further state, “Clinical trials have shown that the benefit of TB preventive therapy is greatest in HIV-infected persons with a positive tuberculin skin test. Where tuberculin tests are feasible and can be performed, IPT should only be offered to those who are TST positive. However, the practicalities and logistics of doing a tuberculin skin test are often an obstacle for provision of TB preventive therapy. Therefore the tuberculin skin test is no longer required to identify HIV infected people eligible for IPT.” [2]

This article deals solely with adults who are not pregnant, who are not health-workers with HIV and not in special high-risk settings such as mines or prisons. The removal of the necessity of the Mantoux test to determine TST status from IPT guidelines is concerning, as the data summarised here demonstrates.

Cochrane Review of IPT trials

A Cochrane Review of short-course chemotherapy trials (6 to 12 months) to prevent TB was published in 2010. [3]

Twelve trials met the strict criteria for inclusion in this meta-analysis. In all, 4811 participants were TST positive, 2030 were TST negative. Of these, 1,640 were known to be unable to mount an immune response to the Mantoux test (ie they were anergic). The TST status in 1737 participants was unknown. No differences were found in trials that compared effectiveness of different combinations of drugs, but all regimens significantly reduced the risk of TB as shown in Table 1.

Table 1: Efficacy of four drug combinations for preventing TB in HIV-positive people (from Akolo et al)

Drug combination	Relative Risk	95% CI	n
INH	0.67	0.51-0.87	4,136
INH+RIF	0.41	0.21-0.81	1,179
RIF+PZA	0.54	0.34-0.86	855
	0.48	0.23-1.00	926

Using INH alone reduced the incidence of confirmed, probable or possible TB by 32% (RR: 0.67 95%CI: 0.51-0.87, n=4136).

However, when analysed by TST status, the effect was only significant for TST positive participants as table 2 shows.

Table 2: Efficacy of INH at preventing confirmed, probable or possible active TB by TST status (from Akolo et al)

Mantoux test result	Relative Risk	95% CI	n
TST positive	0.36	0.22-0.61	1,311
TST negative	0.86	0.59-1.26	2,490
Unknown	0.86	0.48-1.52	335

IPT showed no mortality benefit (RR: 0.95; 95%CI 0.85-1.06). When analysed by TST status, the benefit only just reached significance in TST positive participants (RR: 0.74; 95%CI 0.55-1.00) and there was no benefit to TST negative (RR: 1.02; 95%CI: 0.90-1.16) or TST status unknown participants (RR: 0.81; 95%CI: 0.52-1.27).

Botusa Trial

The Botusa trial has previously been reported in HTB South. [4]

Since then it has been published in the New England Journal of Medicine. The results of the trial, contrary to the way it has been reported, are not a resounding success for long-term IPT; on the contrary the trial raises difficult questions. [5]

In this double-blind randomised controlled trial in Botswana, 989 HIV-positive participants were randomised to receive six months of isoniazid and 1,006 were randomised to receive 36 months of isoniazid. All participants received open-label isoniazid for the first six months, after participants either took placebo or isoniazid for 30 months. Only 2% of participants were on ART at the start of the trial. At the end of the open-label phase, 821 participants continued in the placebo group and 834 in the isoniazid arm.

TB incidence between the two groups diverged at 200 days after the open-label phase, indicating not unexpectedly that the benefits of short-course IPT were transient.

The protocol defined definite, probable and possible TB as follows:

- Definite: one or more culture was positive M tuberculosis or if two or more sputum smears were positive for acid-fast bacilli
- Probable: one sputum smear or one biopsy specimen was positive for acid-fast bacilli
- Possible: if smears and cultures were negative or not done. A death defined as possibly related to tuberculosis was one that had clinical or verbal autopsy evidence consistent with tuberculosis as the proximate cause of death.

In an analysis of participants that actually remained on the study after the open-label phase ended, the only statistically significant result in favour of long-term IPT was the reduced incidence of definite, probable and possible TB, and here the confidence interval was wide (25 on placebo versus 12 on isoniazid; HR: 0.47; 95%CI: 0.24-0.94). No significant difference between the arms could be found when only definite and probable cases were counted (18 versus 10; HR: 0.55; 95%CI: 0.25-1.18). Nor was there significant difference if TB (definite, probable and possible) and deaths were combined (41 versus 37; HR 0.89; 95%CI: 0.57-1.39). However there were more deaths in the long-course arm, although this was not significant (16 versus 25; HR 1.54; 95%CI: 0.82-2.88).

When analysed by TST status, TST positive participants benefited from 36 months IPT. There were 11 cases versus only 1 case of definite, probable and possible TB (HR: 0.08; 95%CI 0.01-0.61). There were 10 cases versus only 1 case of definite and probable TB (HR:0.09; 95%CI 0.01-0.67). TB (definite, probable and possible) and all deaths were also significantly better (20 versus 4; HR: 0.17; 95%CI: 0.06-0.50). When just deaths were looked at, the 36 month arm did better though this was not significant (9 versus 3; HR: 0.28; 95%CI: 0.08-1.03).

However, the results for TST negative participants were surprising and worrying. There were no significant differences or even trends with respect to TB. But there were 21 deaths on the 36 month arm versus 7 on the short-course arm and this was significant (HR: 2.99; 95%CI: 1.27-7.04).

The reasons for this are unclear. Only one death, due to hepatic encephalopathy, appeared to be due to a known isoniazid side-effect. The adverse event rates between the arms were almost

identical (1% versus 1.3%). Nevertheless, this was a double-blinded RCT and the significantly higher deaths in TST negative people in the 36 month arm should not be ignored.

COMMENT

The findings of the Cochrane Review and the Botusa trial show that TST status is relevant. There is no evidence that TST negative people benefit from any form of IPT prophylaxis.

In the case of long-term prophylaxis, which is now recommended by WHO guidelines and likely where other guidelines are heading, TST negative people could be put at risk of harm unnecessarily.

Guideline writers appear to be focusing on reduced TB incidence demonstrated by IPT studies. But mortality is surely a more important measure from the perspective of patients than TB incidence.

Overall, the short-course IPT studies show no significant mortality benefit when TST status is not taken into account. And in the one major long-course IPT trial there is unequivocally no mortality benefit if TST status is not taken into account. The Mantoux test should therefore not be removed from guidelines.

There is a concern that implementing the Mantoux test is too burdensome for many health facilities. If that is the case, then we need to ask if such facilities should be implementing IPT, especially long-course IPT.

References

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PREVENTION

DSMB stops oral tenofovir monotherapy arm of VOICE PrEP study due to lack of difference compared to placebo

Research into the use of tenofovir as daily prophylaxis to prevent HIV infection (PrEP) was further complicated by news that one of the key ongoing studies has discontinued women using tenofovir as monotherapy.

On 28 September 2011, the Microbicides Trial Network (MTN), announced that following an interim review by the Data and Safety Monitoring Board (DSMB), the study would be unable to show a reduction in transmissions in patients using daily oral tenofovir and that this arm of the study would be stopped.

Previous studies have reported a strongly protective effect in both high-risk MSM (iPrEX study) and heterosexual populations (Partners in Prevention and TDF2 studies) with a negative result reported in heterosexual women (FEM-PrEP study). The Caprisa 004 study found a 43% protective effect of daily tenofovir gel.

The phase 2b VOICE (Vaginal and Oral Interventions to Control the Epidemic) study has enrolled more than 5,000 HIV-negative women at 15 clinical research sites in Uganda, South Africa and Zimbabwe.

The study randomised women to one of five groups: daily oral tenofovir, daily oral Truvada, daily oral placebo tablet, daily tenofovir gel or daily placebo gel.

The remaining four arms will continue to be studied, with results expected in 2013.

Information on the numbers of HIV infections that have occurred in any of the study arms will not be available until this time. Without this analysis it is impossible to know explain the current study results.

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MTN press release. MTN statement on decision to discontinue use of oral tenofovir tablets in VOICE, a major HIV prevention study in women. (28 September 2011).

<http://www.mtnstopshiv.org/node/3619>

Questions and Answers about the modification of VOICE study:

<http://www.mtnstopshiv.org/node/3622>

Summary of other PrEP studies:

<http://www.avac.org/ht/d/sp/i/326/pid/326>.

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:

- If I am exclusively breastfeeding, is it still safe to give my baby water or ORS?
- Will my CD4 increase using ARVs in pregnancy?
- Why does my doctor want to switch me from Combivir...?
- What is my risk of viral load rebounding?
- If I donated blood does this mean I am HIV-negative?
- What is the cost of Truvada?
- Are meds working ok in pregnancy?
- How long will we be taking pills?
- How can my partner test HIV positive and I test HIV negative?
- Am I addicted to sex since my diagnosis?
- Can I get HIV from a cold sore?
- How do I know if my meds are causing bone problems?
- What are the risks of cocaine on CD4 counts for someone on HIV meds?

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>



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Southern African HIV Clinician's Society
www.sahivsoc.org

HIV i-Base, 4th Floor, 57 Great Suffolk Street, London, SE1 0BB.
T: +44 (0) 20 7407 8488 F: +44 (0) 20 7407 8489