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C O N T E N T S

htb south

EDITORIAL

Welcome to the first issue of 2011. In this issue we start with reports from the first (yes, 30 years into the epidemic) international workshop on HIV and women.

Conference reports also include exciting news on a new TB medication and diagnostic test (from the 41st Union World Conference on Lung Health); early data, presented at Glasgow, suggesting boosted PI monotherapy maintenance may not be a viable option in settings without access to viral load monitoring and promising results from the Caprisa 004 microbicide trial.

We also include a report from the iPrEX study and a summary of US CDC preliminary guidance for use of PrEP.

Richard Jeffery's basic science reports include the published results from the single case of functional cure in an HIV-positive man who received stem-cell transplantation from a donor with the delta-32 deletion.

As usual, we don't have room for all of our reports here, further conference reports and other news from HTB can be found on our website.

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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CONFERENCE REPORTS

1st International Workshop on HIV and Women

10–11 January 2011, Washington

Introduction: what took so long?

Polly Clayden, HIV i-Base

Thirty years into the history of the epidemic, the 1st International Workshop on HIV and Women was convened in Washington by Virology Education at the beginning of January 2011.

This meeting included some excellent overviews and all the slides are online.

http://www.virology-education.com/index.cfm/t/Workshop_materials/vid/7F5C7280-BB2F-AFB8-9E1C67CB7C0278B1

Many of the presentations underlined how little we know. In her talk on HIV Treatment in Women, Kathleen Squires reminded us that from 1987–1990 only 6.7% of the 11,909 participants in ACTG trials were women. Despite increased representation by women, most studies since 1990 lack statistical power to definitively answer many important questions. And a meta-analysis of antiretroviral registrational trials from 2000–2008, showed that only 20% of 22,411 participants overall were women.

The good news is that the number of HIV-positive women participating in trials is increasing although sex/gender based analyses are relatively uncommon. Most analyses show higher discontinuation rates in women, although the factors that drive this are unclear.

In the session on pharmacokinetics, Angela Kuasaba described "what is important?" with regards to drug exposure in women. Whether increased drug exposure may translate to better efficacy or more adverse events; dosing in pregnancy and post partum; interactions with progestins and oestrogens and oral and topical concentrations when using antiretrovirals in prevention all need to be better characterised.

Quarraisha Abdol Karim looked at where we are with microbicides and Glenda Gray at the challenges a woman faces in her lifetime living with HIV from adolescence, through pregnancy, ageing and menopause.

The slides from all the lectures are worth looking at for anyone wishing to learn about or get an update on the current state of the art.

Overall this meeting is a welcome addition to the conference calendar and will provide researchers with a dedicated forum to present their work (and perhaps drive more research), as there are still many unanswered questions. At the moment, making recommendations concerning HIV treatment and women is often an exercise in how many different ways can you say, "there are no data".

Articles from this meeting in this issue of HTB include:

- Lopinavir/ritonavir: women versus men
- Quality of life in the GRACE study
- Antiretroviral pharmacokinetics in women with undetectable viral load
- No association between bone mineral density and lipodystrophy in women receiving antiretroviral therapy
- The impact of antiretroviral treatment on fertility intentions in South Africa

Lopinavir/ritonavir: women versus men

Polly Clayden, HIV i-Base

Lopinavir/ritonavir (LPV/r) is used frequently in pregnancy and in second line regimens in resource limited settings.

An FDA meta-analysis showed that women made up only 21% of overall participants in phase 2-4 HIV studies from 2000-2006. LPV/r (Kaletra) was approved in 2005.

The originator manufacturer, Abbott, performed a meta-analysis from company data to provide some information on the efficacy, safety and tolerability of LPV/r in women compared to men.

Ashwaq Hermes presented findings from this analysis of seven randomised controlled trials that met the following inclusion criteria: prospective adult trials using the standard dose as part of a three drug regimen with available data to 48 weeks on viral load, CD4, adverse events and discontinuation rates.

The investigation included 2022 trial participants. Of these, 492 were women (286 treatment naïve and 206 experienced) and 1530 were men (1137 naïve and 393 experienced).

Treatment naïve women, treatment naïve men and treatment-experienced women were all younger, having mean ages of 39.2, 38.2 and 38.7 years respectively, than treatment-experienced men, who had a mean age of 41.6 years. White participants made up a greater proportion of both groups of men compared to women, 76.4 vs 48.3 and 58.5 vs 37.9, in the treatment naïve and experienced groups respectively. More treatment-experienced men had a CD4 count of <50 cells/mm3 at baseline, 12.6 vs 5.8. All comparisons p<0.05.

Intent-to-treat analysis revealed similar proportions of women and men with viral load <50 copies/mL at 48 weeks: 69 vs 74% in treatment naïve women and men, p=0.73, and 52 vs 57% in experienced women and men, p=0.3. Mean increases in CD4 count from baseline were also similar between sexes at 48 weeks: 209 vs 200 cells/mm3 in naïve women and men, p=0.42 and 138 vs 123 cells/mm3 in experienced, p=0.253.

Incidence of moderate to severe adverse events also did not differ greatly overall between sexes: 34.3 vs 34.9% in treatment naïve women and men, p=0.89, and 28.2 vs 25.4% in experienced women and men, p=0.495. Although there was a significant increase in the incidence vomiting, 6.6 vs 2.4%, and dyspepsia, 2.3 vs 0.7%, in naïve women compared to men, both p<0.05. Laboratory abnormalities were again similar overall, but with a greater incidence of raised triglycerides (>750 mg/dL) in 7.2 vs 1.4% in treatment-naïve and 7.6 vs 2.0% in treatment-experienced men vs women, respectively (both p<0.05).

When the investigators looked at overall rates of discontinuation of treatment for any reason, they found that these were greater in treatment-naïve women compared to men, 21.7 vs 15.4%, p=0.013. Lost to follow up made up a high proportion of this group, 8.7 vs 4.1%, of women compared to men, p=0.004.

Among experienced women and men, the overall rates of discontinuation were similar: 23.8 vs 21.9%, p=0.608.

Discontinuation due to adverse events was greater in treatment naïve women compared to men: 8.7 vs 5.2%, p=0.034. However, these rates were similar among the treatment experienced group: 7.8 vs 4.6% of women compared to men, p=0.136.

Dr Hermes noted that the older gel formulation was used in the treatment naïve trials whereas the tablet formulation was used in the trial of treatment-experienced patients.

The investigators concluded that this analysis revealed no substantial overall differences between women and men with regards to efficacy, safety and tolerability. They are continuing their evaluation of these data.

COMMENT

Overall this meta-analysis of seven randomised controlled studies including 492 women and 1530 men did not find significant differences in virological or immunological response or overall incidence of adverse events.

Although there are always difficulties with interpretation with any post hoc analysis it seems a good idea for companies to look at their own data in this way.

Reference

Hermes A et al. Efficacy, safety and tolerability of lopinavir/ritonavir in HIV-infected women: results of a meta-analysis of 7 prospective, randomised clinical trials through 48 weeks. 1st International Workshop on HIV and Women. 10–11 January 2011, Washington. Oral abstract O_17.

Quality of life in the GRACE study

Polly Clayden, HIV i-Base

One study that was designed to enroll and evaluate a high proportion of women was the Gender, Race And Clinical Experience (GRACE) open label trial of darunavir/ritonavir (DRV/r)-based regimens. [1]

This trial also included a high proportion of black participants and everyone was treatment experienced.

Of the 429 people enrolled, 66.9% were women, 61.5% black, 22.4% Hispanic and 15.2% white.

This trial found significant differences in discontinuations with substantially more women than men discontinuing for reasons other than virological failure, 32.8% vs 23.3%, p=0.042. A higher proportion of black participants did not complete the study compared to hispanic or white participants.

Intent-to-treat analysis showed 50.9% of women compared to 58.5% men had viral load <50 copies/mL at week 48, p=0.067. In the analysis that censored the patients that discontinued for reasons other than virological failure, the response rate was 73.0 in women compared to 73.5% in men, p=0.44.

Health-related quality of life (HRQoL) measures are used to quantify the physical and mental aspects of being HIV-positive that can have an impact on someone's overall well being. Several studies have demonstrated a correlation between HRQoL and survival of people with HIV.

Judith Feinberg reported the HRQoL results by sex and race from the GRACE study. [2]

HRQoL was measured by the validated Functional Assessment of HIV Infection (FAHI) questionnaire. This was completed at baseline, at weeks 4, 12, 24 and 48 (or when a participant left the study, if they discontinued early).

FAHI consists of 47 questions to measure aspects of physical, emotional, functional and social well-being, and cognitive functioning. The total score (range 0-176, higher scores better) is calculated as the sum of the scores from the five subscales.

The investigators also conducted some post hoc analyses to look at factors associated with an improvement in scores. Analyses were performed on the observed population.

The total FAHI scores at baseline were 118.1 (n=423) overall, 116.8 (n=283) women and 120.8 (n=140) men. They were 119.5 (n=261), 114.1 (n=94) and 119.5 (n=64) for black, Hispanic and white ethnicity respectively.

The overall score of the total population improved significantly by week 4, with a mean increase from baseline of almost 30%, p<0.05. By week 12, near maximum changes of just over 70% were achieved overall and these remained consistent through to week 24 and week 46. Patterns of improvement were similar for men and women, but improvements were greater for women, with over 80% at 48 weeks, than men whose improvement was less than 60%. Black participants also demonstrated greater improvement in total FAHI score that either Hispanic or white participants.

The investigators found that patients with lower baseline HRQoL scores were significantly more likely to discontinue the study than those who scored higher, p=0.044. They noted that this is the first time lower baseline HRQoL has predicted study discontinuations.

In order to assess whether the QoL improvement was due to participants with lower HRQoL scores discontinuing early, the investigators conducted a sensitivity analysis evaluating only those who completed the study. They found, the baseline value with patients who discontinued excluded was 120.1 and the total FAHI score still improved to the same extent from baseline to 48 weeks compared to the total study population, p<0.05.

Multivariate analysis identified four factors that were significantly associated with the improvement in FAHI score over 48 weeks: lower baseline FAHI score, p<0.001; lower baseline CD$ count, p=0.0077; virological response, p=0.0045 and the timepoint of analysis (total FAHI score increased over time. Neither sex nor ethnicity was independently found to be associated.

The investigators concluded that HRQoL improved significantly for the study population overall and that sensitivity analysis suggests that this was not due to people with low HRQoL scores discontinuing the trial.

The largest improvements in total FAHI scores were seen in women and black participants, despite these two groups having lower virological response rates and higher discontinuation rates when compared to men and to Hispanic and white patients, respectively.

"In future, it may be possible to identify patients with a higher risk of discontinuation based on their baseline HRQoL scores; these patients could then be more closely monitored and supported, potentially improving retention."

COMMENT

These are interesting findings and GRACE must be applauded for conducting this study in harder to reach trial populations.

Gender sub-analyses from ARTEMIS and CASTLE trials also show similar virological response between women and men.

References

1. Currier J et al. Sex-based outcomes of a single-group trial. Annals of Internal Medicine. Volume 153. Number 6. 21 September 2010.
2. Feinburg J et al. Association of sex and race with health-related quality of life in patients treated with darunavir/ritonavir-based therapy in the GRACE trial. 1st International Workshop on HIV and Women. 10–11 January 2011, Washington. Oral abstract O_15.

Antiretroviral pharmacokinetics in women with undetectable viral load

Polly Clayden, HIV i-Base

Although some studies have shown higher antiretroviral concentrations in women versus men, data are limited.

Mona Loufty presented findings from a Canadian study to look at whether or not non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI) drug levels are significantly higher in women compared to a largely male historical population. This analysis also examined whether or not there was an association between weight and drug concentrations.

This was a cross-sectional study conducted at 14 sites across Canada. Women, 18 years and above, on their first antiretroviral regimen, receiving current agents at standard doses (atazanavir, atazanavir/r, lopinavir/r, efavirenz or nevirapine- containing regimens), with an undetectable viral load <50 copies/mL were included.

Timed blood samples for Cmin and Cmax occurred weekly for three weeks. Demographic and clinical data were also collected.

Each individuals median Cmin and Cmax were used to calculate the ratio to the published population's mean values for the antiretroviral.

Data from 79 women were included in the analysis. They were a median age of 41 (IQR 36-48) years, had been receiving HAART for a median of 21 (IQR 8-45) months and had a median CD4 cell count of 484 (IQR 380-620) cells/mm3.

Median antiretroviral Cmin and Cmax ratios to population mean were 1.22 (p<0.01) and 0.83 (p=0.01) respectively. With 32.2% and 8.9% with values %>1.5 population mean. See table 1 for Cmax and Cmin ratios by antiretroviral.

In linear regression models, including age, ethnicity, CD4 and weight, the investigators found no variables correlated with Cmin or Cmax ratios. They noted that both ratios were highly variable within and between women in this cohort.

They also noted that the study was limited having no real time male control group, inclusion criteria that resulted in limited range in the covariates and possible selection bias due to the commitment required for participation.

They suggested that these pharmacokinetics may result in better viral suppression in women and that women with side effects may benefit from drug level monitoring if drug concentrations may be the culprit.

COMMENT

As Angela Kashuba discussed in her overview, it seems sex/gender based differences in PK are often subtle and may disappear with weight adjustment.

Although these differences may have a small impact at population level, for some individuals they could be significant and TDM may be useful here. However, nuanced drug dosing is challenging (and not feasible in settings with limited resources).

Reference

Loutfy M et al. Antiretroviral pharmacokinetics in HIV-positive women with full virological suppression on current regimens. 1st International Workshop on HIV and Women. 10—11 January 2011, Washington. Oral abstract O_22.

Table1: Cmax and Cmin ratios by antiretroviral

ARVs N	Ratio of Cmin to population mean			Ratio of Cmax to population mean		
	%>1.5 pop. mean	Median	p-value	%>1.5 pop. mean	Median	p-value
Atazanavir N=8	25.0	0.95	0.72	0	0.64	0.08
Atazanavir/r N=17	17.6	0.95	0.85	0	0.66	<0.001
Lopinavir/r N=19	31.6	1.23	0.07	0	0.89	0.44
Efavirenz N=16	37.5	0.95	0.37	25	0.79	0.63
Nevirapine N=19	52.6	1.62	<0.01	15.8	0.96	0.47

No association between bone mineral density and lipodystrophy in women receiving antiretroviral therapy

Polly Clayden, HIV i-Base

A number of studies have found an association between lipodystrophy and bone mineral density.

Rebecca Hicks presented data from a study of 47 HIV-positive women enrolled from the Maple Leaf Medical Clinic and Sunnybrook Health Services Clinic in Toronto. The study was conducted to examine the potential correlation between lipodystrophy and reduced bone mineral density (BMD) in women receiving antiretroviral treatment.

This was a cross-sectional study and participants were 18 years or older, on stable HAART for at least two months, not pregnant, and had a DXA BMD test.

The women completed a questionnaire that collected demographic data and information on the presence and severity of lipodystrophy. Lipodystrophy was diagnosed according to the HIV Outpatient Study criteria. Women were considered to have lipodystrophy if they had at least one severe symptom of fat redistribution, or at least two symptoms with one being of at least moderate severity.

Data on DXA BMD test results, osteoporosis risk factors and fracture history were collected from patient charts. A z-score was used to measure BMD (> –2.5 classified as low bone mass).

Almost half (25/47) of the women evaluated met the study definition for lipodystrophy. There were no significant differences in age, 42 vs 39 years, p=0.42; ethnicity 72 vs 68%, were black, p=0.73; duration of HIV infection, 7 vs 8 years, p=0.73, duration of HAART, 3 vs 4 years, p=0.75 or current CD4 count 500 vs 540 cells/mm3, between those with or without lipodystrophy respectively.

The investigators found similar BMD z-scores at the L1-L4 location, –0.60 vs –0.52, p=0.86; femoral neck –0.22 vs 0.05, p=0.44 and total hip –0.48 vs –0.58, p=0.83 in women with and without lipodystrophy.

Multivariate analysis adjusted for age (–0.036, 95% CI –0.094–0.023, per 10 years, p=0.222) and ethnicity (0.133, 95% CI 0.036–0.231 for black vs other, p=0.009), in which only ethnicity remained significant, revealed no association between lipodystropy and femoral neck BMD z-scores (0.014, 95% CI –0.072-0.100) p=0.744.

The investigators suggested this finding that lipodystrophy and reduced BMD were not associated with each other in this study may have been due to reduced power caused by small sample size. They noted that as BMD was significantly associated with black ethnicity, with 70.2% of the sample population identifying as black, the results may have been skewed.

COMMENT

These data were hard to interpret, particularly as the investigators used a definition of lipodystrophy that did not differentiate between fat loss and fat gain.

Reference

Hicks R et al. Pilot study exploring the association between bone mineral density and lipodystrophy in HIV-positive women taking antiretroviral therapy. 1st International Workshop on HIV and Women. 10–11 January 2011, Washington. Oral abstract O_15.

The impact of antiretroviral treatment on fertility intentions in South Africa

Polly Clayden, HIV i-Base

There is limited information about the impact of expanding access to HAART in settings with limited resources and large epidemics on women's reproductive decisions and outcomes.

Angela Kaida showed findings from an investigation conducted to assess whether the use and duration of HAART was associated with: fertility intentions, contraception use and method preference, and the incidence of live birth, among women attending the Perinatal Research Unit (PHRU) in Soweto, South Africa.

The study was cross-sectional and used an interviewer-administered survey and a case note review. A total of 751 women, aged 18-49, took part. Of these, 253 had received HAART for a median duration of 31 months. The mean CD4 count was 406 cells/mm3 and 81% had undetectable viral load (group 1). A further 249 women were also HIV-positive but HAART-naïve, with a mean CD4 count of 351 cells/mm3 (group 2). A reference group included 249 HIV-negative women (group 3).

Multivariate analysis (n=674) revealed HIV-positive women were nearly 60% less likely to report fertility intentions than HIV-negative women but the difference between those receiving treatment and naïve women was modest. With HIV-negative women as reference, the investigators reported adjusted odds ratio (AOR) 0.35 (95%CI 0.21-0.60) and AOR 0.4 (95% CI 0.23-0.69) for women HAART-naïve and receiving HAART respectively.

When the investigators looked at the prevalence of contraceptive use among non-pregnant sexually active women (n=563) in this cohort, they found that use was high–nearly 80%, compared to an average of just over 60% among South African women in general. Women receiving HAART were significantly more likely to use contraception: 86% of women receiving HAART, 82% of HAART-naïve women and 69% of HIV-negative women reported contraceptive use, p<0.001. Multivariate analysis, compared to HIV-negative women, found AOR 1.59 (95% CI 0.88-2.85) and AOR 2.40 (95% CI 1.25-4.62) for women HAART-naïve and receiving HAART respectively. The investigators also noted that women receiving HAART were more likely to use dual contraception.

Finally Dr Kaida presented preliminary data from an assessment of lifetime incidence of live birth by time period. For this analysis each participant (n=748) contributed woman-years of follow up based on dates of HIV diagnosis and starting HAART (for those who had). With the HIV-negative time period as a reference, this analysis showed a 69% higher incidence of live birth in the HAART naïve time period than the HIV-negative period—adjusted relative risk (ARR) 1.69 (95%CI 1.48–1.93)—but 66% lower in the period when women received HAART, ARR 0.34 (95% CI 0.23–0.49).

The investigators suggested that this study highlights the potential value of improved integration between HIV prevention, testing and HAART services with sexual and reproductive health programming.

Reference

Kaida A et al. The impact of expanding access to HAART on fertility intentions, contraceptive use and fertility among women in an HIV hyper-epidemic setting. 1st International Workshop on HIV and Women. 10–11 January 2011, Washington. Oral abstract O_09.

CONFERENCE REPORTS

41st Union World Conference on Lung Health

11–15 November 2010, Berlin

Introduction

Organised by the International Union Against Tuberculosis and Lung Disease (The Union), this conference is the largest annual lung health event focusing on the issues as they affect low- and middle- income populations.

The theme this year was "TB, HIV and Lung Health: From Research and Innovation to Solutions" pointing to the need for new drugs and vaccines, but also for the resources and policies required to put these new tools to use to help some of the poorest citizens, where demand and need is the greatest.

Approximately 2500 delegates attended from over 100 countries.

An impressive programme of webcasts from the meeting ensure that most of the oral sessions can now be viewed online, including slide presentations.

http://uwclh.conference2web.com/content/all#/?groups=3

The programme and abstract book from this meeting can also be downloaded from the conference website.

http://www.worldlunghealth.org/confBerlin/index.php?lang=en

Faster conversion rates with TMC-207 versus placebo plus OBT for the treatment of MDR-TB

Polly Clayden, HIV i-Base

TMC207 is the first in a new class (diarylquinoline) of anti-tuberculosis (TB) drugs to inhibit mycobacterial ATP synthase. It has the potential to improve treatment of both drug-sensitive (DS) and multidrug- resistant (MDR) TB.

In an oral presentation, David McNeely first provided some background information on this drug. [1] TMC-207 previously increased culture conversion by approximately 40% in MDR TB patients in an 8-week trial (see below). These findings were published in the NEJM and we reported them in the August 2009 issue of HTB. [2, 3]

He also showed several key pharmarmacokinetic findings from the phase 1 trials. These were: a positive food effect with TMC-207 giving a two-fold increase in drug exposure when taken with a meal; coadministation of rifampicin lowers TMC207 levels by 50% and coadministartion of lopinavir/ritonavir (LPV/r) modestly increases TMC-207 exposure by 22%. Unpublished information on nevirapine shows a similar interaction. These data suggest the potential to administer the drug with antiretrovirals. Dr McNeely noted that this did not occur in the early trials in patients, as this

information was not available. The drug also has a long terminal half-life and does not reach steady state by day 14.

He reported that, to October 2010, 595 participants had received TMC-207 in all trials: 217 healthy volunteers; 147 DS and MDR-TB patients (79 for 24 weeks). There is also an open label trial (Breathe) in which 231 MDR TB patients have been enrolled that is ongoing.

In the second part of this presentation, Andreas Diacon showed findings from TMC-207 C208 stage 2. This randomised, double-blind, placebo-controlled trial is in two stages. It is conducted in patients with newly diagnosed smear positive pulmonary MDR-TB. Following a one-week washout period, patients were randomised to receive optimised background therapy (OBT) plus TMC-207 or placebo.

TMC-207 was dosed at 400mg once daily for 14 days and then 200mg TIW (three times a week).

In Stage 1, conducted in South Africa, 47 patients received 8 weeks of TMC207 (n=23) or placebo (n=23). They then continued their MDR-TB treatment with background regimen alone. All stage 1 patients have completed the trial. Stage 1 found a significant increase in the proportion of culture negative subjects among those who received TMC207 compared to placebo (48% vs. 9% at week 8). There was a 58% reduction in mean time to culture conversion in those who received TMC-207 compared to placebo.

In Stage-2, 161 patients were randomised to receive 24 weeks of either TMC207 or placebo added to the same 5-drug background regimen. All stage 2 patients have completed 24 weeks of TMC207/placebo plus OBT. They are now completing 18–24 months treatment with 2nd line TB drugs (without TMC207/placebo).

Stage 2 was a multi country trial conducted in Brazil, India, Latvia, Peru, Phillipines, Russia, South Africa and Thailand.

The objective was to demonstrate superiority of TMC-207 compared to placebo at 24 weeks. The primary endpoint was time to sputum culture conversion (MGIT). Participants who discontinued during 24 weeks were considered failures irrespective of their culture status at time of discontinuation.

The secondary endpoint was culture conversion rates at 24 weeks.

At baseline about 65% of patients were men, with a median age of 33 years, 85% were HIV-negative and they weighed about 53kg. Patients had confirmed resistance to isoniazid and rifampicin and had not received second line TB treatment previously. HIV-positive patients had a CD4 count greater than 300 cells/mm3 and were not receiving antiretroviral treatment. No patient had significant extrapulmonary TB or other illness.

Of the total randomised patients (80 TMC-207, 81 placebo), 160 were included in the ITT analysis (one patient randomised to the TMC-207 arm, did not receive study drug). The researchers also conducted a modified ITT analysis of 132 patients. Exclusions included, non-MDR patients (4 TMC-207 and 8 placebo), XDR patients (3 TMC-207 and 4 placebo) and patients, for whom, culture results were not evaluable.

OBT was a 5-drug standardised background regimen: ethionamide, pyrazinamide, ofloxacin, kanamycin and terizodone/cycloserine.

Dr Diacon noted that there were high rates of baseline resistance

to kanamycin at baseline among patients from European sites. He also noted worryingly high rates of resistance to pyrazinamide across all sites. In vitro evidence suggests there may be good synergy between TMC-207 and pyrazinamide.

Adverse events were similar across both groups. None were serious and discontinuations were unrelated to the study drug.

He reported that the addition of TMC-207 to a 5-drug OBT regimen resulted in faster culture conversion within 24 weeks, p=0.003. It also gave a shorter median time to 50% culture conversion of 12 vs 18 weeks. And there was a higher sputum conversion rate at 24 weeks of 79 vs 58%, p=0.008.

COMMENT

These results are very promising and phase 3 trials will begin this year. Discussions between Tibotec and regulatory authorities in the US and Europe are ongoing and data should be submitted to the FDA and EMA for accelerated or conditional approval this year.

Demand for early access to this drug is already considerable. Activist organisations published an open letter to Tibotec calling for expanded access. This letter was handed over at the beginning of the World Lung conference at which the presentations discussed here were made. The company has committed, both in a teleconference on 7 January and in the OpenForum meeting in Addis Ababa in August 2010, to accelerate access. In countries that have a regulatory framework for pre-registration access, such as South Africa, this will be the preferred method. Although expanded or accelerated access has been the norm for HIV drugs, TMC 207 could set precedence for these strategies with TB drugs. Tibotec needs to maintain a balance between making it available fast to those in greatest need and ensuring it is used judiciously.

Tibotec intends to carry out a trial that will collect safety data in countries that do not provide for pre-registration access and this will allow drug-resistant patients with limited options to access TMC207. Quite reasonably, Tibotec is concerned that it only partners with health-delivery institutions that are capable of ensuring high adherence. There are also plans to include TMC207 in studies with the investigational drug in development from Otsuka Pharmaceuticals, OPC-67683. This is a nitroimidazole and is in phase 2b. It is especially important that OPC-67683 or other drugs under investigation for DR-TB, such as PA-824, become available soon after TMC207, so as to reduce the risk of continuously adding TMC207 to potentially failing second-line regimens and consequently risking a high rate of TMC207 resistance.

References
1. McNeeley D et al. TMC-207 versus placebo plus OBT for the treatment of MDR-TB: a prospective clinical trial. The International Journal of Tuberculosis and Lung Health. S3 41st Union World Conference on Lung Health. 11-15 November 2010.
   http://uwclh.conference2web.com/content/187
2. Diacon AH et al. The diarylquinoline TMC207 for multidrug-resistant Tuberculosis. NEJM. 2009 June 4. 360, 2397-2405. (4 June 09).
   http://content.nejm.org/cgi/content/abstract/360/23/2397
3. Geffen N. TMC207 reduces time to sputum conversion in phase II trial on patients with drug-resistant TB. HIV Treatment Bulletin. August 2009.
   http://i-base.info/htb/4403

Xpert MTB-RIF validation study from Tanzania

Polly Clayden, HIV i-Base

The Xpert MTB-RIF assay (Xpert, described in detail in the article below) gained a lot of attention at this meeting.

This is a cartridge-based, real-time PCR test with automated sample processing, amplification, detection of M. tuberculosis and resistance to rifampicin (RIF).

Andrea Rachlow presented data from an evaluation study of this test performed in Tanzania.

This study enrolled 292 consecutive symptomatic patients. These patients were classified as TB positive or negative following results of sputum smear, culture on solid and liquid media on three different sputum samples (plus chest X-ray and HIV test), and sustained recovery after two months follow-up.

Stored samples were then tested with the Xpert (three frozen, untreated sputum samples per patient).

The investigators reported, that of 69 culture-positive TB cases, Xpert detected 88.4% (95% CI 78–95%). Sensitivity was notably different between smear-positive and only culture-positive patients, with sensitivities of 98% and 61% respectively.

Among all TB negative patients, Xpert detected one positive result (99% specificity). One of the samples from 45 patients that were culture-positive for non-tuberculous mycobacteria (NTM) also tested positive with Xpert.

Additionally, the test performed well in HIV-positive patients (n=50) with 88% sensitivity and 89% specificity.

The investigators noted that the test is easy to use and the short time to a result could mean avoidance of loss to follow up during the diagnostic process, which could result in a 5-15% decrease in TB deaths worldwide.

They added that further studies are required to confirm the tests performance on fresh sputum samples and on other clinical material.

Reference

Rachlow A et al. Detection of TB using the Cepheid Xpert MTB/RIF® Assay: a clinical validation study from Tanzania. The International Journal of Tuberculosis and Lung Health. FA-101098-13

http://uwclh.conference2web.com/content/667

Further information
http://www.treatmentactiongroup.org/press.aspx?id=4320
http://www.tac.org.za/community/node/2962

Gene Xpert demonstrates good sensitivity and specificity but at high cost

Nathan Geffen, TAC

We published a report on the Gene Xpert in the April 2010 edition of HTB South. [2] Catherine Boehme of FIND and her colleagues have since published the test results of Cepheid's Gene Xpert TB diagnostic technology in the NEJM. [1] This device aims to diagnose TB and determines rifampicin resistance in less than two hours. Preliminary results have been good. This study confirms that this device has high sensitivity and specificity in a variety of settings in both HIV-positive and HIV-negative patients and in culture-positive sputum-negative patients.

Over 1,800 patients were screened at five sites located in Lima, Baku, Cape Town, Mumbai and Durban. 1,730 patients were able to provide three sputum samples with sufficient volume and were consequently eligible for the study. Of these, 268 were excluded from final analysis, 115 because they were culture-negative and suspected of MDR TB while receiving treatment, 28 because three or more of their cultures were contaminated, 23 because they had growth of non-MTB only, 10 because they had indeterminate phenotypic rifampicin results, 39 because they were smear-positive but culture-negative, seven because they had suspected culture cross-contamination and 46 because they died or were lost to follow-up.

Of the 1,462 included in the main analysis 741 were culture-positive, of whom 567 were smear-positive and 174 were smear-negative. Of the 721 culture-negative cases, 105 had clinical TB and 616 did not have TB (as determined by a clinical review committee).

As explained in our previous article the Gene Xpert consists of a computer installed with Cepheid's proprietary software and a machine –the smallest of which is about the size of a desktop computer– that takes cartridges loaded with sputum and reagents. The cartridges consist of a syringe barrel, a sonicator dome, a reverse-transcriptase PCR tube and a rotary valve. The smallest version of the machine takes four cartridges. The highest capacity one apparently contains 100 cartridges. As explained below, two or even three cartridges might be needed for a patient.

The screening results and consequent inclusion and exclusion criteria of patients in various analyses is complicated in this study. Table 1 presents an overview that readers can refer to when reading the remainder of this summary.

Table 1: Screening results. Adapted from Boehme et al.

Number of patients screened	1,843
Number of patients eligible	**1,730**
Number of eligible patients excluded	268
Excluded because culture-negative suspected MDR TB while receiving therapy	115
Contamination of ≥3 of 4 cultures	28
Had growth of non-MTB only	23
Indeterminate phenotypic rifampicin result	10
Smear-positive sample with all cultures negative	39
Suspected Cross culture contamination	7
Died or lost-to-follow up	46
Included in main analysis	**1,462**
Culture-positive	741
Smear-positive	567
Smear-negative	174
Culture-negative	721
Clinical TB	105
No TB	616

TB sensitivity and specificity

With one sputum sample, the Gene Xpert had a sensitivity of 92% for all culture-positive specimens. This increased to 96% for two samples and 98% for three. Specificity on non-TB cases was 99% with one sputum sample, declining marginally to 98% with three samples. However, for culture-positive, sputum-negative specimens, sensitivity using one sputum sample was 73% rising to 90% with three samples. No site had a sensitivity lower than 83% for culture-positive, sputum-negative specimens.

Further details including confidence intervals are provided in Table 2.

Sensitivity was 94% in HIV-positive patients with pulmonary TB versus 98% in HIV-negative patients (p=0.02). Of the 105 patients with culture-negative samples excluded from the main analysis but who had clinical signs of TB, 29.3% had positive results on the Gene Xpert.

Rifampicin sensitivity and specificity

Of the 723 culture-positive patients correctly identified as having TB by the Gene Xpert, 720 were tested phenotypically for rifampicin resistance (for the remaining three, the Gene Xpert gave indeterminate resistance results). The Gene Xpert identified 200 out of 205 rifampicin resistant specimens correctly for a sensitivity of 98%. It identified 505 out of 515 rifampicin sensitive specimens correctly for a specificity of 98%.

Details of resistance testing with confidence intervals are presented in table 3.

Table 3: Sensitivity and specificity of Gene Xpert on phenotypically determined rifampicin susceptibility. Adapted from Boehme et al.

Site	Sensitivity - number of specimens correctly identified as rifampicin resistant (%)	Specificity - number of specimens correctly identified as rifampicin sensitive (%)
Lima	16/16 (100)	190/193 (98.4)
Baku	47/49 (95.9)	90/94 (95.7)
Cape Town	15/16 (93.8)	126/126 (100)
Durban	3/3 (100)	38/38 (100)
Mumbai	119/121 (98.3)	61/64 (95.3)
Total	200/205 (97.6) [95%CI: 94.4–99.0]	505/515 (98.1) [95%CI: 96.5-98.9]

The authors also did a second analysis that included the results of gene sequencing of the 15 discrepant results between phenotyping and the Gene Xpert. After three of these were excluded from analysis because sequencing gave indeterminate results, sensitivity was 99.1% [95%CI: 96.6-99.7] (209/211 correct) and specificity was 100% [95%CI: 99.2–100.0] (506 correct).

Importantly, 195 out of 200 of the rifampicin resistant specimens were also resistant to isoniazid. This suggests that rifampicin resistance is a good predictor of MDR TB in practice.

In 115 patients, excluded from the main analysis in the study, who were culture-negative but who were diagnosed with MDR TB and consequently received treatment, 51 had positive results on the Gene Xpert. Rifampicin resistance was detected in eight. Interestingly, the authors note that all eight patients were later started on second-line therapy by physicians unaware of the results of the Gene Xpert results.

Table 2: Sensitivity and specificity of Gene Xpert on culture-positive patients and culture-negative patients not treated for TB. Adapted slightly from Boehme et al.

Site and No of Tests	All culture-positive Number correct/Total (%)	Culure-positive and smear-positive Number correct/Total (%)	Culture-positive and smear-negative Number correct/Total (%)	No TB Number correct/Total (%)
Lima	209/211 (99.1)	199/199 (100)	10/12 (83.3)	102/102 (100)
– 95% CI	96.6–99.7	98.1–100.0	55.2–95.3	96.4–100.0
Baku	144/149 (96.6)	80/80 (100.0)	64/69 (92.8)	68/70 (97.1)
– 95%CI	92.4–98.6	95.4–100.0	84.1–96.9	90.2–99.2
Cape Town	142/148 (95.9)	95/96 (99.0)	47/52 (90.4)	186/189 (98.4)
– 95%CI	91.4–98.1	94.3–99.8	79.4–95.8	95.4–99.5
Durban	43/45 (95.6)	30/30 (100.0)	13/15 (86.7)	213/219 (97.3)
– 95%CI	85.2–98.8	88.6–100.0	62.1–96.3	94.2–98.7
Mumbai	185/188 (98.4)	162/162 (100.0)	23/26 (88.5)	35/36 (97.2)
– 95%CI	95.4–99.5	99.7–100.0	71.0–96.0	85.8–99.5
Three sputum samples used	723/741 (97.6)	566/567 (99.8)	157/174 (90.2)	604/616 (98.1)
– 95%CI	96.2–98.5	99.0–100.0	84.9–93.8	96.6–98.9
Two sputum samples used	1423/1482 (96.0)	1127/1134 (99.4)	296/348 (85.1)	1215/1232 (98.6)
– 95%CI	94.6–97.1	98.6–99.7	79.7–89.2	97.5–99.2
One sputum sample	675/732 (92.2)	551/561 (98.2)	124/171 (72.5)	604/609 (99.2)
– 95%CI	90.0–93.9	96.8–99.0	65.4–78.7	98.1–99.6

COMMENT

These results are promising. The Gene Xpert is much easier to use than sputum microscopy. It has a high sensitivity and specificity and appears to be better than culture in a subset of patients who are culture-negative but nevertheless have TB. It has high sensitivity and specificity for detecting rifampicin resistance. The diagnostic can be used in facilities that offer consistent electricity supply. One drawback, as with most TB diagnostics, is that patients need to provide sputum and preferably as many as three samples.

But the main obstacle to wider use of the Gene Xpert will be its price. The cheapest machine reportedly costs $20,000. Each cartridge costs approximately $20. There is a great need for better TB diagnostics primarily in poor communities. Pressure needs to be exerted on Cepheid to bring down the price of this system, which was in any case developed with substantial public investment. Conversely pressure needs to be placed on international TB bodies to fund the implementation of diagnostics such as this one in resource-poor settings.

References

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CONFERENCE REPORTS

10th International Congress on Drug Therapy in HIV Infection

7–11 November 2010, Glasgow

Introduction

The 'Glasgow conference' is held every two years and attracts a broad interest from both European and US clinicians and researchers.

This year the conference abstracts are already posted online as a supplement to the Journal of the International AIDS Society (Volume 13, Supplement 4).

http://www.jiasociety.org/supplements/13/S4

In the references to our reports we include both the conference abstract numbers and the IAS publication link.

A PDF file of the abstracts is also available (direct download):

http://www.biomedcentral.com/content/files/pdf/1758-2652-13-S4-full.pdf

Approximately 200 posters are online as PDF files, categorised by general topics, and posted to the 'webcast' pages of the conference website. A few webcasts are included in this selection.

http://www.hiv10.com/webcastsearch.asp

Reports in this issue include:

- Virological findings from the SARA trial of boosted protease inhibitor monotherapy

- Nevirapine exposure was not associated with hypersensitivity in patients from Malawi

- Estimating the number of people in a country or region with HIV who are undiagnosed and in need of ART

- Pharmacokinetics of lopinavir/ritonavir in combination with rifampicin based TB treatment in children

- Efavirenz versus nevirapine based first line treatment in a South African cohort

Virological findings from the SARA trial of boosted protease inhibitor monotherapy

Polly Clayden, HIV i-Base

There is currently an interest in using boosted protease inhibitor monotherapy as a maintenance strategy in resource rich countries.

A pilot substudy of the DART trial, Second-line Anti-Retroviral therapy in Africa (SARA), randomised 192 patients who had received 24 weeks of lopinavir/ritonavir-based (LPV/r) second-line combination therapy to either continue on this combination or to receive LPV/r maintenance monotherapy. Prior to the switch, DART patients had taken first line therapy for a median of 4.4 years.

Data were presented as a late breaker poster at IAS 2010 suggesting few differences between the two groups in CD4 increases or adverse events in the short term. [1] At week 24 the mean CD4 gain was 48 vs 42 cells/mm3 in the combination and monotherapy arms respectively. For those completing 72 weeks the gains were 159 vs 153 cells/mm3.

No real-time virology was performed in DART but plasma samples were stored from: time at switch to second line, time of SARA randomisation, 24-weeks after SARA randomisation and latest time point (35-107 weeks after SARA randomisation).

Dave Yirrel presented results at Glasgow 2010 from a retrospective analysis of viral load, measured by Roche Amplicor v1.5 on the stored samples. In addition, genotype resistance was assessed on samples with viral load >1000 copies/mL at 24 weeks. Analyses were intent to treat. [2]

The median CD4 counts overall were 86 cells/mm3 at switch to second line and 245 cells/mm3 at SARA randomisation. The majority of patients (86%) had received a triple nucleoside first line regimen and the remainder two nucleosides and an NNRTI. At SARA randomisation 22% were receiving LPV/r + 2/3 NRTIs, 15% LPV/r + NNRTI and 62% LPV/r + NNRTI + NRTI. Of those with viral load measurements 135/173 (77%) had viral load <50 copies/mL.

The investigators found a higher proportion with undetectable viral load among patients on combination therapy compared to monotherapy at week 24, p=0.007. They reported 77% (70/91) vs 60% (66/94) had viral loads <50 copies/mL and 94% vs 84% had viral load <1000 copies/mL.

Among the small number of patients for whom 96-week data were available for analysis, the proportion with rebound to ≥200 copies/mL was greater in the monotherapy than combination therapy arm: 50% vs 20% (n=7 per arm). This difference was similar among those with rebound ≥1000 copies/mL: 40% vs 10% (n=7 in the monotherapy and , n=8 in the combination therapy arms).

Genotype results from the patients with viral load ≥1000 copies/mL at 24 weeks showed 0/5 patients with major protease inhibitor mutations of those in the combination therapy arm and 4/16 (of 19 patients with rebound to 1000 copies/mL) in the monotherapy arm.

The investigators concluded that, over the relatively short period of follow up (median 60 weeks) since SARA randomisation, there was an increase in low level viraemia with monotherapy compared to combination therapy, but no evidence of systematic increase in viral load after loss of suppression.

The EARNEST trial due to start next year will provide data on the long-term effectiveness of PI maintanance monotherapy in this setting. [3]

COMMENT

Neither the numbers involved, nor the duration of the trial make it possible to make any definite conclusion from these data. But it does seem that boosted PI monotherapy may not be a viable option in settings without access to viral load monitoring.

References
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Nevirapine exposure was not associated with hypersensitivity in patients from Malawi

Polly Clayden, HIV i-Base

Although there is a risk of hypersensitivity, nevirapine (NVP) is used widely in first line regimens in resource- limited settings.

The relationship between drug exposure and hypersensitivity with NVP is unknown. It is possible that it is influenced by the effect of polymorphisms in CYP2B6 and CYP3A5 on drug metabolism.

Laura Dickenson and colleagues from Malawi and Liverpool showed findings from a study designed to develop a population pharmacokinetic (PK) model for NVP serum concentrations, and, in turn, to determine the impact of patient demographics, hypersensitivity and genetics on the PK of the drug.

The population PK model included 180 drug-naïve HIV-positive patients (of which 101 were women), starting NVP-based treatment at Queen Elizabeth Central Hospital, Malawi between March 2007 and September 2008. At the time of PK sampling, they were a median age of 34 years old, with a median CD4 cell count of 156 cells/mm3 (range 1-812). The median duration of treatment was 6 weeks (1-26). Twenty-five patients were hypersensitive and 23 coinfected with hepatitis B or C.

The investigators performed rich and sparse sampling in 40 and 140 patients respectively. PK data were available for single nucleoside polymorphisms (SNPs): CYP3A5*6, CYP3A5*3, CYP2B6 983T>C, CYP2B6 516G>T and CYP2B6 785A>G in 89/180 patients. Genotyping was performed using Sequenom iPLEX.

The investigators used non-linear mixed effects modelling (NON-MEM, VI 2.0) to investigate the effects of patient demographics, hypersensitivity, hepatitis and CYP3A5 and CYP2B6 on NVP apparent oral clearance (CL/F).

They found a one-compartment model with first order absorption best described the data. For the final model (n=89) NVP CL/F (relative standard error RSE%) was 2.67 (5%) with interindividual, interoccasion variability of 30% (29%) and 32% (26%) respectively.

The apparent volume of distribution and absorption rate constant were 141L (22%) and 0.77h-1 (31%) respectively.

They reported that none of the available patient demographics were associated with NVP CL/F. Nor did they find an association between NVP CL/F and hypersensitivity or hepatitis.

Only CYP2B6 983T>C and CYP3A5*3 had an impact on NVP CL/F; reducing it by 25% in 983C heterozygotes (allelic frequency 18%) and 40% in CYP3A5*3 homozygotes (allelic frequency 5%).

They concluded that NVP exposure was not associated with the development of hypersensitivity, "which is more likely to be an immunological phenomenon." They added that further studies are warranted to determine the mechanism of NVP hypersensitivity.

Reference

Dickenson L et al. Population pharmacokinetic and pharmacogenetic analysis of nevirapine in hypertensive and tolerant HIV-infected patients from Malawi. 10th International Congress on Drug Therapy in HIV Infection, November 7-11. Glasgow. Poster abstract P181. Published in Journal of the International AIDS Society 2010 13(Suppl 4):P181.

http://www.jiasociety.org/content/13/S4/P181

Estimating the number of people in a country or region with HIV who are undiagnosed and in need of ART

Polly Clayden, HIV i-Base

Estimating the number of people in a country or region with undiagnosed HIV in need of ART is essential for testing and treatment programmes.

Rebecca Lodwick and colleagues from the University College London showed a simple method for making this estimate, which uses data on simultaneous HIV/AIDS diagnoses at low CD4 count.

The HIV surveillance data needed for this method are the number of previously undiagnosed people presenting with AIDS (simultaneous HIV/AIDS) in a year with CD4 count at diagnosis. The number of people with simultaneous HIV/AIDS in a CD4 stratum represents a proportion of the total undiagnosed people with CD4 count in that stratum. The proportion is equivalent to the annual incidence of AIDS in people in that stratum, which can be estimated from cohort studies.

For each stratum the number of people with undiagnosed HIV is estimated by dividing the number of people with simultaneous HIV/AIDS diagnoses (with CD4 count in the stratum) by the CD4 specific AIDS rate.

The investigators obtained an uncertainty range associated with this estimate by assuming the AIDS rate varies according to a normal distribution and the observed number of diagnoses according to a Poisson distribution. They accounted for these two sources of uncertainty simultaneously over 10,000 runs.

They illustrated this method for people with undiagnosed HIV and CD4 count below 200 cells/mm3. Using data from CASCADE the incidence of AIDS in this CD4 stratum among ART naïve patients has been estimated to be 0.25 per year (95% CI, 0.21-0.28). They used an example that supposed during the past year there were 50 simultaneous HIV/AIDS diagnoses with CD4 counts below 200 cells/mm3. Then the estimated number of undiagnosed people in this CD4 stratum would be 50/0.25=200.

The estimated 95% uncertainty range would be 144-268.

They acknowledged that a potential source of bias is the possible under-diagnosis and under-reporting of simultaneous HIV/AIDS diagnoses.

They also note that the method depends on high levels of ascertainment of people presenting with simultaneous HIV/AIDS and on availability of CD4 count at diagnosis.

The investigators intend to make a SAS programme available that will perform this calculation.

References

Lodwick RK et al. A method to estimate the number of people in a country or region with HIV who are undiagnosed and in need of ART. 10th International Congress on Drug Therapy in HIV Infection, November 7-11. Glasgow. Poster abstract P165. Published in Journal of the International AIDS Society 2010 13(Suppl 4):P165.

http://www.jiasociety.org/content/13/S4/P165

Pharmacokinetics of lopinavir/ritonavir in combination with rifampicin based TB treatment in children

Polly Clayden, HIV i-Base

Lopinavir/ritonavir (LPV/RTV) is first line treatment for young children in South Africa. Concomitant treatment for TB is common in children with HIV. There is a complicated interaction between this boosted protease inhibitor and the first line TB drug, rifampicin (RIF), which reduces the bioavailabilty and Cmin of LPV by approximately 75% and 99% respectively.

Two strategies are possible to increase the LPV levels when it is dosed with RIF - either increasing the dose of RTV to a LPV:RTV 4:4 ratio or doubling the dose to a LPV:RTV ratio 8:2.

Chao Zhang and colleagues from the University of Cape Town showed a population pharmacokinetic (PK) model developed to describe the interactions between LPV, RTV and RIF in children. They used this to look at the effect of various factors (age, BSA, weight, gender, haemaglobin, albumin, ALT) on LPV and RTV PK, and make dosing recommendations for HIV/TB coinfected children receiving these drugs concurrently. [1]

In this study, 39 children with HIV only received the standard dose of LPV/RTV, 4:1, (control group); 15 coinfected children received the super-boosted dose, 4:4; and 20 the double dose, 8:2. Then 11 coinfected children received the standard dose following RIF-based treatment. Repeated sampling was performed (4-6 from each child) up to 12 hours post dose.

The children were a median age of 21 months (range 6 months to 4.5 years) and a medium weight of 10.2kg (range 5-17kg).

Using a one-compartment model with first order absorption for LPV and a one-compartment model with transit absorption for RTV, the investigators modelled the effect of RTV concentration on LPV clearance as direct inhibition with an Emax model.

The investigators found that, during concomitant treatment with RIF, the relative oral bioavailability of LPV was reduced by 79% in children receiving the twice the standard dose of LPV/RTV. RTV clearance was 18 L/h with RIF and 13L/h without.

The estimated baseline clearance of LPV, when there was no detectable RTV was 4.34 L/h. As the concentrations of RTV increased, the clearance of LPV decreased in a sigmoid relationship (EC 50, 0.051 mg/L). They found volume of distribution for LPV and RTV were 11.7 and 102 L respectively.

When the investigators performed simulations for dose optimisation during RIF-based TB treatment with a target of LPV concentrations with Cmin >1mg/L in 95% of children, they predicted doses of LPV/RTV as described in Table 1. They noted that smaller children required higher mg/kg doses of LPV/RTV, in both 4:1 and 1:1 ratios, than larger children.

Table 1: Simulation for dose optimistion of LPV/RTV during RIF-based TB treatment

Body weight	LPV:RTV 4:1		LPV:RTV 1:1
	12 hourly LPV dose (mg/kg)	8 hourly LPV dose (mg/kg)	12 hourly LPV dose (mg/kg)
4-6 kg	50	25	20
6-8 kg	42	22	17
8-12 kg	37	21	15
12-18 kg	30	18	12

COMMENT

The same group previously presented data to show that the double dose LPV/r is not sufficient for children when coadministration with rifamipicin. [2]

The current median LPV dose using double dose strategy in this study is 23 mg/kg,

The investigators suggestion for dose adjustment in this study is much higher than double dose. Or they suggest switching to an 8 hourly dose strategy considering the adverse effect slinked to higher doses. [3]

References

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Efavirenz versus nevirapine based first line treatment in a South African cohort

Polly Clayden, HIV i-Base

A poster authored by Peter Block and colleagues compared the effectiveness of efavirenz and nevirapine in a multisite cohort of South African adults attending public health facilities.

This was a retrospective analysis of routine data from 27,350 adults initiated on ART between March 2004 and March 2007 in public health facilities. Participants were a median age of 34.4 (IQR 29.4-40.8) with a median CD4 count of 113 cells/mm3 (IQR 57-165).

The investigators found, over a median follow up of 9.3 months (IQR 4.6-17.7), in multivariate analysis, participants receiving efavirenz-based combinations were more likely to achieve undetectable viral load at six months, OR 1.31 (95% CI, 1.1--1.54) and at any time between six and 36 months, OR 1.28 (95% CI, 1.16-1.41). They were also more likely to die, AHR 1.24 (95% CI, 1.07-1.45) and less likely to change regimen OR 0.53 (95% CI, 0.48-0.59).

Additionally, a subset analysis of 18,527 participants for whom pregnancy and TB status were known revealed no difference in mortality risk between those receiving efavirenz and nevirapine based regimens AHR 1.17 (95% CI, 0.99-1.37).

COMMENT

This study adds to a body of evidence showing superior results with EFV for first line ART when compared to NVP. Given the resource constraints in developing countries EFV should therefore be the preferred NNRTI for first line use. Protease inhibitors are not suitable for first line in developing countries due to increased cost. However; the possible link between EFV use in the first trimester and teratogenicity complicates its use with many women receiving EFV or initiating ART presenting only in the second trimester of pregnancy.

In the absence of suitable alternative NNRTIs or protease inhibitors, recommendations against the use of EFV in pregnancy need to be reviewed. In addition more work needs to be done to advocate for the reduction in price of suitable alternatives.

Reference

Bock P et al. Comparing the effectiveness of efavirenz and nevirapine for first-line antiretroviral treatment amongst an adult treatment cohort from South Africa. 10th International Congress on Drug Therapy in HIV Infection, 7–11 November 2010, Glasgow. Poster abstract P10. Published in Journal of the International AIDS Society 2010 13(Suppl 4). P10.
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CONFERENCE REPORTS

XVIII International AIDS Conference

18–23 July 2010, Vienna

Introduction

Treatment access will always dominate the programme of World AIDS Conferences. Since the Durban conference in 2000, every scientific advance at this meeting is rightly seen in the context of which populations, in a global health emergency, will have the opportunity to benefit.

This is one of the strengths of this meeting, which now has over 20,000 delegates, and many of the access-related sessions are online as webcasts and transcripts produced by the Kaiser Foundation.

A joint report from UNAIDS and Kaiser launched prior to the conference clearly and disturbingly showed that international donor funding, which now supports close to five million people on treatment, has leveled. This threatens to overturn the accumulated health benefits from the last ten years. Flat-lined funding means treatment programmes will be closed to new patients and this will have a disastrous impact on HIV prevention.

Without treatment, not only is there little incentive to test, and an increase in AIDS and death, but also the beneficial impact that antiretroviral therapy has on the risk of transmission will be reduced. And treatment is still likely to be more effective in preventing HIV than any other intervention.

This global crisis demands international support, and this involves funding. So while the US leads funding initiative, as the world's richest country, it is just as important that other wealthy nations meet, for example, the commitments made at the G8 summit. The expense and investment in the conference itself, did not sit easily with the decision to hold the meeting in country that has not supported the Global Fund since 2002. Currently the Global Fund to Fight AIDS, TB and Malaria (GFATM) is faced with a $3 billion shortfall for 2010. Similarly, very few African nations have met their pledge in the Abuja Declaration 2001 to target at least 15% of GDP on healthcare.

The global demand for treatment challenges the concept of universal access using todays medications. Research into ARV drug delivery using nanotechnology is proceeding extremely slowly with only one abstract at this meeting, and yet this has the potential to address many obstacles to wider access. The volume of active ingredient is dramatically reduced with a nanoformulation requiring perhaps monthly dosing, both of which dramatical reduce costs.

This was a conference that highlighted access issues from a human rights perspective:

- The Vienna Declaration - is the official conference statement seeking to improve community health and safety by calling for the incorporation of scientific evidence into illicit drug policies (viennadeclaration.com).

- Many sessions addressed access to evidence-based harm reduction stategies including opioid substitution therapy (OST) and needle exchange progammes.

- Access to treatment to prevent mother-to-child transmission (PMTCT) – currently only 10–20% of HIV-positive women worldwide are able to access testing and treatment during pregnancy.

- The criminalisation of same sex relationships and discrimination against men and women whose sleep with partners of the same sex, highlighted most recently by extreme cases in Uganda, Malawi and Iran, was the focus of several sessions.

We will cover treatment access in the next issue.

In terms of medical and scientific research, there were a few important headline-grabbing studies and a good selection of interesting but preliminary research findings.

As with all meeting reports we include links to original abstracts and webcasts when available, and for this meeting we also start with a guide on how to navigate the conference website for other material.

Abstracts from the conference are published on the conference website:

http://www.aids2010.org/

Reports in this issue include:

- Navigating the conference online

- Results from the Caprisa 004 tenofovir microbicide trial

- Impact of antiretroviral PMTCT prophylaxis regimens on subsequent maternal disease progression in Kesho Bora

- Birth outcomes with antiretroviral exposure

- Introduction to paediatric studies at IAS

- New WHO guidelines for children

- Scaling up: what to do first?

- A new point-of care CD4 test

- Efavirenz-based regimens among women of reproductive age receiving ART in Johannesburg

- Male circumcision retains effectiveness at reducing risk of HIV infection: 54 month results

- Cambodian trial shows early ART reduces mortality in patients with very TB with very low CD4 counts

- Intensified TB case finding is feasible

Abstracts from the conference are published on the conference website:

http://www.aids2010.org/

IAS: ON THE WEB

Navigating the conference online

Simon Collins, HIV i-Base

As with previous IAS conferences, much of the conference material is available online and HTB reports include appropriate hyperlinks.

Locating the appropriate files, presentations, webcasts, transcriptions or even the basic abstracts is more challenging. Access is routed through the 'Programme at a glance' link on the conference homepage. This requires a free software plug-in called Silverlight, but an automatic download button should come up if you do not already have this installed.

The search facility requires selecting one of the seven options directly under the search bar ie to search the abstracts, you need to first click 'abstract' which when selected has the tiny white triangle in the red block turn to face down. Then search as you would normally by entering a keyword in the search box and clicking search. Results come up listed below.

The abstract books are available to download as free PDF files, but only for each day, so searching the whole conference requires repeating each search four times.

Although you can browse sessions by day and time, this is not so easy if you are looking for a specific session but don't know when it was presented because there is not a programme that just shows the sessions. For example a search for 'late breaker' brings up no results whether searching 'programme at a glance', 'abstracts', or 'oral sessions'.

If you find a session page, you then have to find and click the yellow 'more info' button at the bottom right of an empty box, and then you finally get to a page that makes sense. Don't be entirely fooled. The 'abstract' links seems to work, but 'slides with audio' are not always available and the 'powerpoint' link doesn't work at all. For presentation slides, scroll further down the page where slides that are available are listed under the 'powerpoint presentations' heading.

The audio works but you need to manually download the powerpoint slides to really follow the presentation.

To make things more confusing, some webcast presentations are provided by Kaiser Foundation on a different website.

http://globalhealth.kff.org/AIDS2010

These webcasts only show the presenter, with no slides and no easy links to slides. Although you often hear two different presentations simultaneously, this accurately captures the conference experience. Only a cloth curtain divided most session rooms, so the webcasts accurately reflect the conference atmosphere, including this difficulty.

Kaiser provide rough transcripts of the sessions that can be more useful with the slide set, than the webcast, though they are draft transcripts only.

Web access should be a leading priority for these conferences. The interface used by the Retrovirus (CROI) conference would be a much more useful model to use and would make this aspect of the meeting far more accessible, whether provided by IAS or Kaiser.

IAS: PREVENTION

Results from the Caprisa 004 tenofovir microbicide trial

Simon Collins, HIV i-Base

In terms of conference headlines, the biggest news came from the results of a prevention study called Caprisa 004. This study reported that a microbicide gel containing 1% tenofovir reduced the risk of infection to women when used before sex to protect against HIV by 39%. [1, 2] Previous microbicides (not using HIV drugs) have not shown a benefit, so a positive result, no matter how slight, was likely to be greeted enthusiastically. When the results were presented, the audience gave the presenters a standing ovation.

Importantly, the presenters stressed that these preliminary results justified further research. This study was based on 98 endpoints for the primary analysis and the sample size ensured that they could be 90% confident of detecting a doubling/halving in the risk (ie an OR of 2 or 0.5). However, because the endpoints are by definition fewer in subgroup analyses, the study is not powered to analyse some of those interesting results. One of the most helpful aspects of the study is that the detailed results were published in a free-access article in Science Express. [3]

The theoretical benefit from an antiretroviral microbicide is similar to the use of pre- and post-exposure prophylaxis (PrEP and PEP) but instead of taking oral drugs, applying a gel enables the active drug to be absorbed in the tissues that are first exposed to the virus. If the cells in the genital tissues have antiretroviral activity, the hope is that this will reduce the risk of infection.

As with all studies, the complexity of the results is in the details, and the presenters themselves cautioned that their results primarily signaled the urgency of running additional studies.

Women were advised to use the microbicide 'up to 12 hours before sex' and 'as soon after as possible', using a maximum of two doses in any single 24 hour period. The gel was applied with a special pre-filled applicator, similar to a tampon container.

This phase 2b study was in around 900 women aged 18–40 years, living in two districts in South Africa where the risk of HIV for women reaches 50% by the age of 24. One trial site was in urban Durban (n=278) and the second was in a rural location 90 miles from Durban (n=611). This was a double-blind study with women randomised 1:1 to either the active gel or a placebo gel. Free condoms and counselling on the importance of safe sex were provided to all women, with monthly HIV testing and monitoring.

There were significant differences between the rural and urban women. Rural women were younger (mean 23.3 vs 25.1), poorer (86% vs 69% monthly income <R1000), less likely to have a stable partner (77% vs 93%), had fewer lifetime partners (mean 2 vs 6), used condoms less consistently (22% vs 42%) and had lower HSV-2 prevalence (48% vs 60%), see Table 1. However, randomisation ensured that there was no difference in these baseline characteristics between the active and placebo group.

Table 1: Demographic differences between rural and urban sites

	Rural site n=611	Urban site n=278	p-value
Mean age (years)	23.3	25.1	<0.001
Monthly income <R1000	86.1%	69.1%	<0.001
Married	6.5%	3.6%	0.085 *NS
Stable partner	77.0%	93.1%	<0.001
Mean age sexual debut	17.3	17.7	0.014
Mean no. sexual partners (lifetime)	2.1	6.0	<0.001
Mean age of oldest partner (past 30 days)	26.4	29.6	<0.001
Sex in the past 7 days	58.9%	68.3%	0.007
Always use condom	22.9%	42.8%	<0.001
New partner (past 30 days)	0.5%	2.5%	0.014
Anal sex (past 30 days)	0.5%	0.4%	1.000 *NS
HSV-2 prevalence	47.6%	59.6%	0.001

* NS = non significant differences

The predetermined endpoint of 98 events was reached after a mean 18 months with 1341 person years (PY) of follow-up, with a low drop-out rate (~5%).

Of the 98 women who became HIV-positive over 12–30 months, 38 were in the active gel group and 60 were in the placebo group. The HIV incidence rate per 100 PY was 5.6 (CI: 4.0, 7.7) in the tenofovir gel arm compared to 9.1 (CI: 6.9, 11.7) in the placebo gel arm (incidence ratio rate [IRR]=0.61; CI: 0.40, 0.94; p=0.017). After adjusting for baseline covariates including, age, site, anal sex history, contraceptive method, HSV-2 antibody status, and condom use, the hazard ratio was 0.63 (CI: 0.42, 0.94; p=0.025). Sensitivity analysis produced similar results. Although this fell just short of the predetermine OR of 0.50, the results remained statistically significant.

The combined rural/urban analysis produced a protection rate of 39% from using the active compared to placebo gel. However, the 95% confidence intervals are 6% and 60%. Further studies are likely to focus on dosing, adherence and other factors in order to see whether higher protection rates can be seen. Although the results were presented by site, showing effectiveness at the rural site of 43% (95%CI 5, 57; p=0.023) but not at the urban site (26%; 95%CI –59, 67; p=0.380), see Table 2. However, as the study was not designed to compare efficacy by site, while interesting, it was not powered for this comparison to be meaningful.

Adherence is essential to monitor in any intervention study, see Table 2. In Caprisa 004, the researchers determined that two applications of the gel were used for over 70% of occasions when participants had sex. While approximately 40% women reported >80% adherence, a similar proportion reported that they used the gel less than half the time. When adherence was 80% or higher (n=336), the protection increased from 39% to 54% (95%CI 4, 80; p=0.025). There appeared to be a trend between adherence and efficacy, and this is clearly plausible, though again the study was not powered for this comparison. The Science Express paper reported 38% protection (95%CI –67, 77; p=0.343) at 50–80% adherence (n=181) dropping to 28% (95%CI –40, 64; p=0.303), when less than 50% (n=367).

The mean number of sex acts in the high, intermediate and low adherence groups was 3.2, 5.0 and 6.7 per month respectively. Median adherence in the women who become HIV-positive was similar throughout the study at approximately 60%, whereas in the HIV-negative women this started at 55% and increased to 75% in the first and last six months respectively. Even with an intensive education and support programme, only a minority of women achieved >80% adherence, and these were the women who had less sex (3 times a month). Condoms were reportedly used 80% of the time, though this may have been over-reported given the rough per-exposure risk this generates for the study, which is not uncommon in prevention studies.

No serious or significant safety issues (from the 4692 reported events) were associated to using the gel in terms of side effects, including renal toxicity or in the 54 unplanned pregnancies that occurred. Mild diarrhoea was reported in 16% people using the active gel compared to 11% of the placebo group. No safety concerns in terms of flares in liver enzymes were seen relating to the use of tenofovir in the small numbers of women who entered the study with active hepatitis B (19 in the active and 15 in the placebo group) or who acquired HBV during the

Table 2: Effectiveness results in Caprisa 004 study

	n	HIV infections/PY		HIV incidence		IRR	Efficacy	95%CI	p-value
		Tenofovir	Placebo	Tenofovir	Placebo				
Overall effectiveness of tenofovir gel (n=889)									
HIV endpoints	98	38/680.6	60/660.7	5.6 (4.0, 7.7)	9.1 (6.9, 11.7)	0.61	39%	6, 60	0.017
Site-specific effectiveness (n=889)									
Rural	611	25/484.7	42/461.2	5.2 (3.3, 7.6)	9.1 (6.6, 12.3)	0.57	43%	5, 67	0.023
Urban	278	13/195.9	18/199.5	6.6 (3.5, 11.3)	9.0 (5.3, 14.3)	0.74	26%	–59, 67	0.380 NS
HIV endpoints by levels of adherence (n=884) †									
Adherence >80%	336	11/259.2	25/269.4	4.2 (2.1, 7.6)	9.3 (6.0, 13.7)	0.46	54%	4, 80	0.025
Adherence 50-80%	181	10/159.8	10/99.7	6.3(3.0,11.5)	10.0 (4.8, 18.4)	0.62	38%	–67, 77	0.343 NS
Adherence <50%	367	16/258.5	25/290.6	6.2 (3.5, 10.1)	8.6 (5.6, 12.7)	0.72	28%	–40, 64	0.303 NS

NOTE: Study was not powered for the subgroup analyses by site and adherence.

† Adherence could not be calculated for the 5 women who reported no sex during their follow-up in the study. NS=non significant

study (22 women, 19 or who cleared the virus without additional treatment). The concern that continued exposure to tenofovir prior to HIV being diagnosed might exert sufficient pressure to generate drug resistance was not supported in genotypic results from 35 women (no K65R, K70E or RTI-associated mutations). Of interest, the use of the active gel had no impact of viral set point after infection (4.65 vs 4.30 log; p=0.15) and participation in the study did not lead to any increase in risk behaviour.

The study also reported an impact on transmission of HSV-2, the virus responsible for genital herpes. Of the 434 women who tested negative for HSV-2 at the beginning of the study, 29 became infected in the active gel group compared to 58 in the placebo group (IR/100PY 9.9 (6.6, 14.2) vs 20.2 (15.3, 26.1). This was reported as tenofovir providing 51% protection against HSV-2 (95%CI: 22%–70%; p = 0.003). Because genital herpes increases the risk of catching HIV, these results are complicated to understand. Although tenofovir has not shown protective effects against HSV-2 in mouse and test-tube studies, drugs with a similar structure to tenofovir such as cidofovir have activity against HSV-2.

Results from the pharmacology substudy of CAPRISA 004 were presented in the same session by Angela Kashuba from the University of North Carolina. [5]

For the HIV analysis, 90 samples were available (37 active and 13 placebo in the HIV-positive women plus 24 active and 16 placebo from women who remained HIV-negative. Tenofovir levels were measured in blood plasma (BP), and cervicovaginal fluid (CVF) for all samples and additionally in vaginal and cervical tissue biopsy samples in the HIV-positive women. Plasma concentrations were minimal (<1 ng/mL), with detectable levels in only 12% of the HIV-positive women (median 0, range 0–0.1 ng/mL) a median 6 days (range 1-25) after application vs 50% of the HIV-negative women (median 0.1, range 0–0.8 ng/mL) after a median of 4.5 days (range 2–28), indicating very low systemic uptake even given the delay in sampling.

Tenofovir was more frequently detected and at higher CVF levels in the HIV-negative compared to HIV-positive women at 45% (median 1 ng/mL range 0–300,000) vs 96% (median 520 ng/mL (range 0–1,340,000), both at 4.5 days. CVF concentrations correlated well with infections and also importantly with intracellular levels of tenofovir diphosphate. This will help establish the target dose in future formulations. A separate PK study of 250 samples from 172 highly adherent HIV-negative women showed a mean half-life of about two days with most concentrations over the first few days of ~1000 ng/mL. It is important to note that there are currently no data on appropriate target levels of either tenofovir or tenofovir diphosphate and that data, as for early absorption (ie how soon before sex would you get protection?) will be the focus of the next studies. These results suggest that drug levels are a marker for adherence rather than poor absorption potentially due to interpatient variability of cellular transporters such as MRPs.

A similar relationship was observed between drug levels and acquisition of HSV-2. While oral tenofovir is not able to achieve sufficient drugs levels to suppress HSV-2 (EC50 ~10,000 ng/mL), this is possible with a topical gel. 24% of the women with levels below this became HSV-2 positive compared to only 6% of women who had levels above.

Very low levels of tenofovir found in two women in the placebo arm was explained by possible shared sexual partners.

The proof of principal that an antiretroviral microbicide can protect against HIV and HSV infection is clearly important news.

The discussion in the published paper suggests that many of the infections may be due to infrequent but very high risk exposures with migrant workers and the investigators noted that the HIV incidence rate was similar in the low frequency placebo group to women who reported much more frequent sex.

In this high-risk setting, infection rates remained high in the women using the active gel (>5/100PY) and protection dropped significantly after 18 months for reasons that are unclear.

The differences in the urban/rural results may just be an issue of overall sample size (as opposed to something connected to the difference in lifetime sex partners or other factors). A good precedent for caution over the adherence analysis however comes from an earlier microbicide study. A similar adherence analysis in the phase 2b PRO2000 HPTN 035 study showed protection rates of 9%, 44% and 78% in low gel users, high gel users, and low condom/high gel users, respectively. Yet this microbicide was subsequently shown not to work.

Of note, the findings on prevention of HSV-2 transmission were more significant and robust than protection against HIV, and this will clearly be the focus for further research study.

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Unless otherwise stated, all references are to the Programme and Abstracts of the 17th International AIDS Conference, 18-23 July 2010, Vienna.

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Further information: www.caprisa.org

IAS: PREGNANCY & MTCT

Impact of antiretroviral PMTCT prophylaxis regimens on subsequent maternal disease progression in Kesho Bora

Polly Clayden, HIV i-Base

HAART regimens used as prophylaxis during pregnancy and breastfeeding are effective in reducing mother to child transmission and are standard of care in industrialised countries.

There are some concerns, particularly since the results from the SMART study, that stopping HAART prophylaxis at the end of breastfeeding may have adverse effects on maternal health and survival.

The Kesho Bora study randomised pregnant women with CD4 counts 200-500 cells/mm3 at 28-36 weeks of pregnancy, to receive either maternal HAART (zidovudine + lamivudine + lopinavir/ritonavir to six months after delivery or breastfeeding cessation if earlier) or short- course zidovudine plus single-dose nevirapine in labour. All infants received single-dose nevirapine post partum. The results, presented at the IAS conference last year (and reported in the August 2009 edition of HTB) showed HIV transmission rates to be almost identical. [1, 2]

These data also contributed to the evidence that enabled the WHO to recommend that HIV-positive mothers or their infants take antiretrovirals while breastfeeding to prevent mother-to-child transmission.

In an oral late breaker, Tim Farley presented findings from an evaluation of maternal HIV disease progression at 18-24 months post delivery. [3]

Disease progression endpoints were stage 4 or CD4 <200 cells/mm3 and stage 3 or CD4 <350 cells/mm3. These represent previous and current WHO thresholds for initiating antiretroviral treatment.

There were 412 women in each arm, who had received prophylaxis for a median of 6 weeks before delivery. Women receiving HAART received it for a median of 19 additional weeks during breastfeeding.

The investigators found lower rates of progression to stage 4 or CD4 200 cells/mm3 among women receiving HAART at all time points from delivery when all women were included in the analysis, p=0.003. See Table 1. But rates were similar after stopping antiretroviral prophylaxis, p=0.159. See Table 2.

Table 1: Progression rates from delivery to stage 4/CD4<200 – all women

Regimen	6 months	12 months	18 months
Short course	(408) 6.4%	(362) 11.8%	(303) 19.6%
HAART	(405) 2.8%	(376) 6.1%	(332) 12.4%

Table 2: Progression rates from stopping prophylaxis to stage 4/CD4<200 – all women

Regimen	6 months	12 months	18 months
Short course	6.4%	11.8%	19.6%
HAART	(386) 2.6%	(358) 7.9%	(213) 14.7%

They performed the same analysis censoring women with CD4 >350 cells/mm3 and there was a significant difference in progression rate from delivery, p=0.002, and no difference from stopping prophylaxis, p=0.107. See Tables 3 and 4.

Table 3: Progression rates from delivery to stage 4/CD4<200 – women CD4 <350 at entry

Regimen	6 months	12 months	18 months
Short course	(226) 10.6%	(192) 20.0%	(152) 32.4%
HAART	(226) 4.9%	(209) 10.1%	(186) 20.4%

Table 4: Progression rates from stopping prophylaxis to stage 4/CD4<200 – women CD4 <350 at entry

Regimen	6 months	12 months	18 months
Short course	(226) 10.6%	(192) 20.0%	(152) 32.4%
HAART	(217) 4.7%	(199) 12.0%	(107) 25.9%

A further analysis was performed looking at rates of progression to stage 3 or CD4 <350 cells/mm3 among women with CD4 ≥350 cells at entry. This gave differences of p=0.002 and p=0.013 from delivery and stopping prophylaxis respectively. See Tables 5 and 6.

Table 5: Progression rates from delivery to stage 3/CD4<350 – women CD4 ≥350 at entry

Regimen	6 months	12 months	18 months
Short course	(182) 12.0%	(151) 15.7%	(129) 24.1%
HAART	(179) 2.9%	(162) 6.1%	(138) 10.4%

Table 6: Progression rates from delivery to stage 4/CD4<200 – women CD4 <350 at entry

Regimen	6 months	12 months	18 months
Short course	(182) 12.0%	(151) 15.7%	(129) 24.1%
HAART	(168) 3.7%	(152) 8.2%	(98) 9.5%

Overall the investigators concluded that receiving maternal HAART as prophylaxis and stopping after breastfeeding did no harm compared to short course zidovudine plus single dose nevirapine. In the discussion following the presentation it was suggested that the conclusion that this strategy did "no harm" was difficult to make without having included an arm in which treatment was continued. Dr Farley agreed that this was also an important question but the study design reflects an era when even using HAART and continuing it through breastfeeding in healthier women was considered quite radical in resource limited settings.

The other important conclusion from the analysis is that the high rate of progression to CD4 <200 cells/mm3 in both arms among women with <350 cells/mm3 at entry, reinforces WHO guidance to treat from 350 cells/mm3 and emphasises the importance of early treatment initiation in pregnant women or women desiring pregnancy.

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Birth outcomes with antiretroviral exposure

Polly Clayden, HIV i-Base

In a session at the IAS 2010 conference entitled Antiretrovirals during pregnancy and breastfeeding: Importance of surveillance, data were presented describing what we know (or don't know) about outcomes among infants exposed to antiretrovirals in utero. [1]

New data from the US was shown by George Siberry that evaluated growth parameters in tenofovir exposed infants. [2]

Lynne Mofenson provided a useful overview of the implications for women and children in developing countries. Nathan Ford presented findings from a meta-analysis looking at the safety of efavirenz in the first trimester of pregnancy (which we reported in the June 2010 edition of HTB) [3, 4, 5]. And Karen Beckerman showed data from the Antiretroviral Pregnancy Registry (APR) that looked at preterm delivery (PTD) and low birth weight (LBW) in this cohort. [6]

There was agreement among the presenters on the importance of surveillance, both from industrialised and resource-limited settings. Nathan Ford rightly pointed out that, although the largest data set contributing to their review was from the APR, the second largest set came from one centre, the Frere Hospital in South Africa. It is very likely that much important pregnancy outcome data is simply not being captured.

During discussions with the audience, Graham Taylor emphasised the role of reporting bias, particularly with respect to efavirenz. This is the only antiretroviral with preclinical primate data and in turn has the strongest FDA category and the most scrutiny in pregnancy. The point was made that the only report of myelomeningocele in the prospective reports section of the APR was of a child exposed to efavirenz during the first trimester. However, the absence of other reports of myelomeningocele in the registry, that might be expected given a general background rate in the order of 1 per 1000 births, despite almost 12,000 evaluable prospective case reports was also commented upon.

There was agreement that when a mother needs treatment for her own health the benefits of antiretrovirals in pregnancy hugely outweigh any theoretical risks.

Tenofovir exposure and low birth weight and infant growth

Preclinical studies showed that tenofovir crosses the placenta. There have been concerns that undermineralisation of foetal bones was observed in animal studies. Tenofovir use in pregnancy is on the increase but there are limited human data describing infant outcomes.

George Siberry presented data on behalf of the Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring of Antiretroviral Toxicity (SMARTT) study. SMARTT enrols antiretroviral exposed uninfected children in the US at two weeks of age (dynamic cohort) and at one year to 12 years of age (static cohort).

This study was conducted to evaluate the association of maternal tenofovir use and growth measures (weight, length, head circumference) at birth and at one year of age.

Maternal information is collected prospectively for dynamic cohort and retrospectively for static cohort.

In this study, LBW was defined as <2.5kg. Z-score < -1.5 was used to define small-for-age for length and HC at birth and length, weight and HC at one year.

Logistic regression models for LBW and growth outcomes were fit, controlling for potential confounders, including demographic and socioeconomic characteristics, maternal health status (CD4< 250, viral load>1000 copies/mL, genital infections) and substance use during pregnancy.

The evaluation revealed 1887 children with birth weight data for which birth length and HC measurements were available from 739 children from the dynamic cohort. Growth measurements at one year were recorded for 532 children (weight length and HC), of which 356 were from the dynamic and 176 from the static cohorts.

The investigators found that maternal tenofovir use increased from 15% in 2003 to 39% in 2009. Overall 21% of the cohort was exposed to tenofovir including 12% receiving it from the first trimester.

Among the 20% of infants with LBW, there was no difference in those exposed to tenofovir (20.7 vs 19.5%). After adjusting for confounders there remained no effect (aOR: 1.03, 95% CI 0.75-1.40, p=0.87). Neither was there an association between tenofovir use and short length or small HC at birth.

However, at one year of age children exposed in utero to tenofovir in this cohort had a marginally increased risk of low weight (aOR:1.76, 95% CI1.01-3.05).

The investigators suggested that this observation requires confirmation in further studies.

Preterm birth in the Antiretroviral Pregnancy Registry

Some reports suggest increase prevalence of PTD and LBW associated with protease inhibitor (PI) exposure, while reports from other cohorts do not.

Karen Beckerman presented data from an evaluation from the Antiretroviral Pregnancy Registry (APR) of birth weight and estimated gestational age of live births reported to this registry.

We have reported findings from the APR in previous issues of HTB. It is a prospective registry with which providers register pregnant women with antiretroviral exposure during their pregnancy and in turn provide outcome data.

In this analysis the investigators compared the prevalence of PTD at <37 and <32 weeks gestation, and LBW <2.5kg and very LBW <1.5kg among infants exposed to one antiretroviral or regimens of two or more antiretrovirals that either included a protease or did not.

Since 1989 and as of January 31st 2009 the APR had enrolled 12451 pregnancies; 426 (3.4%) had outcomes pending and 1082 (8.7%) were lost to follow up. There were 9513/10022 (95%) singleton live births with evaluable data.

Dr Beckerman reported that, in this analysis, the investigators found no differences in the prevalence of either PTD <37 weeks, 14.7% vs 13.0%, or LBW <2.5kg, 15.4% vs 16.1%, between the 1404 infants exposed to one antiretroviral compared to 8109 infants exposed to combination antiretroviral regimens.

Of those exposed to combination antiretroviral regimens, PTD <37 weeks was higher among those receiving PI-containing regimens (n=4658) compared to non PI-containing regimens (n=3451), 14.1% vs 11.8%, p=0.003, as was LBW <2.5kg p=0.001.

But PTD <32 weeks was no different between those exposed to regimens containing a PI compared to regimens without a PI, 2.3% vs 1.8%, p=0.16.

They also found that very LBW <1.5kg was more prevalent in infants exposed to PI-containing regimes compared to those without a PI, 17.4% vs 14.0%. But after controlling for race very LBW <1.5kg, for each exposure group, overlapped prevalence in the background population.

They found that there was no difference in very LBW <1.5kg in infants exposed to PI containing regimens compared to those exposed to one antiretroviral. They also found exposure to PI-containing regimens was protective against PTD <32 weeks, p=0.05.

They noted that very LBW <1.5kg was lower in all groups exposed to combination antiretroviral regimens than published reports of cohorts of HIV-exposed infants not exposed to antiretrovirals.

They concluded that optimised combination antiretroviral regimens offer profound benefit to maternal survival and vertical transmission prevention.

They added: "We hypothesise that exposure to PI could be a surrogate marker for immunologic and other factors contributing to preterm parturition and low birth weight syndromes in HIV-exposed neonates."

COMMENT

The debate on whether combination therapies, particularly PI-based HAART are associated with PTD continues.

Given that most of the data suggesting that there is no association has come from the US and that most of the data (85%) in the APR is also from the US, it should perhaps come as no surprise that no strong link with HAART was found.

The data suggesting a link with PTD is mostly from Europe, however in her presentation Lynne Mofenson drew attention to the recent RCT from Botswana investigating HAART during pregnancy and breastfeeding to reduce HIV transmission in which an increased rate of PTD was found in the PI-based arm compared with the triple NRTI.

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IAS: PAEDIATRIC CARE

New WHO guidelines for children

Polly Clayden, HIV i-Base

The new WHO 2010 paediatric guidelines – Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access - also summarised on their website in a preliminary version for programme planning in June, were released at IAS 2010.

Lynne Mofenson provided an excellent summary of the new guidelines at the paediatric meeting and Shaffiq Essajee in the Early Infant Diagnostics (EID) session at IAS. [1,2] We will review developments in diagnostics including EID in the next issue of HTB.

When to start

Universal treatment is recommended for all infants and young children under two years irrespective of CD4 or clinical indication. The recommendation is strong for less than 12 months and conditional for 12-24 months.

Data to guide when to start for children one to five years old are scant and this is reflected in differences in recommendations between guidelines (see statement from PENTA in the comment below). After five years of age, guidance is similar to that for adults (see Table 1). Table 2 shows a comparison between the 2006 and 2010 WHO guidelines.

COMMENT

PENTA have published a letter in support of the new guidance for resource limited settings and are continuing to recommend PENTA guidance ie universal treatment for infants less than 12 months and immunological and clinical criteria for those above for treating children in Europe. In the letter they write:

"Both PENTA 2009 and WHO 2010 guidelines considered the same body of evidence, and several experts took part in the drafting of both sets of recommendations. The universal treatment of infants is based on evidence from the CHER study, children over five are treated at adult thresholds in both guidelines, based on comparisons between the HPPMCS child cohort and CASCADE adult seroconverter cohort. The recommendations for children aged between 2 and 5 are based on cohort data, largely from the HPPMCS study.

The new recommendations in the WHO guidance for children between age one and five are based on programmatic considerations, in particular the ability to closely monitor a child clinically and by repeat CD4 count measurement if they are not started on ART. Such monitoring is available in Europe, and in many settings

outside Europe. It is also noted that the evidence basis for these recommendations is weak or very weak, and that studies expected to publish results soon may shed more light on the subject. We endorse WHO's recommendation to treat early where the ability to provide monitoring is limited, as well as the call for more research to provide RCT evidence for treatment initiation thresholds after infancy. We continue to recommend PENTA 2009 guidance as appropriate for European and other settings with the facility to monitor closely children in whom treatment is deferred."

http://www.pentatrials.org/PENTA%20letter%20re%20WHO%20jul%202010.pdf

What to start with

Recommended regimens are:

- For children less than two not exposed to maternal or infant nevirapine or whose exposure status is unknown: nevirapine plus two NRTIs.

- For children exposed to maternal or infant nevirapine or other NNRTIs used for maternal treatment or PMTCT: lopinavir/ritonavir plus two NNRTIs (with the caveat that nevirapine is better than nothing).

- For children over two but under three: nevirapine plus two NRTIs.

- All others (irrespective of nevirapine exposure): nevirapine or efavirenz (efavirenz preferred for TB treatment)

Table 1: WHO 2010 Guidelines When to Start Children on ART

Age	WHO 2010 Guidelines
Less than 24 months	
	All
24–59 months	
Clinical	Stage 3 or 4
Immunological*	< 25% or < 750
5 years and older	
Clinical	Stage 3 or 4
Immunological	< 350

*CD4 percentage/absolute CD4 count mm3

- Under three and needs TB treatment: nevirapine plus two NRTIs or abacavir plus lamivudine plus zidovudine/stavudine.

- Adolescents over 12 with hepatitis B: tenofovir plus lamivudine/emitricitabine plus efavirenz/nevirapine (can take FDC of lamivudine/emitricitabine plus efavirenz if this is available).

- Adolescents with hepatitis C: preferred regimen is efavirenz plus two NRTIs.

The guidelines also recommend a preferential order of NRTIs (zidovudine/lamivudine > abacavir/lamivudine > stavudine/lamivudine).

They recommend that any child with active TB begin TB treatment immediately and start ART in the first eight weeks of TB treatment.

For children already on ART who develop TB, they recommend that ART regimens may need to be adjusted to decrease the potential for toxicities and interactions: if on nevirapine substitute for efavirenz if over three years; if under three ensure nevirapine is at high dose (2 mg/m2) and if on lopinavir/ritonavir consider adding ritonavir to a 1:1 ratio lopinavir/ritonavir to achieve the full therapeutic dose of ritonavir.

The guidelines recommend solid in preference to liquid formulations, use of heat stable FDCs or co-packaged formulations wherever possible and dosing in accordance with WHO weight band tables.

When to switch

Switching to second line treatment is recommended when clinical, immunological or virological failures occur.

- Clinical failure is defined as the appearance (or reappearance) of WHO clinical stage 3 or 4 events at least 24 weeks on ART and child is adherent.

- Immunological failure is defined as returning to age related thresholds in a treatment adherent child: CD4 count of ≤200 cells/mm3 or CD4 percentage ≤10% for a child over two and less than five years of age; CD4 count of ≤100 cells/mm3 for a child of five years or more.

- Virological failure is defined as a persistent viral load above 5000 copies/mL after at least 24 weeks on ART for a treatment adherent child.

Table 2: Comparing WHO guidelines 2006 and 2010

2006	Immune marker	Age specific recommendations to initiate ART				Clinical criteria
		<12 months	12-35 months	36-59 months	≥ 5 years	Stage 4 disease
	CD4 percent	All	<20%	<20%	<15%	Stage 3 disease (ART initiation may be delayed in some cases)
	CD4 count/mm3	All	<750 cells	<350 cells	<200 cells	
	TLC/mm3	All	<3000 cells	<2500 cells	<2000 cells	
2010	Immune marker	Age specific recommendations to initiate ART				Clinical criteria
		<24 months	24-59 months	>5 years		Stage 3 and 4 disease
	CD4 percentage	All	<25%			
	CD4 count mm/3	All	<750 cells	<350 cells		

Adapted from WHO 2010 revision. Essajee S.

What to switch to

Choice of second line ART is dependent on the first line regimen received:

- After failure on an NNRTI: boosted PI plus 2NRTIs. Lopinavir/r is preferred.

- After failure on zidovudine or stavudine plus lamivudine: abacavir plus lamivudine is the preferred NRTI backbone, abacavir plus didanosine is an alternative.

- After failure on abacavir plus lamivudine, zidovudine plus lamivudine is the preferred NRTI backbone; zidovudine plus didanosine is an alternative.

COMMENT

These guidelines represent a liberalisation of criteria and if they are followed should ensure that many more children are identified and treated.

They are available on the WHO website. [3]

Annexe E has updated weightband dosing tables and formulations that are needed. We also look at paediatric formulations in the TAG/i-Base Pipeline Report. [4]

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Scaling up: what to do first?

Polly Clayden, HIV i-Base

The revised 2009 WHO guidelines have four major changes since the 2006 edition:

- Routine CD4 counts

- Earlier ART initiation – CD4 threshold of 350 cells/mm3 from 200 cells/mm3

- Changing d4T to tenofovir in first-line regimens

- Increased number of sequential lines of treatment

In an oral session, Rochelle Walensky from Harvard presented findings from a study using a mathematical model simulated to project the clinical and economic outcomes from implementing each of these changes and combinations of these changes.

This study was designed to assist policy makers with their prioritisation process in recognition that implementing all of the guideline changes immediately poses major challenges in most resource limited settings.

The study used input data from a South African cohort with a mean age 32 years and a mean CD4 count of 375 cells/mm3 (ie healthier patients with the potential to benefit from starting earlier). Other input parameters included 24-week ART suppression rates of 75% and 78% rate of suppression at 24-weeks for first and second line ART respectively; annual costs of $36 and $135 for d4T and tenofovir respectively and 1.7-2.6% and 0.4-1.6% incidence of d4T and tenofovir related toxicity were also used.

The investigators ranked, in terms of survival and cost effectiveness, all 13 possible combinations of: (1) ART initiation at CD4 <200 cells/mL or CD4 <350 cells/mm3; (2) Replacing d4T with tenofovir; and (3) Number of available treatment regimens (1 or 2).

They examined 5-year survival, projected life expectancy and incremental cost effectiveness of different treatment scenarios. They used the WHO definition of less than 1x per capita GDP as the threshold for "very cost effective". For South Africa this is <$5,400 per year of life saved.

The baseline assumption was that patients received a single, d4T-based ART regimen, initiated at WHO Stage III/IV.

Dr Walensky reported that the projected baseline survival was 99 months, with a 65% 5-year survival rate. Switching from d4T to tenofovir gave a modest improvement, with a 110-month life expectancy and 67% 5-year survival. Adding ART at <200 cells/mm3 to baseline gave a 116 month life expectancy and 80% 5-year survival. Adding a second line regimen increased life expectancy to 121 months but added little to 5-year survival (66%) compared to baseline. Adding ART started at <350 cells/mm3 increased life expectancy to 124 months and 5-year survival to 87%.

Stepwise additions of switching to tenofovir or adding a second-line regimen to a one line d4T-containing regimen initiated at 350cells/mm3, gave increased life expectancy of 140 and 178 months and 91% five year survival (for both changes) respectively.

Switching to tenofovir from d4T in addition to initiating at 350 cells/mm3 and adding a second-line, ie following the complete WHO revisions, increased life expectancy to 192 months with 91% 5-year survival.

Dr Walensky summarised the above results noting that the incremental life expectancy gains are maximised with the following stepwise programmatic additions: first – the expansion of ART eligibility to CD4 <350 cells/mm3 one-line (124 months); followed by the addition of second line therapy (178 months); finally followed by the replacement of d4T with and tenofovir (192 months).

When examining the incremental cost-effectiveness of alternative programmes, three were found to be economically effective: d4T 350 cells/mm3/one-line (cost-effectiveness ratio $610/year of life saved [YLS]), tenofovir/< 350 cells/mm3/one-line ($1,410/YLS), and tenofovir/<350 cells/mm3/two-lines ($2,230/YLS). The investigators noted that these results persisted despite plausible variation in efficacy and cost assumptions.

The results of this study are extremely sensitive to the price of tenofovir. A sensitivity analysis revealed a decrease in the price of tenofovir from $135 to $51 per person year would make tenofovir more effective and less costly than d4T.

Dr Walensky suggested that the limitations to this study were that it only shows results for people initiating ART and did not address people in ongoing care. Also that while the analysis looks at value for money it does not project the implications of each component of the WHO recommendations on programme budgets.

To the question "What to do first" she concluded that the decision is dependent on a country's current policy and capacity. In countries without laboratory capacity, CD4 monitoring and ART at <350 cells/mm3 is the most crucial priority to start with. Where this is already available, replacing d4T with tenofovir are both cost effective and give survival benefits. The addition of second-line ART offers greater survival benefit but with substantial increases in total costs.

Ref: Walensky R et al. Scaling up WHO recommendations for HIV therapy in resource-limited settings: what to do first? Oral abstract WEAE0205.

Efavirenz-based regimens among women of reproductive age receiving ART in Johannesburg

Polly Clayden, HIV i-Base

South African guidelines recommend efavirenz-based regimens as the preferred first line.

Out of concern about efavirenz use in pregnancy the 2004 guidelines only recommend its use in women of reproductive age when they are using injectable contraception plus condoms; the 2010 revision amended this to "reliable contraception". Nevirapine is recommended for the remainder, who are "unable to guarantee reliable contraception".

Three posters authored by researchers from the Reproductive Health Unit, University of the Witwatersrand and Johns Hopkins Bloomberg School of Public Health, showed findings from investigations into how well these guidelines were being followed, the fertility intentions of women receiving efavirenz based and other antiretroviral regimens, and whether providers discuss these issues with women of reproductive age receiving ART. [1, 2, 3]

Colleen Hanrahan and colleagues looked at the application of guidelines. This prospective cohort study enrolled non-pregnant women on ART aged 18-35 years in September 2009-January 2010 in four Johannesburg clinics. The investigators conducted baseline interviews to determine demographics, contraceptive use and the fertility intentions of the women. A record review was used to confirm ART regimens.

They classified women correctly assigned to first line regimens at baseline according to the 2004 guidelines, which were in use at the time of the evaluation, and two interpretations of the 2010 guidance, "reliable contraception". They used logistic regression to determine predictors of "inappropriate assignment".

The investigators reported, out of a cohort of 805 women on first line ART, 44.6% (95% CI, 41.2–48.0%) were receiving efavirenz-based regimens at baseline. Overall 26.5% (95%CI: 23.4–29.5%) of women were receiving hormonal contraception.

Of those receiving efavirenz, 90% (95% CI, 86–93%) were incorrectly assigned according to 2004 guidance, but only 11% (95% CI 9–15%) were wrongly assigned to nevirapine. These proportions reduced to 77% for efavirenz and 27% for nevirapine

and 24% for efavirenz and 73% for nevirapine interpreting the 2010 guidance as using hormonal contraception and hormonal contraception or consistent condom use respectively.

In a multivariate analysis including: age, time on ART, CD4 count, number of living children, relationship and employment status and enrollment site, none were significant predictors of incorrect assignment to efavirenz. For nevirapine, each additional child gave a two-fold increase in the odds of incorrect assignment, AOR 1.95 (95% CI 1.34–2.84), p<0.001.

In a related study Sheree Schwatz and colleagues presented data from a cross-sectional analysis of the same baseline interviews to compare differences in current and future fertility intentions. This analysis included a total of 851 women; the 805 on first line regimens described above plus a small proportion (5.4%, n=46) receiving second line regimens with a boosted PI.

Multivariate analysis revealed women on efavirenz-based regimens were older and had more living children, both p<0.001. Of these 39% were either currently trying to conceive or planned to do so in the next year. Women receiving nevirapine were more likely to be currently trying to conceive than those receiving efavirenz, p=0.025, but were no more likely to plan to in the next year, p=0.17.

In the third study describing communication between providers and HIV-positive women receiving ART about fertility and reproduction, less than half (40.7%) of the 851 women enrolled reported that providers had talked to them about future pregnancy options.

Older women and those with higher income were more likely to have fertility discussions with providers in multivariate analysis whereas parity, CD4 count, time on ART, regimen, marital status or fertility intentions were not associated with the likelihood of these discussions.

The investigators also found that PMTCT knowledge was significantly higher if their providers has discussed this with them p<0.001. Only about a third (35.4%) understood that efavirenz is contraindicated if trying to conceive and this was not associated with efavirenz use, p=0.774. A small proportion (6.4%) said a provider had told then not to have more children and 36% were unsure whether their provider approved of them having children. Discussion about contraception varied by type: 93.5% of women reported that their providers had discussed male condoms, 71.6% female condoms, 45.2% injectable contraceptives, 41.6% oral contraceptives and 18.8% sterilisation.

COMMENT

These data make the important point that no matter what labeling or guidelines recommend concerning use of efavirenz in pregnancy there is a strong likelihood that it will happen.

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Male circumcision retains effectiveness at reducing risk of HIV infection: 54 month results

Nathan Geffen, TAC

A late breaker by Bailey and Colleagues presented at the International AIDS Conference reported on the follow-up to the randomized male medical circumcision trial conducted in Kisumu, Kenya, involving 2874 men aged 18 to 24 years at enrollment. [1]

The authors had previously reported a 60% protective effect of male circumcision against HIV acquisition at 24 months after enrollment, and 64% at 42 months. This poster indicates that this protective effect extends to at least 54 months after enrollment.

As of March 2010, 1552/1740 men (89%) consented to extended follow-up: 767 in the circumcision group and 785 in the control group. The age and number of sexual partners at baseline were the same in both groups. 49% (387/795) of those in the control group have been circumcised since December 2006.

The number of HIV seroconversions by 54 months of follow-up was 39 in the circumcised group and 79 in the uncircumcised group (RR = 0.34; 95%CI: 0.23-0.51). The estimated cumulative incidence [95% CI] at 54 months was 4.0% [95%CI: 2.8-5.7] in the circumcised group and 10.6% [95%CI: 8.2-13.6] in the uncircumcised group (p<0.0002, RR=0.36; 95%CI: 0.24-0.55). The annualised incidence in the circumcised group was 0.91 per 100 person-years and 2.45 per 100 person-years in the uncircumcised group (p=0.0007).

The authors conclude that they found that the 60% protective effect of circumcision against HIV acquisition over 24 months is sustainable, and possibly strengthened, over 54 months of study. They write that these results provide support for policy makers, donors and implementers to scale up comprehensive, safe, voluntary medical male circumcision in appropriate regions as rapidly as possible.

COMMENT

This important finding demonstrates the lasting preventative effect of voluntary male medical circumcision. On 14 July the Bophelo Pele Male Circumcision Project in Orange Farm, one of the sites for the other two randomised controlled trials that showed the efficacy of circumcision, announced that they had reached the milestone of 20,000 safe circumcisions.

This intervention has long-term efficacy and has been proven that it can be conducted at scale and safely. It is therefore sensible to roll it out in areas with large heterosexual epidemics. It needs to be scaled up across sub-Saharan Africa.

References
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Cambodian trial shows early ART reduces mortality in patients with very TB with very low CD4 counts

Nathan Geffen, TAC

Blanc and colleagues presented the results of CAMELIA, a randomised open-label controlled trial in Cambodia. The trial's purpose was to determine when to initiate ART in patients with TB with low CD4 counts. They randomised patients to either receive treatment at two weeks after commencing TB treatment (ie during the intensive phase) or eight weeks (ie during the continuation phase). [1] The SAPIT trial, also discussed in this issue, is still examining this question but the SAPIT cohort has a much higher mean CD4 count.

CAMELIA was designed as a superiority trial to answer the question of the best timing for the introduction of ART in patients with TB with CD4 counts ≤ 200 cells/mm3. All patients were ART-naive at trial entry. The primary endpoint was survival at the end of the trial.

661 patients with suspected TB were randomised, 332 to the early arm and 329 to the late arm. A high proportion of patients turned out to be culture positive for tuberculosis in both arms (282 in the early arm and 294 in the late one).

The patients were all very sick with no difference between the two arms. The median CD4 count was 25 cells/mm3, median viral load was 5.60 log copies, and the median BMI was 16.7. Of the 645 patients, 587 had (at least) pulmonary TB and 13 cases (2%) of MDR TB were identified.

There was a 34% reduction in mortality in the early arm: 59 deaths versus 90. The mortality rate in the early arm was 8.28 per 100 person years (IQR: 6.42 – 10.69) and 13.77 per 100 person years (IQR: 11.20 – 16.93) in the late arm (p=0.002).

IRIS occurred more frequently (p<0.0001) in the early arm, 4.03 per 100 person-months, (IQR 3.34-4.86) compared to the late arm, 1.44 per 100 person-months (IQR 1.09 – 1.91). It occurred about 2 to 3 weeks after starting ART in both arms, but was easily managed.

More than 95% of patients had an undetectable viral load at week 50. The median CD4 cell count at week 50 had increased by 114 cells/mm3 and this had increased to 200/mm3 by the end of the trial.

COMMENT

This trial provides convincing evidence that patients with TB with low CD4 cell counts should be placed on treatment immediately upon diagnosis. One of the main concerns with early initiation of ART in such patients is the concern about IRIS. Since the patients in this trial are on average more immuno-compromised than those in SAPIT and would therefore be expected to have higher rates of IRIS, it is not clear if they can be any valid reason left for delaying ART in any group of patients with TB with CD4 counts <350 cells/ mm3. The DSMB for the SAPIT study should meet to consider the implications of this data on SAPIT.

Reference: F.X. Blanc et al. Cambodian Early vs. Late Introduction of Antiretrovirals. XVIII International AIDS Conference, Vienna, July 18-23. Late Breaker Session B-1.

http://pag.aids2010.org/PAGMaterial/aids2010/ppt/113126_10013/final.pptx

Intensified TB case finding is feasible

Nathan Geffen, TAC

A late breaker at the International AIDS Conference by Shapiro and colleagues presented the results of a project to trace the contacts of patients with TB in Northwest Province, South Africa. Based on an aerial photograph in the presentation, data was collected from five sites separated by a total approximate distance of 50km. [1]

The authors studied whether intensified case-finding (ICF) in household contacts of known TB patients is a feasible strategy for a high-TB, high-HIV prevalence settings. They also compared the strategy of testing for TB in the households of contacts versus randomly selected households. By way of background, a meta-analysis by Morrison and colleagues in 2008 of household contact tracing in low and middle-income countries found that 4.5% [95%CI: 2.1-2.5] of household contacts of known TB patients also had active TB. Just over 51% had latent TB [95%CI: 50.6-52.2]. But there was substantial heterogeneity across the studies.

In this study by Shapiro, 800 people were screened. Of these, 723 patients with active TB were enrolled over seven months. These are referred to as the index cases. Of these, 607 (84%) were HIV-positive and the HIV statuses of another 28 (4%) were unknown. The basis for TB diagnosis was as follows: 163 had tested smear-positive, 16 were smear-negative but culture-positive and the remainder were diagnosed using clinical criteria and chest x-rays. Three (0.4%) had MDR TB. Each index had an average of four household contacts. A total of 2 812 household contacts were screened for TB.

The mean age of the index cases was 38 (IQR: 18-91) compared to the mean age of 23 (IQR: 0-92) in the household contacts (p<0.01). Of the index cases, 78% were unemployed versus 61% of the household contacts (p<0.01). There were no significant differences between the two groups in sex (about 43% female). A quarter of participants lived in shacks.

A total of 2 146 (76%) household contacts gave sputum for analysis and 164 (8%) were diagnosed with TB. Of these, 95 were confirmed and 69 were probable cases. Of the 666 (24%) who did not give sputum, 60 were already on TB medication. The TB statuses of the other 606 were unknown.

Amongst the household contacts, 205 (7%) were already known to have HIV and of these, 99 were already on ART. Another 1 610 (57%) agreed to voluntary counselling and testing and 164 (10%) tested HIV-positive. Of these, 32 (19%) of these had a CD4 below 250 cells/mm3 and were referred for ART.

154 (94%) of the 164 household contacts with TB were smear-negative and culture-positive. Only 18 (11%) of these had TB symptoms. Five (3%) had MDR TB, 22 (13%) were HIV-positive and four (18% of HIV-positive cases) had CD4 counts <250 cells/mm3 (p<0.01 for all of these compared to the index cases).

A random sample of 350 households was compared to the contact households. Table 1 below shows that they were significantly less likely to have TB. At least one case of TB was found in 138(19%) contact households versus 4(1%) in the randomly selected households.

The authors conclude that undetected TB and HIV are highly prevalent in the households of known TB patients. The undetected TB in contacts is more likely to be in HIV-negative and asymptomatic individuals than in patients who present to care for TB diagnosis and treatment.

Table 1: Comparison of TB in contact households versus randomly selected households (from Shapiro et al.)

Number cases per household	Number contact households	Number randomly selected households
0	585 (81%)	350 (99%)
1	113 (16%)	4 (1%)
2	24 (3%)	0
3	1 (0.1%)	0

The authors suggest that intensified case-finding in household contacts of TB patients resulted in accelerated detection of both TB and HIV in undiagnosed contacts. They explain that their study demonstrated that household contact-tracing is feasible and acceptable in a high TB/HIV burden setting and should be considered as an approach to addressing the co-epidemics.

COMMENT

This is an excellent study that shows the feasibility and usefulness of contact tracing. The contacts on average appear to have been in an earlier stage of active TB. Consequently, an additional advantage of tracing contacts is that they would be treated earlier thereby potentially preventing significant TB transmissions.

The authors are planning to present a cost-effectiveness analysis. It would be surprising if contact-tracing were not cost-effective compared to random household selection. What will be particularly interesting to see is the cost per TB case diagnosed. Interestingly, 81% of contact households did not have TB. It would be very useful if criteria could be found that identify contact households with a higher probability of having someone with TB. If such criteria could be found, an algorithm for contact-tracing could potentially be found that reduces the cost of contact-tracing and requires fewer human resources to speedily identify people with TB.

The meta-analysis by Morrison and colleagues indicates that there is significant heterogeneity amongst contacts. Therefore it would be useful if this study was replicated in several other communities in Southern Africa, possibly as part of a pilot contact-tracing programme.

While contact-tracing will cost money and require an additional intervention to be placed on health systems, the extensive benefits that are likely to accrue from it probably make it worthwhile. Southern African governments should give serious consideration to massive contact-tracing operations.

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2. Morrison J et al. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Infect Dis. 2009 Jan; 9(1):3-4.
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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/d4T 150mg/30mg FDC tablet	Hetero, India	17 May 2010
3TC/NVP/AZT 30mg/50mg/60mg FDC dispersible tablet (paediatric)	Matrix, India	8 July 2010
3TC/d4T 150mg/30mg FDC tablet	Macleods, India	5 August 2010
atazanavir 300mg capsule	Emcure, India	19 August 2010
3TC/NVP/d4T 150mg/200mg/30mg tablet	Macleods, India	30 August 2010
3TC/NVP/d4T 150mg/200mg/30mg tablet	Hetero, India	10 September 2010
atazanavir 150mg and 300mg capsules	Matrix, India	15 September 2010
abacavir 300mg tablets	Hetero, India	29 September 2010
3TC/AZT 150mg and 300mg tablets	Strides Arcolab, India	18 October 2010
AZT 300mg tablet	Cipla, India	27 October 2010
abacavir 60mg tablet (paediatric)	Matrix, India	29 November 2010
3TC/AZT 30mg/60mg FDC tablet (paediatric)	Matrix, Inda	5 January 2011
3TC/TDF 300mg/300mg	Aurobindo, India	7 January 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

ART distribution and adherence support by community groups in Mozambique

Polly Clayden, HIV i-Base

An article in the 1 February edition of JAIDS by Tom Decroo and colleagues, describes a patient-initiated community ART group formed to assist with access, adherence and retention in care and to reduce the workload of a saturated health service. This community programme shows excellent preliminary outcomes.

The programme is conducted in the Tete Province in Mozambique where Medicins Sans Frontieres (MSF) has been involved in HIV care and treatment since 2002. About one in five patients are loss to follow up (LTFU) in this province and at least half of these losses are estimated to be deaths.

In order to improve this situation, consultations took place between patients and counsellors at provincial health facilities. The patients identified the main barriers to ART access as:

• Transport costs

• Perceived stigma from being seen attending clinics

• Long waiting time at clinics (often just for refills)

In Mozambique, ART guidelines only recommend 6-monthly monitoring for stable patients, but supply means drugs must be collected monthly. A Community ART Group (CAG) model was proposed in order to use existing social networks to pool resources so that each person did not have to travel and queue every month for their medicines. CAGs could also provide mutual adherence support.

The groups were established at 12 health facilities in Tete Province. As of May 2010, 11,052 people were on ART of which 5772 were attending facilities with CAGs. CAGs had four key functions: to collect and distribute ART every months to group members; to provide adherence support and treatment monitoring; to establish community-based treatment social support; and to make sure each group member attends a clinic every six months.

The CAGs were publicised in waiting rooms, at clinical appointments and counselling sessions and through information distributed in the community. People were eligible to join a CAG if they were stable on ART for a minimum of six months and had a CD4 count > 200 cells/mm3. Counsellors trained and monitored new groups.

Group members visit the clinic on rotation so that each patient has contact with the health system every six months. Prior to the clinic visit, the groups meet to check adherence and any signs or symptoms or intention to move location. The representative takes all the appointment cards to the facility where each group member is discussed and a clinician prescribes ART and other medicines for each of them. The representative also attends a clinic appointment. They then return to the community and distribute the medicines and cards to the group members and inform anyone who needs to visit the clinic for a follow up.

All CAG members associated with the same health facility are invited to a six-monthly group session providing health education and all attendees have a sample taken for CD4 monitoring.

Between February 2008 and May 31 2010, 1384 patients had joined 291 CAGs. When they enrolled in the CAGs, group members had been receiving ART for a median of 22.3 months.

The majority (70%) were women and their median age was 36 years. The median follow up time within a CAG was 12.9 months.

All doses of ART had been collected by representatives and delivered to members and adherence monitoring was high: 1173/1269 (92%) of members had their last two pill counts recorded correctly.

Only 83/1384 (6%) of patients had been transferred back to more conventional care or moved treatment centre. Of the remaining CAG members, 1269/1301 (97.5%) had remained in care, 30 (2%) had died and only 2 (0.2%) were LTFU.

In addition the health workers reported that having CAGs associated with the facility resulted in a reduction in consultations by approximately 4-fold.

COMMENT

This is a fantastic and innovative model! It could be duplicated among many similar (particularly rural) populations. For people facing long journeys and long waits to get ART this could make a huge difference.

Reducing the burden on already saturated health systems is an ever increasing challenge in resource limited settings. Stable patients, will need to have limited interaction with their health facilities if these are to continue with new ART initiations. So monitoring and adherence support in the community is critical.

Sharonann Lynch from MSF wrote: "It relies upon the simplest component: mutual self interest. And while there is of course self-selection at work here (it is based on a self-formed group model after all), it is still the best adherence rates that I've seen within MSF and in all the cascade literature."

Reference

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First-line ART outcomes: Trial finds nurses non-inferior to doctors

Nathan Geffen, TAC

Sanne and colleagues have reported the results of a randomised controlled trial that compared the outcomes of first-line antiretroviral therapy (ART) patients managed by nurses versus those managed by doctors. The trial was undertaken at two primary health care clinics (one in Masiphumelele in Cape Town and another in Soweto) between February 2005 and January 2009. [1]

Inclusion criteria were HIV-positive patients who had been initiated on ART for less than six weeks, were older than 16 and had a CD4 count <350 cells/mm3 or a previous AIDS-defining illness. Women in the first trimester of pregnancy were excluded, but not women who had previously received short-course prevention of mother-to-child transmission. Of 917 patients assessed, 812 were randomised, 404 to the nurse arm and 408 to the doctor arm. Four treatment-limiting endpoints –mortality, viral failure, toxicity and schedule adherence– were analysed as a composite endpoint. The study was powered to detect a 1.4 times greater difference between the arms.

There were no significant differences at baseline between the two arms in sex (74% female on the nurse arm versus 68% on the doctor arm), age (average of 32 years on both), BMI, CDC classification, CD4 count (64% < 200 cells/mm3 versus 63%), viral load (55% > 100,000 mL versus 58%). All patients were initiated on stavudine containing regimens.

After a median follow-up of 120 weeks (IQR 60-144) the composite primary endpoint was reached by 46% of the participants (48% and 44% in the nurse and doctor group respectively). The hazard ratio for treatment failure on the nurse arm was 1.09 [95% CI: 0·89–1·33]. No significant differences between time to death, viral failure (failure to achieve 1.5 log decline in viral load from baseline to 12 weeks of treatment or two consecutive viral loads 4 weeks apart of more than 1000 copies per mL), toxicity failure (grades 3 and 4 adverse events or other events needing treatment interruption for more than 42 days), and loss to follow-up were recorded between the nurse and doctor groups. 44 versus 39 patients had virological failure, 68 versus 66 had toxicity failure, 70 versus 63 were lost to the study (withdrew consent, defaulted on clinic schedule or lost to follow-up), and 10 versus 11 died on the nurse and doctor arms respectively.

Although immune response was not a component of the primary endpoints, median increases in CD4 cell counts at 2 years were 239 cells [IQR 217-290] and 220 cells [IQR 174-274] in the nurse and doctor arms respectively.

The authors explain that the results of this study support observational data from other studies that ART programmes managed by nurses are not inferior to those managed by doctors. They note that their study supports task shifting, as no significant difference between the composite endpoints of the two groups were noted, although further study with longer follow-up might be needed for individuals with advanced HIV starting ART.

They drew attention to the high frequency of hyperlactataemia associated with stavudine treatment. There were 80 hyperlactaemia cases in 815 person years on the nurse arm [9.8/100py 95%CI: 7.9-12.0] and 87 cases in 831 person years on the doctor arm [10.5/100py 95%CI: 8.5-12.7]. Two patients on the doctor arm died of lactic acidosis.

Doctors were more likely than were nurses to make a grade 3 or 4 neurological diagnosis (incidence rate ratio 0.32 [95% CI: 0.16–0.65] for HIV related neurological events and 0.39 [95% CI: 0.14-1.10] for non-HIV-related ones).

When the trial started they were using 40mg stavudine, but this was eventually changed to 30mg after the first year. They concluded that it is likely that reducing stavudine to 30mg (in line with WHO recommendations) reduced the number of toxic events during the trial.

The authors pointed out that widespread task shifting will need increased training, a redefinition of scope of practice for nurses and a clinical support structure. They concluded that nurses were non-inferior to doctors in monitoring first-line ART in a public health ART programme in South Africa and that their results support expanding access to treatment by task shifting to nurses.

This is an important study that provides a sound evidence base for the clinical safety of task-shifting. The positive outcome of this study was not obvious in advance because, as the authors state, findings from several studies in industrialised settings have shown that outpatients have better outcomes when cared for by a physician with HIV expertise than do those without such a physician. This study therefore shows that what is the case in the industrialised world cannot easily be transposed to a developing world public health setting.

This study was limited to patients already initiated on treatment. Further research is needed to examine the initiation of ART by nurses.

The state recently has taken several steps to reduce the burden on human resources:

· Following changes to regulations in May, lay counsellors can, following training, do finger stick HIV tests.

· The new Department of Health ART guidelines specify nurse-initiated treatment as a goal of the ART programme.

· In July, the Department of Health released a memorandum giving facilities permission to prescribe three months of ART to patients instead of one month.

This is yet another study that highlights the problem of hyperlactataemia associated with stavudine, although the researchers point out that it was lower than other studies have reported, probably due to the switch from 40mg to 30mg after the first year. Now that there is an option to replace stavudine with tenofovir in patients already on ART in the new Department of Health ART guidelines, doctors and nurses should be encouraged to change the regimens of patients with possible stavudine side-effects.

Reference

Sanne et al. 2010. Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomized non-inferiority trial. Lancet. 2010 Jul 3;376(9734):33-40.

Cotrimoxazole prophylaxis reduces mortality in patients on ART with low CD4 counts or WHO stage 3 and 4 disease

Nathan Geffen, TAC

Cotrimoxazole preventative therapy (CPT) has been shown in many studies, including randomised controlled trials, to reduce mortality and morbidity in people with HIV. However its benefit to people on ART is unclear.

A retrospective cohort analysis by Hoffmann and colleagues of the Aurum Institute assessed the effectiveness of cotrimoxazole preventive therapy (CPT) at various WHO clinical stages and CD4 strata in patients on ART. [1] This study was based on data originally presented at CROI 2010. [2]

The authors explained that in industrialised countries CPT is principally used to prevent PCP and toxoplasmosis. But in resource-limited countries it is mainly used to prevent malaria,

bacterial pneumonia and sepsis and diarrhea. The evidence driving the WHO guidelines for CPT use in resource-limited settings has primarily been derived from regions with high malaria. The authors were therefore interested in the effectiveness of cotrimoxazole in a low-malaria setting, which is characteristic of most of South Africa. Furthermore, the authors noted that cotrimoxazole resistance is high in this study's setting and they were therefore interested in seeing if it was still beneficial.

Patients older than 18 years of age who were antiretroviral-naive at ART initiation, had a CD4 count within six months of ART initiation and who either started on CPT from 30 days before to seven days after ART or did not receive CPT for the first 12 months of ART were included. Of approximately 16,000 patients initiated on ART from January 2003 to January 2008 at 164 public health facilities and 67 workplace ART clinics, just over 14,000 met the inclusion criteria. The first-line regimen used was 3TC, with either AZT or d4T and either efavirenz or nevirapine.

The study compared mortality between patients who received CPT against those who did not. All clinics used similar monitoring systems and the study was adjusted for clinic level confounding throughout. Deregistration forms (which record death), active defaulter tracing and human resources data were used to determine deaths. Terminally ill workers separated from work were counted as deaths.

At baseline the median CD4 cell count was 132 cells/mm3 and 62% of the patients were men. The baseline median CD4 cell count was lower (118 [IQR: 53-184] vs 153 cells/mm3 [IQR: 70-236]) among the approximately 7,500 patients who received CPT compared with the over 6,500 patients who did not (p<0.001), but viral loads were similar. The median age was 39 [IQR: 33-46] and 62% of the patients were men.

Mean time on CPT was nine months [95%CI: 8.8-9.2]. Of those who discontinued ART or were lost to follow-up, nearly 1,200 (18%) were not receiving CPT versus just over 900 (12%) who were (p<0.001). A total of 1,137 patients died and a further 152 were medically separated for a total of 1,289 (11%) patients reaching the study endpoint .

The following were associated with lower mortality: receipt of CPT (HR: 0.6; 95%CI: 0.53-0.68), younger age (p=0.03), female sex (p<0.001), higher baseline CD4 count (p<0.001), receipt of isoniazid therapy (p<0.001), higher time updated CD4 count (p<0.001) and lower baseline WHO stage (p<0.001).

In analysis adjusted for age, sex, WHO stage, history of TB, time-updated HIV viral load suppression and clinic-level effects the hazard ratio of death with CPT compared to no CPT was as follows: <200 cells/mm3: 0.64 (95%CI: 0.56-0.72); 200-350 cells/mm3: 0.62 (95%CI: 0.41-0.94); >350 cells/mm3: 0.8 (95%CI: 0.38-1.7). So for CD4 count < 350 cells/mm3, cotrimoxazole use was associated with reduced mortality. For an analysis restricted to patients in WHO stage 1 or 2 only, the association with mortality was only significant in patients with CD4 counts <200 cells/mm3 (HR: 0.53; 95%CI: 0.4-0.68).

The authors noted that their findings were consistent with other CPT studies from areas with higher malaria and diarrheal disease and lower cotrimoxazole resistance. It was not the study's purpose to ascertain cause of death but the authors speculate that CPT reduced mortality by reducing bacterial infections such as salmonella, streptococcus infection, diarrhea and PCP. They noted that their study is observational and therefore subject to confounding. However, they indicated that they have likely

underestimated deaths in the non-CPT group, biasing the study against CPT use.

The authors recommended that CPT be initiated in patients on ART with CD4 counts < 200 cells/mm3 or WHO clinical stage 3 or 4. They noted that the optimal length of time of CPT needs to be determined in further research, but speculated that 9 to 12 months or more may be appropriate.

COMMENT

This study provides an evidence base for the recommendation in the Department of Health's Clinical Guidelines for the Management of HIV & AIDS in Adults and Adolescents, which recommends "Patients with CD4 ≤ 200 cells/mm3 or stage 2, 3 or 4 HIV disease (including TB) need Cotrimoxazole prophylaxis." [3]

While the evidence for initiating patients with low CD4 counts or clinical signs of AIDS on CPT is unequivocal, the optimal duration of time on cotrimoxazole needs further investigation. Randomised controlled trials comparing different durations of CPT are warranted.

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PREVENTION

Pre-exposure prophylaxis with tenofovir/ FTC reduces sexual transmission of HIV between men at high risk: results from the iPrEX study

Simon Collins, HIV i-Base

The published results and the supportive supplementary appendix from a large international study (conducted in Peru, Equador, Brazil, US, Thailand and South Africa) provide the first human evidence that daily tenofovir/FTC (Truvada) can reduce the risk of HIV sexual transmission in men who have sex with men (MSM) at a high risk of HIV exposure. [1, 2]

The results should challenge approaches to HIV prevention and they have the potential to drive improved access to tenofovir as an ARV treatment.

The iPrEX study results, together with the full protocol and supplementary information was published online in the New England Journal of Medicine, and are all available without subscription. The top-level results - reducing infection by 44% with minimal safety side effects were widely publicised but the adherence and drug level analyses suggest a far higher potential for protection.

The study randomised just under 2500 men (including 29 transgender women (male-to-female, <1%) to either daily tenofovir/FTC or placebo. As with other prevention studies, iPrEX included intensive risk-reduction counselling, free condoms (monthly), behaviour interview (quarterly) and sexual health monitoring (at least 6-monthly).

Importantly, participants were at high risk of infection due to their behaviour risk. Ten percent of the approximately 5000 people initially screened for the study were already HIV-positive and a further 10 became infected between screening and enrolment.

Participants were young (~50% aged 18-24; 20% 25-29 and 20% 30-39 years); sexually active in the previous 12 weeks (18 partners; SD ±35); at high risk (~80% having had unprotected anal intercourse (UAI) in the previous 6 months with a partner of unknown HIV status); high STI incidence (13% syphilis, 35% HSV-2 at baseline). Over 40% participants had transactional sex in the previous 6 months, alcohol use was common and high (>4 drinks per drinking day in >50% participants) and HIV awareness/disclosure was low (only 2% had knowingly have sex with an HIV-positive person in the previous 6 months). Baseline characteristics were similar between the two arms.

The primary endpoint of at least 85 HIV infections was therefore reached quickly - after a median of 1.2 years (maximum 2.8 years), and total of 3324 patient years of follow-up (PYFU). This was despite a self-reported reduction in risk behaviour (a 50% reduction in the number of partners for receptive intercourse and increasing condom use for receptive intercourse from 50% to 75% of partners) - both potentially the result of a greater focus on HIV risk form the counselling and/or awareness of risk from using a daily prophylaxis.

New infections were reported in 100 participants (36 vs 64 in the active vs placebo group) and demonstrated a crude 44% protection rate (95%CI: 15 to 63; p=0.005) for the active group. Protection was higher in people who reported highest risk sex (recent UAI); 58% protection, 95% CI, 32 to 74). There was no significant between-group difference in protection by geographical region, race or ethnic group, circumcision, level of education, alcohol use, or age.

The analysis of adherence (>95% by self report and 90-95% by pill count; both from week 8 onwards, and slightly lower during the first 8 week) reported higher protection with greater adherence. In a post hoc analyses, pill use on 90% or more of days was recorded at 49% of visits on which efficacy was 73% (95% CI, 41 to 88; p<0.001)

However, results from a small pharmacokinetic sub-study looking at drug levels (both in plasma and intracellular) suggested actual adherence rates could have been dramatically lower. Although the drug level results should be interpreted with caution due to their low number, the associations with infections and suboptimal or undetectable levels were compelling.

Drug levels (testing was sensitive to tenofovir and FTC taken within 14 days, though tested a median of 35 days (IQR 28–56) post-infection) were only detected in plasma or cells in 3/34 (9%) newly infected people in the active arm. Of the 3 people with detectable levels, none had cell-associated drug levels higher than median levels in 22 HIV-negative controls. Conversely, 91% of infections in this sub-group appeared not to be taking tenofovir/FTC on a fortnightly–let alone daily–basis). Rates in an active-arm matched control group of 43 people who were not infected, detected drug levels in approximately 50% of people. Only 8% of this HIV-positive group who were considered high adherence (>50% pills) by self-report were considered on treatment by drug level (compared to 54% of HIV-negative controls).

The odds of HIV infection in people in the active arm with detectable drug levels were 12.9-fold lower (95%CI;1.7 to 99.3; p<0.001), corresponding to a relative reduction in HIV risk of 92% (95% CI, 40 to 99; p<0.001). After adjustment for reported unprotected receptive anal intercourse, the relative risk reduction was 95% (95% CI, 70 to 99; p<0.001).

There was a reassuringly high concordance (>95%) between both plasma and their respective intracellular active moieties and between each drug (both drug were similarly detected in each compartment).

Side effects and tolerability

Although side effects were frequently reported, these were similar between active and placebo groups (70% each, p=0.50) and a similar incidence of serious adverse events (5% each group, p=0.57; NS). Moderate nausea (Grade 2 or higher) was reported more frequently in the active group during the first four weeks (p=0.04)). Unexplained weight loss (>5% weight) occurred more frequently in the active arm (34 vs 19 events, p=0.04).

Creatinine levels were raised (1.1 x ULN or 1.5 x baseline) for 26 measurements in the active arm vs 15 times in the placebo group (2% vs 1% respectively, p=0.08), with 44% remaining in the normal range and 88% of elevated levels not confirmed on the subsequent test. Seven people in the active arm and three in the placebo arm discontinued due to elevated creatinine.

Resistance

While correlation between protection and active drug levels suggests that pre- and post-exposure dosing may be more critical than daily dosing, the risk of resistance in people who become infected is more complicated. Although resistance was not detected in any of the 34 people in the active arm who became infected - potentially exposed to intermittent or continuous dual-therapy - the lack of difference between viral load in infected people in the active and placebo arms (5.15 vs 5.10 log copies/mL in the tenofovir/FTC and placebo groups respectively, p=0.72) suggests low or non-adherence.

However, in 2/10 people in the active arm who were subsequently found to be HIV-positive at baseline, were found to have M184 mutations that could have potentially developed during early exposure to dual tenofovir/FTC therapy. While this could also be explained by infection with drug-resistant HIV (a third person had broad NNRTI and RTI resistance). Further studies, supported by modelling, would help determine whether a higher risk of resistance would be likely to come from daily PrEP (exposure to dual therapy during seroconversion) or intermittent PrEP (exposure to suboptimal drug levels between drug use).

COMMENT

These results are overwhelmingly supportive for a potent new prevention option to reduce the risk of sexual acquisition of HIV in gay men. On an individual risk with good drug levels (PK supports this being taken 24 hours before and within 2 hours after exposure) the reduction in single exposure risk may be as significant as that conferred by an undetectable viral load (<50 copies/mL) in reducing infectiousness of an HIV-positive partner (each >90% reductions). Nevertheless, results from ongoing studies of intermittent PrEP will inform this assumption.

These data do not address the practicality of daily PrEP as a population intervention to reduce infection but they do strongly inform individual protection in the context of high adherence prior to and after exposure risk.

Concerns about the practicality of PrEP as a population-based intervention were quickly raised to challenge the optimism of these positive results: and the efficacy levels in iPrEX clearly don't support policy changes. Three of these concerns focus on i) 44% efficacy being too low to support population-based widespread use, ii) the ethics of using a lifesaving treatment that is currently accessed by less than 20% of people on treatment in resource-limited settings and iii) implementation. distribution and access.

The first issue may change significantly given positive impact that use of PrEP has now shown, especially if PrEP is combined with other risk reduction options. The second may determine that PrEP will initially be an option used more in Western countries - as with condoms, or antiretroviral treatment. If PrEP safely reduces he risk of sexual transmission then it should be an option that people can chose, whether through private or public health care - as with condoms. If PrEP really works (with careful adherence) the global demand should theoretically drive greater demand, lower prices and more rapid access within ARV treatment programmes.

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Further information

iPrEx Study press release and fact sheets:

http://www.iprexnews.com

iPrEx study materials NIAID: Press Release:

http://www.niaid.nih.gov/news/newsreleases/2010/Pages/iPrEx.aspx

Q&A:

http://www.niaid.nih.gov/news/QA/Pages/iPrExQA.aspx

US CDC issue preliminary guidance for use of PrEP

Simon Collins, HIV i-Base

On 27 January 2011 the US Centre for Disease Control (CDC) issued preliminary guidance for the use of tenofovir/FTC (Truvada) as primary prophylaxis against HIV infection for gay men at high risk of exposure. [1]

This was based on results from the iPrEX study [2] and is notable as Truvada is not licensed as a prevention medication. The preliminary guidelines were issued in the hope they will reduce "potentially less effective PrEP-related practices" by health providers and in the community. Completing the full guidelines and obtaining expert input and public comment is expected to take several months.

The guidelines emphasise PrEP use only in a similar setting to the iPrEX study – ie only in men who have sex with men and only if they are at high risk. Additionally this should be part of broad health protection care, with limited prescriptions and regular HIV testing.

The guidance in Table 1 is an outline for healthcare providers who decide to prescribe Truvada for PrEP prior to licensing.

Table 1. CDC interim guidance for health-care providers electing to provide preexposure prophylaxis (PrEP) for the prevention of HIV infection in adult men who have sex with men and who are at high risk for sexual acquisition of HIV

Before initiating PrEP

Determine eligibility

- Document negative HIV antibody test(s) immediately before starting PrEP medication.

- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection.

- Confirm that patient is at substantial, ongoing, high risk for acquiring HIV infection.

- Confirm that calculated creatinine clearance is ≥60 mL per minute (via Cockcroft-Gault formula).

Other recommended actions

- Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision about prescribing PrEP.

- Screen and treat as needed for STIs.

Beginning PrEP medication regimen

- Prescribe 1 tablet of Truvada (tenofovir 300 mg plus FTC 200 mg) daily.

- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected.

- If active hepatitis B infection is diagnosed, consider using TDF/FTC for both treatment of active hepatitis B infection and HIV prevention.

- Provide risk-reduction and PrEP medication adherence counseling and condoms.

Follow-up while PrEP medication is being taken

- Every 2–3 months, perform an HIV antibody test; document negative result.

- Evaluate and support PrEP medication adherence at each follow-up visit, more often if inconsistent adherence is identified.

- Assess STI symptoms and, if present, test and treat for STI as needed.

- Every 6 months, test for STI even if patient is asymptomatic, and treat as needed.

- 3 months after initiation, then yearly while on PrEP medication, check blood urea nitrogen and serum creatinine.

On discontinuing PrEP (at patient request, for safety concerns, or if HIV infection is acquired)

- Perform HIV test(s) to confirm whether HIV infection has occurred.

- If HIV positive, order and document results of resistance testing and establish linkage to HIV care.

- If HIV negative, establish linkage to risk-reduction support services as indicated.

- If active hepatitis B is diagnosed at initiation of PrEP, consider appropriate medication for continued treatment of hep B.

Abbreviations: HIV = human immunodeficiency virus; STI = sexually transmitted infection; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine.

Reference

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2. The iPrEX study was reported in HTB November/December 2010 http://i-base.info/htb/14191

Trial finds high adverse event rate of circumcision device being marketed in Africa

Nathan Geffen, TAC

Orange Farm, a township about 40 kilometres from Johannesburg, was the site of one of three randomised controlled trials that demonstrated that medical circumcision reduces the risk of heterosexual men contracting HIV. [1]

The Orange Farm researchers have also examined operational issues such as how to reduce circumcision time and costs. In 2005 they conducted an open-label subtrial on members of the control group of the trial to test an alternative circumcision technique using a device manufactured in Malaysia called the Tara KLamp (TK). [2] (Note the capital L is the spelling used by the manufacturer.)

The device is being marketed in several African countries including Botswana, Lesotho, Swaziland and Kenya according to the manufacturer. The manufacturer claims, that the TK "… enables circumcisions to be performed not only safely and easily but also enables circumcisions to be performed just as aseptically, at home, on the roadside or out there in the bush, as in an operating theater."

The TK is made of plastic and is disposable. It comes in various sizes. A measuring card with holes of several diameters is used to determine the size chosen. The device is clamped onto the foreskin, necrotising it. It remains on the penis for 7 to 10 days before it falls off with the foreskin or has to be removed surgically.

The study compared the TK to the standard forceps-guided surgical technique. 166 patients were asked to participate, but 97 refused, of whom 94 gave as their reason that they did not want to be circumcised with the TK. Of the 64 remaining participants, 35 were randomised to the TK arm. General practitioners performed the circumcisions.

The median age at randomisation in both arms was 22 years (IQR: 20-23.5 in the control arm and 21-24 in the TK arm). There were no statistically significant baseline differences in ethnic group, religion, level of education, sexual experience, genital hygiene, hospitalisation in the last 5 years or genital ulcerations in the last 12 months.

Two patients randomised to the TK had to be circumcised using the forceps-guided method because of problems with the TK. There were 12 adverse events, all in the TK arm, reported by the general practitioners in the course of the study. Two people randomised to be circumcised with the TK had to be circumcised with the forceps-guided method following problems with the TK.

Participants were interviewed and examined by a male nurse in a follow-up visit six weeks after the circumcision. The nurse was blinded as to the technique used but could identify which group subjects were in from scarring. Participants also reported levels of satisfaction with penis appearance and answered a pain measurement questionnaire. 29 (91%) forceps-guided method subjects and 19 (79%) TK subjects attended this visit. The statistically significant results were as follows:

- Any sign of adverse event: 1 (3.4%) on the forceps-guided arm versus 7 (37%) on the TK arm (p=0.004).

- Delayed wound healing: 1 (3.4%) versus 4 (21%) (p=0.004 – NOTE: p value in paper appears wrong here).

- Problem with appearance: 1 (3.4%) versus 6 (31.6%) (p=0.001).

- Postoperative pain (scale of 1 to 10 in increasing levels of pain): 6.1 versus 9.5 (p=0.003)

- Bleeding within the 2 weeks after circumcision: 0 versus 4 (21%) (p=0.02, one answer missing)

- Lesion to the penis: 0 versus 4 (21%) (p=0.02)

- Infection following circumcision: 0 versus 6 (32%) (p=0.002)

- Swelling or haematoma within the 2 weeks after circumcision: 0 versus 15 (83%) (p<0.001)

During the study, the circumcision doctors became concerned with the high rate of adverse events with the TK. The manufacturers were therefore asked to provide additional training. Even after this additional training, the high rate of adverse outcomes continued.

The authors explained that unacceptably high rates of adverse events in the TK group resulted in an early interruption of the study. They concluded that the TK is unsuitable for adolescents and adults but may prove useful for children. They noted another non-peer reviewed study of adolescents of the TK in which a 32% adverse event rate was reported.

Studies in children

Two studies on the TK have been done in children, both by Schmitz and colleagues.

In a 2001 article in Tropical Doctor, Schmitz and colleagues reported on 64 circumcisions using the TK in Malaysia. Mild pain was reported and no complications. 90% of parents indicated they would recommend the TK to others. [3]

In a study in Holland, a facility in Rotterdam performed conventional surgery and a facility in Utrecht offered parents a choice of either conventional surgery or the TK to perform the circumcision. The median age of the children was 3 in both facilities (IQR 2-5 v 2-4 in Rotterdam and Utrecht respectively). There were 143 participants in the Rotterdam facility and 160 in Utrecht. 132 participants were circumcised using the standard technique and 143 using the TK. The countries of origin of most participants were Turkey and Morocco and most were Muslim. [4]

The TK performed well in this study. The median time of the operation was 7 minutes for the TK versus 15 minutes for standard operation (p<0.001). There were no significant differences in complication rate, postoperative pain or parental satisfaction. The cosmetic results were better for the TK group (p<0.001).

COMMENT

The TK is being marketed aggressively in sub-Saharan Africa. In communication with the Treatment Action Campaign, the company claims that it is marketing in Botswana, Lesotho and Kenya amongst others. About 600 circumcisions with the device have been performed in Kwazulu-Natal already.

The device needs to be withdrawn from use in adolescents and adults until such time as a randomised controlled trial shows that it is safe. While its use in children appears to be safe based on the Dutch study by Schmitz and colleagues, this was not a randomised study. Ideally there should be a randomised study on it in children before it is recommended for general use. It might be more appropriate, given the Orange Farm study, to prioritise testing other circumcision devices before attempting to re-examine the TK.

The approach of the manufacturers of the TK to independent research about their product is exemplified by this comment written in email correspondence by the device's designer, Dr G. Singh of Taramedic, to one of the Orange Farm researchers to try to dissuade publication of the Orange Farm study, "We should all accept that mistakes have been made by your circumcisers. All it needs is a simple withdrawal of your manuscript and gracefully accept the reality. I am even not asking for an apology, for I am a very forgiving man … but there is a limit!" (correspondence supplied to TAC by the manufacturer)

The World Health Organisation drafted a one-page statement cautioning against the use of circumcision devices pending further research. This statement was not released. However, the WHO has released a report of a meeting held in Nairobi on 11-12 March 2009 titled "Consultation to Review Manufacturing, Clinical and Regulatory Requirements for Male Circumcision Devices to Support Programme Expansion in High HIV Incidence Settings in Africa". The report contains a review of the evidence indicating caution about the use of circumcision devices.

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PREGNANCY AND PMTCT

Pregnancy outcomes in women exposed to efavirenz and nevirapine in Cote d'Ivoire

Polly Clayden, HIV i-Base

Another report, this time by Didier Ekouevi and colleages in the 1 February issue of JAIDS, shows no increased risk of adverse outcomes in infants exposed to maternal efavirenz (EFV) in pregnancy. [1]

Although a retrospective analysis, this study, conducted in Cote d'Ivoire, is the largest to date looking at pregnancy outcomes following first trimester EFV exposure.

It was conducted in Abidjan across four centres participating in the International epidemiological Databases to Evaluate AIDS (IeDEA) West Africa and in two ANRS trials.

The investigators searched the trial databases and the computerised information systems from the participating centres. Women who conceived receiving EFV or nevirapine (NVP) between January 2003 and July 2009 were included.

Five outcomes were evaluated: 1. Abortion, defined as voluntary termination of pregnancy. 2. Miscarriage <20 weeks gestation. 3. Stillborn, between 20 weeks and delivery. 4. Preterm delivery (PTD) <37 weeks and low birth weight (LBW) <2500 grams. 5. Congenital abnormalities observed in the first six weeks of age.

A total of 344 women met the study criteria. Of these, 213 (61.9%) conceived while on EFV-based HAART and 131 (38.1%) while on NVP-based HAART. Their median age at initiation of treatment was 29 (IQR 26-32) years; CD4 count 217 (IQR 146-280) cells/mm3 and just over half were WHO stage 3 or 4.

Nucleoside backbones were d4T/3TC, AZT/3TC, ddI/d4T or TDF/FTC. Baseline characteristics were similar for women receiving EFV or NVP except that more women received AZT/3TC with EFV than NVP, p<0.001.

Similar proportion of women in both groups were lost to follow up during pregnancy: 4.7 vs 6.1% in the EFV and NVP arms respectively, p=0.57. The majority of women (190/213, 89.2%) switched to either a PI or NVP when they found they were pregnant. Two women that conceived while receiving NVP switched to a PI due to side effects. The median duration of exposure after conception was 52 (IQR 37-75) days in the EFV group and 264 (IQR 222-285) days in the EFV group, p<0.001.

The investigators found, of the 203 women in the EFV group and 123 exposed to NVP for whom pregnancy outcome was known, there were no statistical differences in incidence of miscarriage or stillbirth among the two groups; 5.2% and 6.7% respectively overall. However the proportion of women having an abortion was greater in the EFV group than the NVP group, 14.3 vs 7.3%, p=0.05.

Birth weight data were available for 223 (89.6%) infants who had a median birth weight of 2800 (IQR 2500-3250) grams. PTD occurred in 27 (10.8%) infants, 9.5 vs 12.7% in the EFV and NVP groups respectively, p=0.76. LBW occurred in 45 (20.2%) infants, 17.2 vs 24.2%, p=0.2. No abnormalities were observed in infants exposed to either EFV or NVP, upper limits of 95% CI, 2.5% and 3.6% respectively.

This study needs no new comments to those previously reported on this subject, with an acknowledgement of the limitations of retrospective analyses.

These data were included in the meta-analysis looking at birth outcomes following EFV exposure by Ford et al. [2]

Once again, there is a high rate of voluntary abortion, which may be explained by health workers attitude to EFV in pregnancy.

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Cotrimoxazole with or without sulfadoxine-pyrimethamine reduces malaria in pregnant women

Polly Clayden, HIV i-Base

In countries where malaria is rife, women receive sulfadoxine-pyrimethamine (SP) intermittent preventative therapy during pregnancy.

Several countries, including Malawi, recommend daily cotrimoxazole for all pregnant women to prevent opportunistic infections. WHO recommends that HIV-positive pregnant women receiving daily cotrimoxazole should not be given SP in order to avoid potential sulfa drug toxicity.

However no study has evaluated the effects of cotrimoxazole compared to SP in HIV-positive pregnant women.

A paper published in the 15 February 2011 edition of the Journal of Infectious Diseases, authored by Atupele Kapito-Tembo and colleagues, showed an analysis of the prevalence of malaria parasitaemia and anaemia in HIV-positive pregnant women taking daily cotrimoxazole, either with or without SP, compared to those just taking SP.

The study was conducted between 2005 and 2009 at Thyolo Hospital, Malawi. This hospital provides free antenatal care and has a well-established PMTCT programme.

The study was cross-sectional. It was possible because of confusion over implementation of recommendations for cotrimoxazole and SP during the study period. In the earlier years of the study, Malawian national policy for prevention of malaria in HIV-positive women was SP-IPT, later this changed to daily cotrimoxazole. This resulted in some women receiving both during the period of transition.

Women were enrolled from another study investigating the effects of iron supplementation on maternal morbidity. A total of 1142 women, were a median age of 27 years (range 16-46), with a median CD4 count of 423 cells/mm3 (range 11-1528). About 60% used bed nets and 48.5% received HAART.

Data on the use of SP and cotrimoxazole were available for 1121 (98.2%) women. Of these, 49.7% reported receiving SP only, 29.8% cotrimoxazole only and 15.5% received both. Only 5.1% reported receiving no prophylaxis. The women were similar with respect to CD4 count and clinical stage, but the women in the SP group were younger, less likely to use bed nets and less likely to be receiving ARVs compared to the women in the other groups.

The investigators found that the prevalence of PCR-detected malaria was nearly twice as high, 113/1128 (10%), than that of microscopic malaria, 61/1114 (5.5%). The prevalence of any anaemia and moderate to severe anaemia (haemoglobin <8g/dL) were 514/1140 (45.1%) and 18/1140 (1.6%) respectively.

After adjusting for age, gravidity, number of antenatal visits, bed net use and socioeconomic status, microscopic malaria infection was significantly lower in women taking cotrimoxazole plus SP, AOR 0.9 (95% CI, 0.01-0.66) or cotrimoxazole alone, AOR 0.44 (95% CI, 0.25-0.78) than in women taking SP alone. The odds for PCR-detected malaria were similar.

After adjusting for age, gravidity, number of antenatal visits, CD4 count and BMI, the presence of anaemia was also significantly lower in women taking cotrimoxazole plus SP, adjusted prevalence ratio (APR) 0.67 (95% CI 0.54-0.83) or cotrimoxazole only, APR 0.72 (95% CI, 0.61-0.83) than in women taking SP alone.

The investigators acknowledge several limitations to this study, particularly that changes in potential confounders may have occurred at the same time as the change in antimalarial prevention policy, and that controlling for these factors may leave residual confounding because the study was not randomised.

They also note that because women were only enrolled in the third trimester of pregnancy the impact of cotrimoxazole may be underestimated, as women are at an increased risk of malaria in the earlier stages of pregnancy.

They suggest that these results support the policy of daily cotrimoxazole instead of SP. Also, the observation the cotrimoxazole plus SP was more effective than cotrimoxazole alone warrants a randomised controlled study to look at both the efficacy and safety of this strategy.

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Test and treat for all pregnant women in low and middle income countries?

Polly Clayden, HIV i-Base

An opinion piece, published ahead of print in JAIDS by Maria Zolfo and colleagues, argues for a universal "test and treat" strategy in all HIV-positive women in high burden countries.

They cite the WHO/UNAIDS/Unicef statistics showing that in low and middle income countries, only 21% of pregnant women tested for HIV while they were pregnant, only 24% HIV-positive pregnant women had a CD4 test to determine their eligibility for ART, only 45% received antiretrovirals and only 32% of infants of positive mothers received post natal prophylaxis.

They compare this to the extremely low rates of MTCT in industrialised countries.

They note that provider initiated testing strategies have reached 60-80% amongst pregnant women in 6 out of 10 counties with the highest burden of HIV among pregnant women suggesting that the majority will access services if they are available.

They suggest that the WHO recommended option, of a two tiered antiretroviral strategy in pregnancy of treatment for women indicated for their own health (at clinical stages 3 and 4 and ≤ 350 cells/mm3), and antiretroviral prophylaxis (either short course AZT plus single dose nevirapine or a triple combination regimen stopped after breast feeding) for mothers not indicated for treatment, may not be feasible in settings with limited infrastructure. Not least when there is limited access to CD4 tests.

In some high burden countries, they write, "a low tech test-and-treat intervention for all HIV-positive women not yet on ART – regardless of the CD4 count and clinical stage – will be a more feasible option to reach large numbers of women." They suggest that this should be life-long and not discontinued after breastfeeding.

Based on current evidence this strategy would mean about 50% of women would be eligible for treatment for their own health and 25% would start with CD4 between 350 and 500 cells/mm3. More controversial would be the group that starts treatment with CD4 counts above 500 cells/mm3.

In their arguments they note that the SMART study showed the disadvantages of stopping and starting treatment in non-pregnant adults, even at higher CD4 counts. Additionally lack of availability of CD4 tests may increase the risk of undetected disease progression in women stopping treatment. There is also the likelihood of a subsequent pregnancy.

There are concerns, however, about the sustainability of long term adherence and this may be particularly difficult for healthy women who do not require treatment for their own health.

The IMPAACT PROMISE study is being conducted to look at these questions and others, but results will not be available until 2014 at the earliest.

In the meantime the authors advocate for a universal "test and treat" strategy to be rapidly implemented in HIV-positive women in high burden countries.

COMMENT

One of the authors of this article, Erik Schouten, from the Department of HIV and AIDS, Ministry of Health, Malawi gave a presentation in a satellite session at IAS 2010, explaining changes to their national programme for pregnant women. They have decided that the best option for Malawi is exactly as described above, to start all pregnant women on one universal regimen for treatment and prevention continuing for life.

In Malawi, they take a public health approach to treatment. Universal access to reliable CD4 count will not be reached within a few years. Additionally their fertility rate is high – 5.6, and breastfeeding is recommended.

Although they acknowledge the challenges, they believe the advantages to this strategy outweigh the disadvantages and this is, "The only realistic option for Malawi."

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PAEDIATRIC CARE

Initiating nevirapine with fixed dose combination "mini-pills" in Zambia

Polly Clayden, HIV i-Base

The shortage of appropriate paediatric antiretroviral formulations has been a major barrier to scale up of treatment of children in resource-limited settings. The initiation of nevirapine is complicated by the recommendation to escalate the dose, requiring a regimen change two weeks after starting treatment.

The Children with HIV in Africa – Pharmacokinetics and Adherence of Simplified Antiretroviral Regimens (CHAPAS) Trials, are investigating new antiretroviral formulations and strategies for children. This is a joint project of the University of Zambia and University Teaching Hospital Zambia, the Medical Research Council (UK), Radboud University Nijmegen, Netherlands and the University of Padova, Italy, began in 2005. [1] We have followed this project in HTB for some time.

CHAPAS-1 looked at treatment with Triomune Baby/Junior - fixed dose combination (FDC) scored, dispersible "mini pills" of stavudine (d4T), lamivudine (3TC) and nevirapine in the correct ratios for children, manufactured for the trial by Cipla. The doses of the tablets are: 6 and 12 mg d4T, 30 and 60 mg 3TC and 50 and 100 mg nevirapine in Triomune Baby and Junior respectively. Data from this trial contributed to the tentative approval by the FDA for these formulations, and to the WHO dosing recommendations by weight band for fixed dose combinations of these drugs, down to 3kg.

Nevirapine toxicity has been reported to be uncommon in children receiving full dose nevirapine at initiation, but there have been no randomised trials to evaluated the safety of this strategy. CHAPAS-1 compared the initiation of antiretroviral therapy (ART) with full dose nevirapine versus half dose nevirapine for the first two weeks of treatment.

An article, authored by Veronica Mulenga and colleagues and published in the November 1, 2010 issue of Clinical Infectious Diseases, showed findings from this trial.

Children aged 3 months to 14 years, indicated for treatment in accordance with WHO 2006 guidelines, were randomised 1:1 to receive either Triomune Baby or Junior twice daily for the first two weeks (full dose group, or Triomune Baby/Junior once daily plus once daily Lamivir-S, Baby or Junior - dual 3TC and d4T combination tablets (dose escalation group).

The primary end point was grade 3 or 4 adverse events (AEs) related to nevirapine.

A total of 211 children were randomised and included in the intent to treat analysis. Children in the two groups were similar. The median age at ART initiation was 5 years (IQR 2-9 years) and 35% were less than 3 years. The median CD4 percentage was 13% and 99% of children had WHO stage 3 or 4 disease. Severe wasting and/or stunting were common.

All children were seen by a nurse at 2 and 4 weeks from initiation and subsequently every 4 weeks. Children were weighed and measured, any adverse events or new WHO events were recorded and additional ART prescribed. They were also routinely seen by a doctor at weeks 2, 4, 8 and 12 and then every 12 weeks where they had a clinical examination and blood samples were obtained.

There were 60 (31 the full dose and 29 in the escalated groups), grade 3 or 4 AEs reported in 49 children (25 in the full dose and 24 in the dose escalated) that were considered definitely or probably related to nevirapine (n=8), or there was uncertainty as to their relation to nevirapine (n=52). This gave 18 vs 16.5 events per 100 child years in the full dose and dose escalated groups respectively; incidence rate ratio [IRR] 1.09 (95% CI 0.63-1.87), p=0.74.

All AEs were asymptomatic and the children continued treatment with nevirapine. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) were the most common; 11 events in the full dose and 3 in the dose elevated groups), and elevated bilirubin levels (n=34).

There was no grade 3 or 4 rash, but 13 and 2 children had grade 1 (2 in the full dose group) or grade 2 (11 in the full dose and 2 in the dose elevated groups) rashes, p=0.003. One child in the full dose group developed a second grade 2 rash after reintroducing nevirapine at half dose. Rashes started at a median of 17 days (range 8-25 days) after initiation and lasted for a median of 9 days 9range 2-24 days).

Of the 15 children who developed rashes, 3 continued full dose nevirapine; 9 (8 full and 1 elevated dose) stopped nevirapine temporarily and then successfully dose escalated; 1 in whom the rash returned after changing from full dose to half dose, substituted efavirenz and 2 (1 full and 1 dose escalated) substituted efavirenz without retrying half dose nevirapine. All but 2 children in the full dose group were managed as outpatients.

In multivariate analysis, older age (per year increase), OR 1.35(95% CI, 1.10-1.64) p=0.003, and higher CD4 count for age (per unit increase), OR 1.51 (1.03-2.20) p=0.03 were associated with nevirapine rash. More rash occurred in the full dose group versus dose escalated, OR 9.79 (1.97-48.6), p=0.005.

Twenty-two children (10%) died (12 in the full dose and 10 in the dose escalated groups). More than half the deaths occurred within the first 3 months of ART, and were most frequently due to diarrhoea and pneumonia. Most children who died had advanced HIV disease and very low weight-for-age z-scores. No deaths were judged to be drug-related.

Children in both groups had similar increases in weight for age and height for age z-scores and CD4 counts or percentages (+17.3%) at 96 weeks.

The investigators concluded that rash occurred more frequently among children starting nevirapine at full dose but 88% had no clinical toxicity. Where possible they recommend using dual d4T/3TC paediatric tablets for dose escalation

If children are initiated on full dose Triomune, caregivers need to be aware of the timing of rash. For those in whom this occurs the options are to treat through under careful observation or to manage temporarily with half dose Triomune or efavirenz.

They noted that the elevated AST or ALT values were unconfirmed, transient and resolved spontaneously. They suggested that their results concur with that of the DART trial, which showed no difference in AEs requiring regimen modifications among adults receiving routine versus clinical biochemistry monitoring, including those receiving nevirapine. The results from both DART

and CHAPAS-1 suggest that routine liver function tests are not necessary after nevirapine initiation in resource-limited settings.

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Daily cotrimoxazole preferable to intermittent preventative therapy in HIV-infected children

Polly Clayden, HIV i-Base

WHO recommends daily cotrimoxazole preventative therapy (CPT) for infants and children. US guidelines recommend either daily or three days a week. Adult studies suggest that thrice-weekly CPT is as effective as daily but with a decrease in side effects and an increase in tolerability. The optimum frequency for CPT in children has not been determined.

A paper, published in AIDS, by Heather Zar and colleagues, reported results from a South African study of children randomised to receive either daily or thrice-weekly CPT.

The study looked at mortality, bacterial infections, hospitalisation and adverse events.

A total of 339 children, attending, either Red Cross War Memorial Children's Hospital, University of Cape Town or Tygerberg Hospital at Stellenbosch University, aged eight months and above were enrolled. Of these, 10 tested negative and five were lost to follow up within a month from randomisation.

The study, which commenced in December 2002, originally had a factorial design and compared both three times weekly CPT vs daily CPT, and isoniazid (INH) vs. placebo. The placebo arm was stopped in May 2004, on the advice of the DSMB, and all children were switched to INH. INH was then discontinued in December 2007 as most children were receiving HAART. The investigators continued to study three times weekly CPT vs daily CPT. Results are from this investigation from January 2003 through December 2007.

Of the 324 children, 165 (50.9%) were randomised to receive intermittent therapy and 159 to daily therapy. They were a median age of 23 months (IQR 9.5-48.6 months). Almost one third (30.3%) were less than 12 months of age. The majority (88.6%) were symptomatic and the median CD4 percentage was 20%. At enrolment 8.6% of children were receiving HAART, and 63.9% received it during the study. Malnutrition was common. Baseline characteristics were similar in both groups.

Overall 9% of children were lost to of which 57% were in the group receiving daily CPT. An additional 24% withdrew from the study, 13% from the daily group, mostly due to logistics. Median follow up was 1.97 years (IQR 1.3-3.3 years) vs 1.92 years (IQR 0.5-3.29 years), p=0.37, in the intermittent and daily groups respectively. The investigators reported excellent adherence in both groups.

They found similar mortality rates in both groups: 24/165 (14.5%) vs 29/159 (18.2%) deaths in the intermittent and daily groups respectively, HR 0.75 (95% CI, 0.44-1.29), p=0.3. The difference in the cumulative survival proportions estimated at one year was 0.04 (90% CI -0.03- 0.10). Therefore thrice weekly was defined as non inferior to daily CPT as the CI for difference included zero and exceeded the predefined delta of -0.1 at one year of follow up. The choice of inferiority margin was based on expert opinion.

Infants had a six-fold higher incidence of death compared to children greater than one year of age (20 vs 3.6 per 100 child years), IRR 5.91 (95% CI 3.3-11.2) p<0.0001.

Causes of death were similar in both groups. Overall this was, 32% sepsis, 25% pneumonia and 15% diarrhoea.

However intermittent CPT was associated with a two increased incidence of bacteraemia, IR 9.6 vs 4.07 per 100 child years, IRR 2.36 (95% CI 1.21-4.87), p=0.006.

Additionally children receiving intermittent IPT spent significantly more days in hospital than those receiving daily, 228.5 vs 198.5 days per 100 child years, IRR 1.15 (95% CI 1.04-1.28), p=0.004. The admission rate was similar between the two groups.

Toxicity was similar in both groups, with an overall incidence of 6.8 grade 3 or 4 events per 100 child years (46 events; 25 intermittent, 21 daily).

The investigators concluded that their results support the current WHO recommendations of daily CPT for infants and children. They acknowledge that their results may not apply to settings with different burdens of bacterial disease. They wrote: "Widespread implementation of CPT is needed in areas of sub-Saharan Africa where this intervention is not available."

Reference

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EPIDEMIOLOGY

Estimate of changing HIV incidence in South Africa

Nathan Geffen, TAC

Thomas Rehle of the Human Sciences Research Council (HSRC) and colleagues published an article in PLoS One that estimated the change in HIV incidence in South Africa. [1]

The study found a non-significant reduction in HIV incidence in the period 2005 to 2008 compared to the period 2002 to 2005. However there was a significant reduction in incidence amongst women aged 15 to 24.

The HSRC conducted country-wide surveys in 2002, 2005 and 2008. These surveys measured HIV prevalence for the whole population, as well as by gender, age group and race. By using a recently developed methodology that involved examining differences in prevalence across surveys and correcting for deaths in people with HIV the authors measured incidence from 2002 to 2005 and also from 2005 to 2008.

The methodology worked as follows: Ideally incidence would be measured by a longitudinal study, ie following the same set of HIV-negative people over a period of time and determining how many become infected. But this is impractical on a countrywide scale. However, such a study can be approximated using what is called the synthetic cohort principle. This assumes that individuals of age x in the first survey are represented by individuals aged x+t in the second survey, where t is the interval between surveys, even though the surveys do not include the same individuals. The change in HIV prevalence across this group of individuals is assumed to be due to new infections less deaths of people with HIV. Deaths in people with HIV in an age group cohort can be determined by estimating the rate of AIDS deaths based on historical distributions of survival after infection.

The interval between the 2002 and 2005 surveys was 2 years and 8 months, and the interval between the 2005 and 2008 surveys was 3 years and 7 months. But survey participants reported only their age in years (not date of birth) and so prevalence had to be interpolated in the synthetic cohorts.

The calculation of the rate of death in HIV-positive people was complicated by the scale up of antiretroviral treatment that began in South Africa in 2004. The authors accounted for this by subtracting the proportion of HIV-positive people who were alive in the 2008 survey that would have died without treatment. They were able to approximate this because HIV-positive blood samples in the 2008 survey were tested for the presence of antiretroviral medicines thereby giving an estimation of the proportion of HIV-positive people on treatment.

The researchers further assumed that on average people initiated treatment a year before they would have otherwise have died and that people starting treatment have a 10% annual mortality rate in the first years of treatment. They consequently calculated that 58% of those receiving treatment in 2008 were alive at the time of the survey due to being on antiretroviral treatment.

They estimated HIV incidence in people aged 15 to 49 in the period 2002 to 2005 to be 2.0 per 100 person years (95%CI: 1.2-3.0). This was compared to 1.3 per 100 person years in the 2005 to 2008 period (95%CI: 0.5-2.1), but this difference was not significant. There was however a significant decline in incidence across the two periods between women and men aged 15 to 24 years (5.5/100 py [95%CI: 4.3-6.6] v 2.2/100 py [95%CI: 1.3-3.1]).

The authors, in order to account for the uncertainty of the effect of treatment on the death rate of people with HIV, stated that they estimated incidence under a range of assumptions. They concluded that there remains clear evidence for a reduction in incidence among women under all credible assumptions for the effect of antiretroviral treatment.

The authors discussed how a decline in incidence could have occurred. They stated this was unlikely to have been a consequence of the natural course of the epidemic in which those groups at most risk of infection become saturated with infection and die. They also argued it was unlikely due to antiretroviral treatment because "access to treatment has only increased significantly in recent years, it is expected that such an effect would take longer to develop and require higher levels of [antiretroviral treatment] coverage for an extended period of time." Instead, they give greater weight to the possibility that the decline was due to increased condom usage reported across the three surveys.

COMMENT

The HIV National Strategic Plan 2007-2011 (NSP) set a target of halving HIV incidence between 2007 and 2011. [2] Therefore methods of measuring incidence and changes in incidence are needed to determine progress towards this target. However, calculating country-wide incidence is extremely difficult. This study is an ambitious effort to do so. Although its estimates do not coincide with the NSP period, if the limitations of this study can be overcome, it is conceivable that a practical way of measuring the NSP prevention target could be found. The study's limitations are:

- **The 2002 HSRC survey was widely criticised for having a low response rate and anomalous results. The accuracy of the results of this study is dependent on the accuracy of the 2002 survey.**

- **The method used to calculate the 95% confidence intervals assumes the data were collected in a simple random sample, but the data was from clustered samples. Therefore, the confidence intervals around the estimates of incidence should be larger.**

- **The researchers make several assumptions about the effects of antiretroviral treatment, such as the length of time people would have lived if they did not access ARVs and the speed and size of the scale up of the antiretroviral treatment rollout from 2004 to 2008. Therefore their calculation of the number of people with HIV who died between surveys has a wide margin of error.**

Furthermore, Rehle and colleagues arguments for what could and could not be causing a possible decline in incidence are speculative. Only further research can provide more assured answers. To facilitate this and other research, several organisations have released a statement calling for the HSRC to make their data from the 2002, 2005 and 2008 surveys public. [3]

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BASIC SCIENCE

Anchors away: new HIV entry inhibitor study creates a splash

Richard Jeffreys, TAG

In December, the journal Science Translational Medicine published results from a phase I trial of a new type of anti-HIV drug named VIR-576. [1]

The drug inhibits the entry of HIV into target cells by blocking the mechanism the virus uses to anchor itself to the cell. This mechanism involves a harpoon-like extension called the gp41 fusion peptide, which shoots into the cell membrane. VIR-576 gloms onto the end of the gp41 fusion peptide, preventing its penetration (a bit like covering the spear end of a harpoon so it just bounces off the target). Although VIR-576 is not the first entry inhibitor HIV drug, it is the first to target the gp41 fusion peptide. The researchers have dubbed it an "anchoring inhibitor."

The phase I study administered three different doses of VIR-576 to three groups of six untreated HIV-positive people with viral loads over 10,000 copies and CD4 counts above 350. Because VIR-576 is a peptide, administration was via continuous intravenous infusion. The total duration of treatment was 10 days. At the highest dose of 5 grams per day, VIR-576 caused an average viral load reduction of 1.2 logs (over 90%). The drug was well tolerated but two participants (one in each of the two lower dose groups) showed signs of an allergic reaction that resolved once treatment was stopped. No evidence of resistance to VIR-576 was documented.

The findings are potentially encouraging for several reasons:

- They show that HIV's gp41 fusion peptide is a viable drug target, which was previously uncertain.

- The gp41 fusion peptide does not appear able to tolerate mutations as easily as other drug targets, suggesting resistance will be slower to develop.

- The activity of VIR-576 is not affected by resistance to available anti-HIV drugs.

- Fusion peptides are essential to the replication of most enveloped viruses, suggesting the general approach could be applied to other viral pathogens.

However, there are also caveats that were not clearly articulated in some of the media stories that appeared when the study was published. Most obvious is that the current formulation of VIR-576 cannot practically be used as a treatment due to the requirement for continuous intravenous infusion. The high dose and potential cost are additional impediments; the dose of the approved HIV entry inhibitor Fuzeon (T-20) is 0.18 grams/day (with a cost of around $25,000 per year) whereas the most effective dose of VIR-576 was a daunting 5 grams/day. The researchers highlight these concerns in the discussion section of the paper and state: "to overcome these drawbacks in costs and administration, we are currently working on the development of small-molecule inhibitors with an analogous mode of action." In interviews, investigator Frank Kirchoff has estimated that it will likely be at least a year before any oral analogs of VIR-576 are ready for testing.

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TB vaccine including a latency-associated protein shows pre- and post-exposure efficacy in mouse model

Richard Jeffreys, TAG

In a new paper published yesterday by Nature Medicine [1], researchers from the Statens Serum Institut (SSI) in Denmark [2] describe encouraging results obtained with a new TB vaccine candidate. The design of the vaccine was informed by data showing that a particular TB protein, Rv2660c, remains strongly expressed during latent infection. This knowledge prompted the development of a "multistage" vaccine including Rv2660c along with two other TB antigens, Ag85B and ESAT-6. The resulting fusion protein vaccine is named H56. The goal is to create a vaccine capable of preventing active TB regardless of whether it is given before or after exposure.

In a mouse model of TB infection, the H56 vaccine was shown to be significantly superior in reducing bacterial load when compared to both the standard BCG vaccine and another candidate, H1, which contains only Ag85B and ESAT-6 antigens. The differences in efficacy took some time to become evident: 12 weeks after challenge in comparison to H1, and 24 weeks in comparison to BCG. Immune responses to the Rv2660c protein were weak early on but grew in magnitude over the period of follow up. In an experiment designed to evaluate the potential for post-exposure protection, H56 was found to provide a significant degree of protection against TB reactivation.

Based on these results, SSI is now initiating clinical development of H56. The current status of new TB vaccine candidates in clinical trials, including SSI's, is summarised in a recent report from the 2010 Global TB Vaccines Forum. [3]

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Berlin man remains free of detectable HIV 3.5 years after CCR5-negative stem cell transplant

Richard Jefferys, TAG

At the 2008 Conference on Retroviruses & Opportunistic Infections, a piece of paper pinned to a poster board conveyed some surprising information: an HIV-infected man who had received two stem cell transplants for acute myelogenous leukemia (and the dauntingly toxic ablation regimens that go with them) had remained off antiretroviral therapy for nearly ten months since, without any evidence of the virus coming back. [1]

The finding did not rest entirely on serendipity; his doctors had intelligently sought out a stem cell donor homozygous for the CCR5 delta 32 mutation, which prevents expression of the HIV co-receptor CCR5 on the surface of cells. Most people, including me, wandered past the poster oblivious to its potential import. But Marty Delaney, the much-missed leader of Project Inform who passed away in January 2009, was more alert. He wrote an article for the PI website describing the case, which was posted February 12, 2008. It concluded: *"This is another one of the kind of "one step at a time" approaches that we hope will one day lead to an outright cure of HIV infection, a state in which people who were once actively infected can remain "HIV undetectable" without any ongoing use of therapy. We urge other researchers to replicate or build upon this impressive case study, and we salute the patient and his doctors for taking this bold approach to treating HIV disease."* [2]

Many months later, in November 2008, the story finally broke in the mainstream media when Mark Schoofs authored an article for the Wall Street Journal entitled "A Doctor, a Mutation and a Potential Cure for AIDS;" many other outlets followed his lead. [3] The article was prompted by a September 2008 scientific workshop on the case, sponsored by amfAR, at which the man's doctor—a cheerful German hematologist named Gero Hütter— spoke. A detailed case report followed in the 12 February 2009 issue of the New England Journal of Medicine. [4]

This month, in the first edition section of the journal Blood, the latest update on the individual in question appeared. [5]

Follow-up is now out to 3.5 years and HIV remains undetectable in blood and every tissue studied, including gut and brain. CD4 T cell counts have climbed back into the normal range (the highest they have been since the original HIV diagnosis). There are some immunological deficits reported: the numbers of naïve T cells and newly-produced T cells known as recent thymic emigrants remain lower than those of healthy individuals, but are at similar levels to those seen in stem cell transplant recipients without HIV infection. Of concern to the researchers was the fact that, before his transplant procedures, the individual showed evidence of the presence of HIV capable of entering cells via the CXCR4 receptor (X4-tropic HIV).

It was initially assumed that this virus would re-emerge at some point, but that has not occurred despite the documented presence of activated, CXCR4-expressing CD4 T cells in the gut (which would be expected to be prime targets). The paper closes with this sober statement: "From these results, it is reasonable to conclude that cure of HIV infection has been achieved in this patient."

As Marty Delaney had advocated, an expanding number of projects are aiming to build on this result. The National Institutes

of Health will soon be funding a multi-researcher project named after him, the Martin Delaney Collaboratory: Towards an HIV-1 Cure. [6]

Several potentially far safer approaches to abrogating CCR5 expression via genetic modification are in—or will soon enter—human trials. In April of next year, the AIDS Policy Project, amfAR, Project Inform and TAG are sponsoring a workshop to specifically address issues related to advancing cure-related clinical research. What was once written small in a cavernous Boston conference hall now looms large, providing hope that a cure for HIV infection is possible.

The individual has now gone public in Stern magazine; his name is Timothy Ray Brown, a 44 year old US citizen. [7] A rough google translation of the article, which describes the series of difficult medical challenges he faced, including a bout of leukoencephalopathy that he is still recovering from. [8]

Given the media attention that is likely to follow, it's important to stress the not-so-good news: the extremely risky procedures that Timothy Ray Brown underwent to treat his cancer carry a very high risk of mortality, and they cannot be used to try and cure HIV in people without acute myelogenous leukemia (AML). Even for people with HIV who have AML and need a stem cell transplant, the likelihood of finding an appropriate (HLA-matched) donor with the CCR5 delta 32 mutation is extremely low due to its rarity.

COMMENT

We also reported this case from the CROI conference when it was first presented and this continued follow-up is impressive. Given how quickly HIV rebounds when treatment is discontinued, usually to detectable levels with a weeks and to pretreatment levels within a month or two, this person appears to be cured.

Source: Source: TAG basic science blog. (06 December 2010). http://www.treatmentactiongroup.org/basicsciblog.aspx

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FUTURE MEETINGS

2010–11 conference listing

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

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

9th European Workshop on Treatment Strategies & Antiviral Drug Resistance

23-25 March 2011, Paphos, Cyprus

http://www.virology-education.com

15th International Workshop on HIV Observational Databases

24–26 March 2011, Prague

http://www.hivcohorts.com

17th Annual BHIVA

6–8 April 2011, Bournemouth

http://www.bhiva.org

12th International Workshop on Clinical Pharmacology of HIV Therapy

13–15 April 2011, Miami, Florida

http://www.virology-education.com

6th International Workshop on HIV Transmission - Principles of Intervention

14–15 July, Rome, Italy

http://www.virology-education.com

13th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV

14–16 July 2011, Rome, Italy

http://www.intmedpress.com

3rd International Workshop on HIV Paediatrics

15–16 July, Rome, Italy

http://www.virology-education.com

6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011)

17–20 July 2011, Rome

http://www.ias2011.org/

2nd International Workshop on HIV & Ageing

October 2011, Baltimore, USA

http://www.virology-education.com

4th Annual BHIVA Conference for the Management of HIV / Hepatitis Co-infection

16 November 2011, London (venue tbc)

http://www.bhiva.org

HIV i-BASE

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

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

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

All i-Base publications are available online.

http://www.i-base.info

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

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

· Introduction to combination therapy

· A guide to changing treatment

· Avoiding & managing side effects

· HIV, pregnancy & women's health

· Hepatitis C for People living with HIV

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

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

Recent questions include:

· Doubts when I'm told that my life expectancy is good…

· What is the prognosis if diagnosed with these symptoms?

· What is the risk of infecting my girlfriend with HIV?

· News reports of research that 'could' be a cure

· Does treatment work if you start with a low CD4 count?

· Can hepatitis B rea\ctivate?

· Does yohimbe interact with HIV meds?

· Pregnancy without viral load results

· Should I start treatment at CD4 320?

· How do I time my meds when travelling?

· Is a viral load result of 50 really a blip?

· Does skipping a dose have an immediate effect?

· Does masturbation have any effect on HIV-positive people?

· Personal results from a recent diagnosis…

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

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

HIV i-Base

www.i-Base.info

Southern African HIV Clinician's Society

www.sahivsoc.org