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EDITORIAL

Welcome to the first issue of 2011, in which we lead with reports from the first (yes, 30 years into the epidemic), first workshop on HIV and women.

Conference reports also include exciting news on a new TB medication (from the 41st World Conference on Lung Health, and a couple of final reports from the Lipodystrophy Workshop held in London back in November.

This issue also has a brief summary on changes to the main US adult treatment guidelines (DHHS) which are important given that the UK guidelines (from BHIVA) were last updated in 2008 and are unlikely to be revised for at least another year.

Of note, BHIVA had just produced a CPD accredited (3 points) 40-minutes e-Learning module based on 18 questions on the UK guidelines (see BHIVA news for links).

Together with other treatment news we are saddened to report the now widely-publicised news of the murder of David Kato, and international human rights advocate in Uganga.

We join activists across the globe in sending our deepest sympathies to David's family and friends and honour his bravery in standing up against prejudice and ingnorance.

HTB survey

Included with this issue is a short survey:

http://www.surveymonkey.com/s/8QQLN6X

Your feedback is really important to us.

Please take a few minutes to help us understand how i-Base services (including HTB) is useful to you. Please suggest improvements.

We don't run these survey very often, so your time to help is especially appreciated.

Supplement: Guide to changing treatment

We are also including a copy of a new treatment guide as a supplement to this issue.

"Changing treatment and drug resistance" has been updated and expanded to cover all aspects of changing treatment folllowing virological failure.

As with other i-Base guides, these booklets are available free and in bulk for UK individuals, clinics and organisations. Please order online in the usual way.

http://i-base.info/order/

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.

C O M M E N T

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."

C O M M E N T

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.

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

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.

C O M M E N T

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.

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.

C O M M E N T

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.

C O M M E N T

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

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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

By 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.

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

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.

C O M M E N T

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.

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CONFERENCE REPORTS

12th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV

4–6 November 2010, London

http://www.intmedpress.com/lipodystrophy/

Introduction

This annual workshop continues to be an important forum for its focus on the potential mechanisms behind lipodystrophy and metabolic complications.

The meeting programme includes plenary lectures on HIV related comorbidities by international speakers from outside the HIV field.

Meeting abstracts, published as a supplement to Antiviral Therapy are available to download from a direct link on the conference website

http://www.intmedpress.com/lipodystrophy/default.cfm?itemtypeid=18&title=Programme

Webcasts are available at:

http://www.intmedpress.com

Intestinal microflora and low grade metabolic inflammation

Simon Collins, HIV i-Base

Remy Burcelin discussed metabolic outcomes as dependent not only on genetic and nutritional background but from the perspective of a more recent hypothesis based on the metagenome (of an individuals prokiaryotic microflora). [1]

With an estimated 10 x 10^{13} present in any individual, the balance in diversity between the major families (actinobacteria, proteobacteria, firmicutes and bacteroidetes) have been associated with metabolic disease. From a research perspective, these bacteria have broadly similar genomes across species (E-coli in humans is similar to in mice). Studies in ob/ob mice (genetically altered in their leptin receptor as a model for diabetes and other research because they become obese on a regular diet) showed that it is possible to identify the extent of obesity by the balance of gut microflora and these observations have been supported in human studies. [2, 3] Similarly, analysis of microflora clusters in humans show sufficiently distinct patterns to be able to diagnose broad insulin sensitivity.

Of note, some bacteria have a greater propensity to metabolise energy from food and bacterial diversity having the potential not only to reflect the metabolic phenotype but to play a causal role. Body weight increased significantly more in germ-free mice given obese rather than lean-associated gut flora.

Metabolic diseases, including diabetes, are associated with low grade (2-3 fold higher) inflammation which can be induced by a high fat diet, in adipose tissue (although this is a mild increase compared to the >50-fold increase induced by HIV) . Lipopolysacharides (LPS), are increased in HIV-positive people despite HAART and have been proposed as contributing to HIV-related increased

immune inflammation. They are potential molecules from microflora that both induce inflammation and cause metabolic complications, for example, by inducing cytiokine pathways responsible for insulin resistance. Human and animal studies have confirmed that dietary fat is associated with elevated LPS compared to low fat diets (whether protein or carbohydrate based) and mice that have been genetically altered to have LPS receptors are protected from fat gain when fed a high fat diet. These mice also retain insulin sensitivity, avoid glucose intolerance and maintain low triglycerides (ie they are protected against high fat diet induced diseases). [4] Similarly, normal mice, infused with LPS over one month were shown to develop a metabolic disease phenotype which can be at least partly revered if LPS is reduced by antibiotic treatment.

On a cellular level, LPS is sufficient to increase lipocyte differentiation in vitro and dietary modification results in bacteria levels significantly increasing in adipose tissue, but also reducing lipid accumulation in adipocytes.

This led the presenter to the question of the potential benefit from strategies to control bacterial translocation, for example using dietary probiotic yogurt. Patients and mice fed a high fat diet had reduced bacterial translocation following probiotic yoghurt. In mouse studies, this intriguingly also reduced fasting insulin, improved insulin sensitivity and improved glucose intolerance.

In conclusion, dietary fat was suggested as having a direct role in changing intestinal microflora levels and subsequent microbial translocation increases LPS levels in adipose tissue. In addition to directly impacting on adipogenesis, this can release cytokines that trigger insulin resistance and other metabolic diseases.

In a separate presentation, Blodget and colleagues presented analyses from two brachial arterial flow mediated studies that identified an association between higher LPS levels with endothelial dysfunction in one study but not another. [5]

Kenneth Feingold from San Francisco VA Medical Centre in another plenary lecture discussed the complicated association between LPS and dislipidaemia (in this talk focussing on increased triglycerides and decreased HDL) as factors linking inflammation to the risk of atherosclerosis, including the possibility that lipid changes may be playing a protective role. [6]

References

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Complex connections between bone and fat metabolism

Simon Collins, HIV i-Base

Several studies at the workshop suggested a greater complexity to the associations between bone and fat metabolism than are generally recognised.

In a plenary lecture Clifford Rosen from the Maine Medical Center Research Institute reviewed the pathophysiology of bone metabolism from the perspective of fat metabolism and potential mechanisms that might connect them. Bone health is receiving increased attention as a management issue, especially as antiretrovirals (irrespective of regimen) are associated with both reduced bone density and increased fracture rates. This talk suggested that bone and fat changes are related.

This lecture focussed on the common ancestry of bone and fat cells—both deriving from the same mesenchymal stem cell lineage.

Visceral fat can produce endocrine factors that contribute to reduced bone density an fat redistribution is closely connected to glucose intolerance and abnormal skeletal remodeliing.

Fat distribution is also not just associated with increases in visceral adipose tissue but also marrow adiposity, which may therefore be the major pathogenic feature of HIV-related bone loss. Marrow fat, thought to be brown fat, may be also be acting as a compensatory support mechanism to support skeletal strength in the context of reduce bone density.

Reference

Rosen C. Body composition, fat and bone: what's the connection to drugs and HIV? Session IV plenary, 12th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV Infection, 3—6 November 2011, London. Webcast online.

TREATMENT ACCESS

FDA approval of generic ARVs

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

Drug and formulation	Manufacturer, Country	Approval date
3TC/AZT 30 mg/60 mg dispersible FDC tablets (paediatric)	Matrix, India	5 January 2011
3TC/tenofovir 300 mg/300 mg FDC tablets (adults and children >12 years)	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.

C O M M E N T

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

Decroo T et al. Distribution of antiretroviral treatment through self forming groups of patients in Tete Province, Mozambique. J Acquir Immune Defic Syndr. Vol 56. Number 2. February 1, 2011.

Commentary: corruption by Global Fund grant implementers

Bernard Rivers, Global Fund Observer (GPO)

On January 23, the Associated Press (AP) ran a long story about the Global Fund entitled "Fraud Plagues Global Health Fund." The story was picked up by nearly 200 media outlets in the U.S. and 50 in other parts of the world. This led to Germany putting on hold its 2011 contribution to the Fund pending a full investigation.

The story stated that in Mali, the Fund's Office of the Inspector General (OIG) found that $4 million in funding was misappropriated. Half of Mali's TB and malaria grant money went to supposed "training events," for which signatures were forged on receipts for per diem payments and travel expense claims. Mali has arrested 15 people suspected of committing fraud, and its health minister resigned without explanation two days before the audit was made public. (Note: GFO, in one of its 30 articles on the OIG over the past year, reported on the Mali developments in December.)

The AP story added that in Mauritania, the OIG found "pervasive fraud," with $4.1 million - 67 percent of an HIV grant - lost to faked documents and other fraud. And in Djibouti, the OIG found that about 30 percent of grant funding they examined was lost, unaccounted for or misused. Much of this money went to buy motor vehicles. Almost $750,000 was transferred out of one account with no explanation.

The AP story was quickly seized upon by the Fund's critics in some donor countries. For instance, Fox News ran an interview with Nile Gardiner, director of The Heritage Foundation's Margaret Thatcher Center for Freedom, in which he said, "Potentially, we could be looking at billions of dollars here in terms of missing funds. If that is the case, we are looking at the biggest financial scandal of the 21st Century."

Hmm. Let's take a deep breath. First, the corruption is nothing like as extensive as a fast reader of the AP story would conclude. Second, the story shows that the Global Fund takes corruption seriously and tackles it forcefully - which suggests that the Fund deserves greater, not lesser, donor support. Third, the funding from the Global Fund saves 4,400 lives a day, and the Fund's expenditure on this still represents remarkable value. But fourth, there are some things that the Fund should have done long ago to better tackle corruption. Let's review these points in more detail.

When any entity gives multi-million dollar grants, there will always be corruption. The key issue is what is being done to unearth the corruption and minimise losses. The Global Fund is far better at investigating allegations of corruption and at recovering stolen monies than most or all other major aid donors. Roger Bate of the American Enterprise Institute, a conservative think tank, who has criticised the Fund on some matters, says, "All the focus on the Global Fund is a shame - [the Fund] has done far more than any other multilateral agency to be transparent and expose corruption." Bobby Shriver, founder of (Product) RED, adds, "The Fund was set up to find the bad guys early. Many other international organisations do not have the aggressive tools used by the Fund. Others find bad guys late in the game."

Another thing that distinguishes the Global Fund from other donors is its willingness to publish the details of the corruption that it has unearthed. How many donors such as Pepfar, DFID, USAID, UNDP, Gates Foundation, Norad, SIDA and the World Bank have committed to publish at their website, unedited, the findings of their Inspector General (assuming they even have one)? I'll ask them, and I'll let you know what I learn. Right now, the Fund is paying a price for its toughness and transparency.

Corruption is not unique to developing countries. Defence contractors in the U.S. are notorious for fraud that runs in the billions. Government bureaucracies in all parts of the world exhibit inefficiency, patronage, and occasional graft and corruption. Bobby Shriver asks, "Does anyone think banks [in the US and Europe] have less corruption than the Fund? Not a chance."

The information on corruption in the AP story was not new; it was obtained from OIG reports that were posted at the Global Fund website in December and earlier, and from press releases issued by the Fund.

Well before the AP story was published, the Global Fund had taken steps to recover the misused funds that were the subject of the AP story. In addition, the Global Fund was working with the relevant authorities to ensure that those committing fraud are brought to justice; criminal proceedings were launched in Mali, Mauritania and Zambia; the Fund terminated one grant to Mali and suspended others; and the Fund imposed "special safeguards" on other grants in Djibouti, Mauritania and Mali. Furthermore, the Global Fund Secretariat is devoting additional specialist staff to monitor higher risk countries and to improve the capacity of local fund agents to detect potential fraud.

Reacting to the AP story, one headline writer said that the Global Fund was "rife with fraud." This emotive headline appeared in several blogs and online newsletters. In fact, the total amount of funding that the Global Fund has asked grant recipients to refund because of misuse is $39 million, of which $5 m. has been received thus far. That $39 m. is 0.3% of the $13 billion that the Fund has disbursed in all of its grants worldwide.

But of course, the real percentage must be worse than 0.3%, because the OIG has thus far only audited 25 of the 145 countries to which the Fund gives grants, and in some of those countries it has not audited all grants. (Preliminary work has also been conducted in a further eight countries.) The 25 audited countries have received grant disbursements of $4.8 billion. The $39 million that the fund says has been misused in these countries represents 0.8% of the funding they have received. In reviewing that figure, we have to bear in mind that not all the OIG's audits have been completed; that the OIG may have missed some things; and that the OIG has focussed primarily on countries that are "high risk" or regarding which it has received input from whistle-blowers.

Based on all this, my guess is that the total percentage of money that has been misused across the entire Global Fund portfolio, including what the OIG has missed, is something approaching 1%. If I'm correct, that's still a worrying figure. But it also means that the great majority of grants don't involve corruption and are funding programmes that save huge numbers of lives.

Another factor to bear in mind is that only part of the $39 million claimed by the Fund was used fraudulently. Another part relates to legitimate expenditure for which the principal recipients (PRs) have been unable to provide receipts. And a final part relates to documented expenditure on programme activities that were not in the approved budget. These latter two errors by the PRs or their sub-recipients caused the PRs to be in breach of contract, so the Fund is perfectly entitled to ask for the money back.

Still, while there are reasons to think the problems at the Fund are not nearly as serious as painted, there is ample room for improvement.

For instance, although I fully support a tough OIG, there is a major imbalance of power between the OIG and the PRs it investigates. For some of the smaller PRs, the OIG's published findings could ruin the PR's reputation, and the Fund's consequent demands for restitution from the PR could render the PR insolvent. What if, hypothetically speaking, the OIG's conclusions regarding a particular PR were in error? Because of the Fund's "privileges and immunities" in Switzerland and its lack of legal presence elsewhere, such a development could make it impossible for an unfairly harmed PR to obtain adequate damages through a lawsuit.

Moreover, corruption is not the only factor that can reduce the Fund's impact. Sometimes, incompetence or laziness come into play. In what to me is a shocking instance of this, there was so little activity by grant implementers in one particular country that two grants to that country went through the entire three-year Phase 2 without the Fund being prepared to send a single disbursement. How many lives were saved during that period? None. And what did the Fund do to highlight this problem on the website pages for the relevant country? Nothing. And for that matter, what has the Fund done to highlight, on the web pages for Mauritania, Mali and Djibouti, the OIG's findings regarding corruption? Again, nothing.

And what about the Local Fund Agents (LFAs), those in-country employees of companies like KPMG and PWC who are supposed to be the "eyes and ears" of the Global Fund? Many of the cases investigated by the OIG had been missed by the LFAs, or were found really late. The Fund recently started training LFAs to look for corruption. It should have been doing so since Day 1.

What else could the Global Fund do? First, the Secretariat could thoroughly analyse what happened in the countries where corruption has been detected; it could work out how these problems could have been detected earlier, and how they could have been prevented in the first place; and it could apply, across its entire grant portfolio, the lessons learned.

Second, the Fund's Executive Director could send an email to every Country Coordinating Mechanism (CCM) member, every PR and every sub-recipient, explaining clearly the actions that the Fund will take if corruption or inadequate documentation is identified. And the Fund could create a DVD of the ED making the same statement in English, French and Russian (he is fluent in all three), and send it to each CCM with a request that it be played at the next CCM meeting.

Third, the Fund could develop a way that PRs can "self-report" past violations of Global Fund contractual requirements (such as the requirement that all expenditures are fully documented), and it could permit these PRs to request reduced penalties if they

report these cases of being "fools but not thieves" prior to the OIG discovering them.

Finally, the Fund's board could confront head-on, and resolve, the following problems:

- Most CCMs, which are supposed to exercise grant oversight, have multiple members who have conflicts of interest, because they are, or want to become, grant implementers.
- Tightening grant oversight using external parties will conflict with the Fund's desire to maximise "country ownership."
- If the Fund avoids all risk, it can't get its job done.

The Global Fund says that it has a "zero tolerance" policy with respect to corruption. That's the right approach to take. Every stolen Global Fund dollar is a dollar that can't be spent on saving lives.

Bernard Rivers is Executive Director of Aidspan and Editor of GFO.
http://www.aidspan.org

ANTIRETROVIRALS

US adult treatment guidelines updated – January 2011

The Department of Health and Human Services (DHHS) HIV guidelines are recognised as the most important guidelines produced in the US. As with all updates, changes in this edition are highlighted in yellow throughout the PDF file.

A selected summary of the changes include:

- **Importance of research**

An emphasis on "the importance of clinical research in generating evidence to address unanswered questions related to the optimal safety and efficacy of antiretroviral therapy (ART)". This may be an acknowledgement of some of the community-based concerns to the 2010 guidelines, particularly in reference to the international START study.

- **Routine monitoring**

For clinically stable patients with CD4 counts above the level of risk for opportunistic infections (figure not specified) the guidelines recommend less frequent CD4 count monitoring–every 6–12 months instead of every 3–6 months–unless there are changes in the patient's clinical status or initiation of treatment with interferon, corticosteroids, or anti-neoplastic agents.

Virological failure is defined as confirmed viral load >200 copies/mL defining blips (in most cases) as <200 copies/mL.

Additional resistance testing is suggested for detection of integrase-related resistance in people failing on an integrase-based combination. While currently unlikely to be a significant issue, the guidelines recognise that it may become increasingly important to include testing for integrase mutations in naïve and newly diagnosed individuals.

Phenotype tests are only recommended for co-receptor tropism (unlike European guidelines that now recommend genotype testing). This largely reflects different geographical access to testing technologies.

- **Treatment choices**

Maraviroc is included as an "acceptable regimen" for initial therapy when used with AZT/3TC but only as "may be acceptable but more definitive data are needed" when used with tenofovir/FTC or abacavir/3TC.

Use of ritonavir-boosted saquinavir has been downgraded to a "regimens that is acceptable but should be used with caution."

- **Combination therapy for all women in pregnancy**

More significantly, combination therapy (rather than AZT monotherapy) is now recommended as standard of care for all HIV-positive women to prevent mother-to-child transmission, even when they do not meet CD4 criteria for starting treatment.

Additional testing (viral load, p24) for women who are HIV antibody negative when first accessing antenatal care is recognised as being practiced in some centres.

- **Therapeutic drug monitoring**

The following median (range) trough concentrations from clinical trial data are now included for newer drugs, even though the clinical significance of these levels has not bee demonstrated.

ARV	Median trough (range)
Darunavir (DRV) (600 mg twice daily)	3,300 (1,255–7,368)
Etravirine (ETR)	275 (81–2,980)
Raltegravir (RAL)	72 (29–118)

- **Hepatitis B (HBV)/HIV coinfection**

This section has been revised to provide more specific recommendations for management of HIV patients coinfected with HBV, including recommendations for patients with 3TC/FTC-resistant HBV infection and for patients who cannot tolerate TDF-based regimens.

- **TB/ HIV coinfection**

The guidelines recommend ARV treatment for all HIV-positive patients with diagnosed active TB.

The time for starting ARVs following starting TB treatment is within 2–4 weeks for patients with CD4 count <200 cells/mm3, and within 2–4 weeks for patients with CD4 count 200–500 cells/mm3 (definitely by 8 weeks). For patients with CD4 count >500 cells/mm3, most panel members also recommend starting ART within 8 weeks of TB therapy.

The guidelines also state that both TB and HIV medications should be continued in the context of Immune Reconstitution Syndrome (IRIS).

- **Side effects**

A new simplified table is included for main side effects and associated drug/class (Table 13).

- **Injecting drug users**

The section on injecting drugs users has expanded information on opiate substitution therapy is included below. We also include the useful table on interactions with antiretrovirals (Table 11).

Methadone and ART

Methadone, an orally administered, long-acting opioid agonist, is the most common pharmacologic treatment for opioid addiction. Its use is associated with decreased heroin use, decreased needle sharing, and improved quality of life. Because of its opioid-induced effects on gastric emptying and the metabolism of cytochrome P (CYP) 450 isoenzymes 2B6, 3A4, and 2D6, pharmacologic effects and interactions with ARV agents may commonly occur *[13]*. These may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity, and/or decreased ARV efficacy. Efavirenz (EFV), nevirapine (NVP), and lopinavir/ritonavir (LPV/r) have been associated with significant decreases in methadone levels. It is necessary to inform patients and substance abuse treatment facilities of the likelihood of this interaction. The clinical effect is usually seen after 7 days of coadministration and may be managed by increasing the methadone dosage, usually in 5-mg to10-mg increments daily until the desired effect is achieved.

Buprenorphine and ART

Buprenorphine, a patial u-opioid agonist, is administrated sublingually and is often coformulated with naloxone. It is being increasingly used for opioid dependence treatment. The lower risk of respiratory depression and overdose compared with methadone allows it to be prescribed by physicians in primary care for the treatment of opioid dependency. This flexible treatment setting could be of significant value to opioid-addicted HIV-infected patients who require ART because it enables one physician or programme to provide both medical and substance abuse services. Limited information is currently available about interactions between buprenorphine and antiretroviral agents. Findings from available studies show a more favorable drug interaction profile than that of methadone.

Naltrexone and ART

A once monthly extended-release intramuscular formulation of naltrexone was recently approved for prevention of relapse in patients who have undergone an opioid detoxification program. Naltrexone is also indicated for treatment of alcohol dependency. Naltrexone is not metabolised via the CYP 450 enzyme system and is not expected to interact with protease inhibitors (PIs) or non nucleoside reverse transcriptase inhibitors (NNRTIs).

Table 11 provides the currently available pharmacokinetic interaction data that clinicians can use as a guide for managing patients receiving ART and methadone or buprenorphine. Particular attention is needed concerning communication between HIV care providers and drug treatment programmes regarding additive drug toxicities and drug interactions resulting in opiate withdrawal or excess.

Methylenedioxymethamphetamine (MDMA), GHB, ketamine, and methamphetamine all have the potential to interact with ARV agents because all are metabolised, at least in part, by the CYP 450 system. Overdoses secondary to interactions between the party drugs (i.e., MDMA or GHB) and PI-based ART have been reported.

Table 11 (from DHHS guidelines) Drug interactions between antiretroviral agents and drugs used to treat opioid addiction

Concomitant drug	**Antiretroviral class/drug**	**Pharmacokinetic interactions** **Recommendations/clinical comments**
Buprenorphine	EFV	buprenorphine AUC ↓ 50%; norbuprenorphine* AUC ↓ 71% No withdrawal symptoms reported. No dosage adjustment recommended; however, monitor for withdrawal symptoms.
	ATV	buprenorphine AUC ↓ 93%; norbuprenorphine AUC ↓ 76%; ↑ ATV levels possible. Do not coadminister buprenorphine with unboosted ATV.
	ATV/r	buprenorphine AUC ↓ 66%; norbuprenorphine AUC ↓ 105% Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect, norbuprenorphine AUC ↓ 46% and Cmin ↓ 71% No dose adjustment necessary.
	TPV/r	buprenorphine: no significant effect; norbuprenorphine AUC, Cmax, and Cmin ↓ 80% TPV Cmin ↓ 19%–40% Consider monitoring TPV level.
	3TC, ddI, TDF, ZDV, NVP, LPV/r, NFV	No significant effect No dosage adjustment necessary.
	ABC, d4T, FTC, ETR, FPV +/- RTV, IDV +/- RTV, SQV/r, RAL, MVC, T20	No data
Methadone	ABC	methadone clearance ↓ 22% No dosage adjustment necessary.
	d4T	d4T AUC ↓ 23% and Cmax ↓ 44% No dosage adjustment necessary.
	ZDV	ZDV AUC ↓ 29%–43% Monitor for ZDV-related adverse effects.
	EFV	methadone AUC ↓ 52% Opioid withdrawal common; increased methadone dose often necessary.
	NVP	methadone AUC ↓ 41% NVP: no significant effect Opioid withdrawal common; increased methadone dose often necessary.
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	With ATV/r, DRV/r, FPV/r: R-methadone† AUC ↓ 16%-18%; With LPV/r: methadone AUC ↓ 26%–53%; With SQV/r 1,000/100mg BID: R-methadone AUC ↓ 19%; With TPV/r: R-methadone AUC ↓ 48% Opioid withdrawal unlikely but may occur. No adjustment in methadone usually required; however, monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	FPV	No data with FPV (unboosted) With APV: R-methadone Cmin ↓ 21%, AUC no significant change Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
	NFV	methadone AUC ↓ 40% Opioid withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require increased methadone dose.
	ddI (EC capsule), 3TC, TDF, ETR, RTV, ATV, IDV, RAL	No significant effect No dosage adjustment necessary.
	FTC, MVC, T20	No data

*Norbuprenorphine is an active metabolite of buprenorphine. † R-methadone is the active form of methadone.

Acronyms: 3TC = lamivudine, d4T = stavudine, T20 = enfuvirtide, ABC = abacavir, APV = amprenavir,

ATV = atazanavir, ATV/r = atazanavir/ritonavair, ddI = didanosine, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, IDV = indinavir, IDV/r = indinavir/ritonavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NVP = nevirapine, RAL = raltegravir, RTV = ritonavir, SQV/r = sacquinavir/ritonavir, TDF = tenofovir, TPV = tipranavir, TPV/r = tipranavir/ritonavir, AZT = zidovudine

Reference: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011.

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

FDA safety updates to antiretroviral labels

The following summaries cover revisions to the US drug labels that were recently approved by the US Food and Drug Administration (FDA). Please check the full update for details.

Revised labels are posted to the FDA website:

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory

Darunavir once-daily indication in treatment experienced adults

On 13 December 2010, FDA approved new labeling for darunavir (Prezista) to include a once-daily dosing for treatment-experienced adult patients who have no darunavir-associated resistance mutations.

Darunavir-associated mutations are V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V.

For patients without darunavir-associated mutations the dose is 800 mg darunavir once daily with ritonavir 100 mg once daily and with food.

For patients with one or more darunavir-associated mutations* the indication remains 600 mg darunavir twice-daily taken with ritonavir 100 mg twice-daily and with food.

Adverse reactions (Section 6.3) was modified to include neutropenia, lipoatrophy, and lipodystrophy under *Postmarketing Events* in the package inserts.

For details of other changes, please refer to the full prescribing labeling:

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

PREVENTION

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 hepatitis B.

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

Reference

1. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men. Morbidity and Mortality Weekly Report (MMWR) January 28, 2011 / 60(03);65-68.
   http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a1.htm
2. The iPrEX study was reported in HTB November/December 2010
   http://i-base.info/htb/14191

SIDE EFFECTS

Meta-analysis of RCTs support use of smoked cannabis to treat HIV-related peripheral neuropathy

Simon Collins, HIV i-Base

A review of evidence from randomised clinical trials for pharmacological interventions to manage HIV-related painful sensory neuropathy was published in December 2010 in PLoS One (free online access).

This meta-analysis primarily highlighted the limited research on treatments for HIV-related sensory neuropathy (SN). Studies for some potentially active compounds involve small patient numbers and non-standardised methodology. This remains a major area of neglect given that this paper references evidence for rates of neuropathy of around 40% (in patients not exposed to d-drugs) and up to 60% in resource-limited settings where use of d4T is still standard of care.

Of note, pharmacological interventions that showed benefits in pain relief compared to placebo in randomised clinical trials were only found for smoked cannabis, recombinant human Nerve Growth Factor (rhNGF) and high dose (8%) topical capsaicin.

In the context of HIV-related neuropathy, this analysis failed to find evidence for use of amitriptyline, pregabalin, and gabapentin that are currently recommended in NICE guidelines for treating neuropathy pain management in the non-specific setting.

There has always been a demand for the decision to discontinue research into rhNGF by Genentech, now a subsidiary of Hoffman-La Roche, to be reexamined and the review concludes “Gene microarrays have been used to identify novel drug targets. Ongoing

evaluation of both novel analgesics and existing untested strategies for HIV-SN is a clear research priority".

Reference: Phillips TJC et al. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS ONE 5(12): e14433. doi:10.1371/journal.pone.0014433.

http://clinicaltrials.ploshubs.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0014433#pone-0014433-t002

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 1st February issues 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.

C O M M E N T

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.

Reference

1. Ekouevi D et al. Pregnancy outcomes in women exposed to efavirenz and nevirapine: an appraisal of the IeDEA West Africa and ANRS databases, Abidjin, Cote d'Ivoire. J Acquir Immune Defic Syndr. Volume 56, Number 2. February 1, 2011. http://journals.lww.com/jaids/Abstract/publishahead/Pregnancy_outcomes_in_women_exposed_to_efavirenz.98878.aspx
2. Ford N et al. Safety of efavirenz in first trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. AIDS 2010. Published ahead of print May 24, 2010. http://journals.lww.com/aidsonline/Abstract/2010/06190/Safety_of_efavirenz_in_first_trimester_of.8.aspx

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.

Reference

Kepito-Tembo et al. Marked reduction in prevalence of malaria parasitemia and anaemia in HIV-infected women taking cotrimoxazole with or without sulfadoxine-pyrimethamine intermittent preventative therapy during pregnancy in Malawi. J Infect Dis. Volume 203 Issue 4 February 15, 2011. http://jid.oxfordjournals.org/content/203/4/464.abstract

DRUG INTERACTIONS

Recent updates to the Liverpool University drug interaction website.

Raltegravir and unboosted atazanavir

HIV-druginteractions.org

With the interest in NRTI-sparing regimens containing two drugs it is important that we understand the optimal dosing strategies. One aspect of this is the potential interaction between the components of the regimen. Two studies have been published recently on the interaction between atazanavir and raltegravir, one a cross-over study in healthy subjects and the other a parallel study in HIV+ subjects.

Zhu and colleagues performed a cross-over study which assessed the two-way pharmacokinetic interaction of atazanavir (300 mg twice daily) with raltegravir (400 mg twice daily) in 19 HIV-negative volunteers. [1]

Coadministration of atazanavir and raltegravir (300/400 mg twice daily) decreased atazanavir AUC0-12 by 17% and Cmin by 29%, relative to atazanavir alone. Raltegravir AUC0-12 increased by 54% and Cmin increased by 48%, relative to raltegravir alone. Of interest, the incidence of hyperbilirubinaemia was similar after atazanavir (300 mg twice daily) alone or in the presence of raltegravir.

Cattaneo et al determined the pharmacokinetics of atazanavir (300 mg twice daily) and raltegravir (400 mg twice daily) in 22 HIV-positive people and compared them to values obtained from 24 HIV-positive people receiving raltegravir (400 mg twice daily) plus NRTIs. [2]

Raltegravir trough concentrations were found to be significantly higher in the presence of atazanavir (506 ± 411 vs 177 ± 262 ng/ml). Of interest, patients with atazanavir AUC0-12 above the mean or with atazanavir concentrations exceeding the half maximal inhibitory concentration for UGT1A1 had higher raltegravir AUCs compared to patients with lower atazanavir exposure.

References

1. Zhu L et al. Pharmacokinetics and safety of twice-daily atazanavir 300 mg and raltegravir 400 mg in healthy individuals. Antivir Ther, 2010, 15(8): 1107-14.
   http://www.ncbi.nlm.nih.gov/pubmed/21149917
2. Cattaneo D et al. Exposure-related effects of atazanavir on the pharmacokinetics of raltegravir in HIV-1-infected patients. Ther Drug Monit, 2010, 32(6): 782-786.
   http://www.ncbi.nlm.nih.gov/pubmed/20926993

Etravirine interactions

HIV-druginteractions.org

A comprehensive review by Tibotec colleagues of the pharmacokinetic interaction studies between the NNRTI etravirine and non-antiretroviral drugs.

The data are summarised in tables (least square means ratio of AUC, Cmax and Cmin of either etravirine or coadministered drug) with references. In addition, recommendations are given in relation to dose adjustments. The potential for interaction with some key drugs (eg ribavirin, opioid analgesics, dexamethasone, calcineurin inhibitors, antiepileptics) not yet formally studied is presented based on metabolic profiles.

Although the authors conclude that the potential for interactions between etravirine and non-antiretroviral agents is limited there are some clinically relevant interactions to note:

Not recommended: Antiepileptics (carbamazepine, oxcarbazepine, phenobarbitone, phenytoin), rifampicin, rifapentine, St John's wort.

Consider alternatives: Alternatives to clopidogrel or diazepam should be considered.

Reference

Kakuda T et al. Pharmacokinetic interactions between etravirine and non-antiretroviral drugs. *Clin Pharmacokinet*, 2011. 50(1): 25-39.

http://adisonline.com/pharmacokinetics/Abstract/2011/50010/Pharmacokinetic_Interactions_between_Etravirine.2.aspx

ARVs and targeted cancer therapies

HIV-druginteractions.org

This news item highlights the challenge of administering both the new cancer therapies and antiretroviral drugs. [1]

In 2009 John Deeken and colleagues presented an overview of the disposition of the targeted anticancer drugs imatinib, dasatinib, nilotinib, erlotinib, bortezomib, sorafenib, temsirolimus, sunitanib and lapatinib and suggested the potential for marked drug-drug interactions with some antiretrovirals. [2]

In the present news item, there is mention of an on ongoing trial between sunitinib and *a)* a boosted PI and *b)* efavirenz. The AIDS Malignancy Consortium at the NCI is now planning investigation of interactions with at least three other cancer drugs – vorinostat, sorasenib and dasatinib. The bottom line is that there is an urgent need to define drug-drug interactions for HIV and cancer.

References

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http://www.ncbi.nlm.nih.gov/pubmed/19606034

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.

Source: Source: TAG basic science blog. (04 January 2011).
http://www.treatmentactiongroup.org/basicsciblog.aspx

References
1. Forssmann W-G et al. Short-Term Monotherapy in HIV-Infected Patients with a Virus Entry Inhibitor Against the gp41 Fusion Peptide. Sci Transl Med 22 December 2010: Vol. 2, Issue 63, p. 63re3. DOI: 10.1126/scitranslmed.3001697.
http://stm.sciencemag.org/content/2/63/63re3.abstract

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]

Source: Source: TAG basic science blog. (24 January 2011).
http://www.treatmentactiongroup.org/basicsciblog.aspx

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2. Statens Serum Institut (SSI)
http://www.ssi.dk/sitecore/content/home/english.aspx
3. Jeffreys R et al. Tallying the TB vaccines in clinical trials.
http://69.7.74.112/base.aspx?id=4328

T-cell activation and senescence associate with carotid artery disease in HIV-positive women

Richard Jeffreys, TAG

In the early 1990s, UCLA researcher Janis Giorgi [1] published evidence that the activation of the immune system by HIV (as measured by expression of a marker called CD38 on CD8 T-cells) was a strong predictor of the pace of progression to AIDS. At the time the idea was controversial, but a voluminous amount of evidence has since accumulated confirming Giorgi's finding and demonstrating that immune activation is central to the pathogenesis of HIV infection. Furthermore, it is now clear that while antiretroviral therapy (ART) greatly reduces immune activation, it can often persist at levels significantly higher than those seen in comparable HIV-negative individuals. The magnitude of this residual immune activation is linked to the CD4 count at the time of ART initiation: the lower the CD4 count, the higher the degree of residual activation.

Because the nadir (lowest ever) CD4 count is also the strongest predictor of the risk of illness in people on ART, there has been reason to suspect that residual immune activation contributes to ill health. Studies documenting associations between elevated levels of inflammatory biomarkers and mortality have bolstered this suspicion. However, data linking immune activation to specific clinical conditions is sparse. Similarly, one of the consequences of persistent immune activation is a type of T-cell dysfunction called senescence. Senescent T-cells are essentially old and worn out, and they have a bad habit of producing large amounts of inflammatory cytokines and appear to get in the way of T-cells that do work properly. While the proportion of senescent T-cells has been associated with the pace of disease progression in HIV, their role in specific diseases is unclear.

A new open access paper in the Journal of Infectious Diseases goes some way to addressing these information gaps. [3] Led by Robert Kaplan of the Women's Interagency HIV Study (WIHS), the research reveals that both CD8 T cell activation and CD8 T cell senescence predict carotid artery disease in HIV-positive women. Disease was assessed based on the extent of carotid lesions, which were defined as focal thickening (>1.5 mm) of the intima-media layer. The authors note that while these measures of subclinical vascular disease predict incident cardiovascular disease events in the general population, this has yet to be formally

confirmed in the HIV-positive population. They conclude by stating: “our data provide further evidence that persistent activation of the immune system is associated with vascular abnormalities among HIV-infected individuals. This relationship was suggested by a small prior study [4] that, unlike the present investigation, did not feature multivariate analyses, did not control for potential confounding effects of HIV-related and CVD-related variables, and lacked an HIV-uninfected control group. These results have important implications for assessment of vascular risk among adults with HIV infection.”

An accompanying commentary by Virginia Triant and Steven Grinspoon further discusses the implications of the findings, and posits that “studies investigating the mechanisms of these immunologic alterations in relation to cardiovascular events and exploring therapies to modify T-cell activation and senescence will advance our understanding of this complex field and help to optimise the long-term care of HIV-infected individuals.” [5]

Source: Source: TAG basic science blog. (14 January 2011).
http://www.treatmentactiongroup.org/basicsciblog.aspx

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1. Janis Giorgi, In Memorium.
   http://www.universityofcalifornia.edu/senate/inmemoriam/JanisGiorgi.htm
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   http://www.ssi.dk/sitecore/content/home/english.aspx
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   http://jid.oxfordjournals.org/content/early/2011/01/10/infdis.jiq084.full

BHIVA NEWS

BHIVA responses to DoH consultations

The British HIV Association will be preparing responses to the Department of Health consultations as detailed below and welcome comments from BHIVA members on the following two consultation drafts.

Healthy lives, healthy people: consultation on the funding and commissioning routes for public health

http://www.dh.gov.uk/en/Consultations/Liveconsultations/DH_122916

Please comment on sections: 3.12 and 3.16 in the above linked documents.

Healthy lives, healthy people: transparency in outcomes, proposals for a public health outcomes framework

http://www.dh.gov.uk/en/Consultations/Liveconsultations/DH_122962

Please comment on Domain 4: outcome 9 page 57.

Please send comments by Friday 18 March 2011 to Jacqueline English at BHIVA:

jacqueline@mediscript.ltd.uk

BHIVA e-Learning module online

BHIVA have produced an e-Learning module that includes 3 point CDP accrediation.

The module includes 18 questions based on the current adult treatment guidelines and takes 40 minutes to complete.

http://www.bhiva.org/E-LearningModule1.aspx

CROI feedback meetings

BHIVA are holding five feedback meetings after the next Conference on Retroviruses and Opportunistic Infections being held in Boston this year at the end of February.

Meetings are free to attend but registration is required. Please see the BHIVA website for details:

http://www.bhiva.org

2011 meetings

Monday 14 March 2011, Royal College of Physicians, London

Tuesday 15 March 2011, Birmingham

Wednesday 16 March 2011, Haydock, North West England

Thursday 17 March 2011, Edinburgh

Monday 21 March 2011, Gateshead

OTHER NEWS

David Kato, prominent gay and human rights activist murdered in Uganda

On 26 January, the prominent human rights activist David Kato was murdered in his home in Kampala, Uganda. David was known both internationally and in Uganda for campaigning against the draconian Anti-Homosexuality Bill that has been before the Ugandan parliament since October 2009.

While homosexuality is already illegal in Uganda, this new law proposes to criminalise all homosexuality, making it punishable by a fine and life imprisonment. HIV-positive people, and people convicted a second time would be subject to the death penalty. The proposed bill also states that anyone knowing someone who is a gay man or lesbian would be mandated to report them to the police within 24 hours, or face imprisonment themselves.

David was one of three activists who sued the Ugandan newspaper *Rolling Stone,* not connected to the US magazine, after it published pictures and contact details of 100 gay men and women including David under the headline “Hang Them.”

David was a speaker at the International AIDS Conference held in Vienna last year. His courage at confronting bigotry and homophobia was immense.

A vigil was held at the Ugandan Consulate in Trafalgar Square, London at 11 am on Friday 28th January.

We send our deepest sympathy and condolences to Davids family and friends.

Sources and links

Human Rights Watch:

http://www.hrw.org/en/news/2011/01/27/uganda-promptly-investigate-killing-prominent-lgbt-activist

Justice for Gay Africans Society:

http://jfga.org.uk/2011/01/26/david-kato-assassinated-would-the-lives-of-gay-african-people-ever-be-safer/

AIDS 2010 Vienna programme:

http://pag.aids2010.org/session.aspx?s=97

Uganda law proposes death penalty for homosexuality: can international reaction and vulnerability of treatment access programmes help? HIV Treatment Bulletin, June 2010.

http://i-base.info/htb/10436

BOOK REVIEW

Nutrition and HIV

Nutrition and HIV – Edited by Vivian Pribram

This comprehensive publication, edited by Vivian Pribram, Senior HIV Specialist Dietician at Kings College NHS Trust, London, includes contributions from over 40 specialists based in the UK from a broad spectrum of fields. It looks at the research supporting the role of nutrition primarily in the context of patients in Western countries in the post-HAART era.

The importance of nutritional assessment is emphasised at key stages of the care pathway, from diagnosis through chronic infection and palliative care.

Importantly it looks at complications of HAART including lipoatrophy and lipohypertrophy including the perspective of monitoring, exercise and diet. Common co-morbitities and age-associated health concerns covered in detail include cardiovascular health, bone health, mental health, viral hepatitis, tuberculosis, renal and hepatic disease and cancer.

Although the geographical focus is on the UK, information of international relevance is included.

The book is divided into six main sections:

- Introduction on nutritional care in HIV
- Paediatric nutrition, maternal and child health
- Nutritional management of HIV disease
- Healthy eating and the promotion of well-being and a long life
- The nutritional management of HIV and related co-morbidities
- Nutritional needs at end of life and during palliative care

While nutritional status is often overlooked in routine management, this book will help healthcare workers focus on the importance of this aspect of care, and encourage referrals to appropriate specialists who can help HIV-positive people plan for a healthy life, whether they are currently healthy or dealing with more complicated health issues.

Nutrition and HIV – Edited by Vivian Pribram, 528 pages, Wiley-Blackwell, October 2010; ISBN: 1405182709; price £39.99.

ON THE WEB

Community resources and publications:

FDA guidance on development trials for multidrug resistant HIV

On 16 December 2010 the FDA published new draft guidance for industry entitled "Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination." This guidance is intended to assist sponsors in the codevelopment of two or more novel (not previously marketed) drugs to be used in combination to treat a disease or condition.

This guidance provides recommendations and advice on how to address certain scientific and regulatory issues that will arise during codevelopment. It is open now for public comment, requested by 14 February 2011.

Recent scientific advances have increased our understanding of the pathophysiological processes that underlie many complex diseases, such as cancer, cardiovascular disease, and infectious diseases, including HIV. This increased understanding has provided further impetus for new therapeutic approaches that rely primarily or exclusively on combinations of drugs directed at multiple therapeutic targets to improve treatment response and minimise development of resistance.

In settings in which combination therapy provides significant therapeutic advantages, there is growing interest in the development of combinations of investigational drugs not previously developed for any purpose. Because the existing developmental and regulatory paradigm focuses primarily on assessment of the effectiveness and safety of a single new investigational drug acting alone, or in combination with an approved drug, FDA believes guidance is needed to assist sponsors in the codevelopment of two or more unmarketed drugs.

This guidance is intended to describe a highlevel, generally applicable approach to codevelopment of two or more unmarketed drugs. It describes the criteria for determining when codevelopment is an appropriate option, makes recommendations about nonclinical and clinical development strategies, and addresses certain regulatory process issues.

The guidance is not intended to apply to development of fixed-dose combinations of already marketed drugs or to development of a single new investigational drug to be used in combination with an approved drug or drugs, nor to vaccines, gene or cellular therapies, blood products, or medical devices.

Diseased Pariah News – archive online

This influential community publication has now been archived online.

This magazine was produced before HAART was available, and written by activists who were unable to benefit from treatment when it did arrive.

But the style, anger and humour ("Hostess with the Toxoplasmostest", the "Get Fat, Don't' Die" recipe column, "Ask Aunt Kaposi", centrefold pin-ups with the models CD4 count and current meds, etc) used by these activists to challenge complacency still stands

head and shoulders above most of worthy publications that followed.

This is uncomfortable reading from a historical perspective. Know your history.

http://www.diseasedpariahnews.com/

Free journal articles:

PLoS One

Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials.

Phillips TJC et al.

http://clinicaltrials.ploshubs.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0014433#pone-0014433-t002

A randomised trial to assess anti-HIV activity in female genital tract secretions and soluble mucosal immunity following application of 1% tenofovir gel.

Keller M et al.

http://clinicaltrials.ploshubs.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0016475

A phase I randomised placebo controlled trial of the safety of 3% SPL7013 gel (VivaGel) in healthy young women administered twice daily for 14 days.

Cohen CR et al.

http://clinicaltrials.ploshubs.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0016258

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.

18th Conference on Retroviruses and Opportunistic Infections (CROI)

27 February–3 March 2011, Boston

http://www.retroconference.org

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

BHIVA Autumn Conference including CHIVA Parallel Sessions

17-18 November 2011, London

http://www.bhiva.org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

The i-Base website has been completely redesigned with new portals for healthcare professionals, HIV-positive people and community advocates.

It is even faster and easier to access, use and navigate.

http://www.i-Base.info

All i-Base publications are available online, including editions of the treatment guides. The site gives details about i-Base, the UK Community Advisory Board (UK-CAB), our phone service and meetings, as well as access to our archives and an extensive range of links. It can be used to order publications and regular subscriptions to be delivered by post or email (as PDF files).

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

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

RSS news feed has been introduced for HIV Treatment Bulletin for web and PDA access - we welcome your feedback on this new way to provide treatment updates.

A section on Education, Advocacy and Training includes our training manual for advocates with eight 2-hour modules that include questions and evaluation. Training modules start with basics, including CD4, viral load and other monitoring tests, combination therapy and side effects, and include overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment.

An average of 100,000 pages individual ISP accounts contact i-Base.info each month, with over 6000 hits a day.

Training manual – revised, updated and now fully online

This established training resource has been revised and updated and is now online in new format.

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

The Training Manual for Advocates provides entry-level curriculum relating to HIV and treatment.

It is made up of 8 modules for learning about aspects of HIV care has been updated and published online as an interactive resource. It provides entry-level curriculum relating to HIV and treatment.

Additional support material is included on how to understand aspects of science that might be new to a lay reader.

http://www.i-base.info/manual/en/index.html

Each module includes learning objectives, non-technical review material, test questions, an evaluation and a glossary.

We hope this will be useful for training advocates and other related healthcare workers as well as for HIV-positive people who want to know more about aspects of their healthcare.

The training manual was previously only available online as a PDF document and has been widely translated. Earlier editions are available in Russian, Portuguese, Hindi and Nepalese as are available as PDF files.

Generic clinic forms

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.

These PDF files include record sheets to track CD4 and viral load results, cardiovascular risk, hepatitis, first patient visit, patient update, day case and summary notes.

http://i-base.info/category/publications/clinic-forms

Please contact the i-Base office if you would like help adding your own hospital or Trust logo to these forms.

Report assessing the treatment information needs African people in the UK living with HIV

This report by Winnie Sseruma and i-Base includes an analysis from workshops held last year and details African use and experience of current treatment information resources.

http://i-base.info/home/africans-and-treatment-infomation

i-Base Book: "Why we must provide HIV treatment information"

Photography by Wolfgang Tillmans

i-Base has worked as a treatment literacy project for over six years. Over this time we have always produced copyright-free material and encouraged other organisations to use, translate and adapt our material. Through this work, we have been very lucky to develop links to many other advocacy projects outside the UK.

A meeting, held in Cape Town earlier focused on how to raise the profile of treatment literacy. One result from the meeting is a publication "Why we must provide HIV treatment information".

With text provided by activists from 25 countries and 50 full colour photographs by Wolfgang Tillmans, this limited edition 100-page publication is being sold by i-Base to raise funds to help support our international treatment literacy projects.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting since 2002. It now includes over 300 members from over 100 organisations. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

The CAB has a separate website, where reading material, reports and presentations from these meetings are posted. Membership is free,

http://www.ukcab.net

World CAB - reports on international drug pricing

Two reports from meetings between community advocates and pharmaceutical companies, that focused on pricing issues and global access to treatment, and that are now available online.

Both are available to download as a PDF file from the i-Base website.

i-Base treatment guides

i-Base produce five booklets that comprehensively cover five important aspects of treatment. Each guide is written in clear non-technical language. All guides are free to order individually or in bulk for use in clinics and are available online in web-page and PDF format.

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

- Introduction to combination therapy (May 2010)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)
- Guide to changing treatment: what to do when your treatment fails (February 2011)
- Guide to HIV, pregnancy & women's health (January 2009)
- HIV and your qulaity of life: guide to managing side effects (December 2010)

Translations of i-Base publications

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 35 languages.

More information about this process is available on the i-Base website.

In addition, PDF files of some of the translated publications are available on the i-Base site.

Please be aware that some of these translations are from earlier editions of the treatment guides, and check the publication date before relying on all information.

http://i-base.info/category/translations

Languages currently include:

Bosnian, Bulgarian, Chinese, Czech/Slovak, Croatian, French, Greek, Hindi, Indonesian, Italian, Kosovo, Macedonian, Nepali, Polish, Portuguese, Romanian, Russian, Serbian and Spanish.

Treatment 'Passports'

These popular booklets are for HIV-positive people - whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Like all i-Base publications, they are available free as single copies, or in bulk.

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published 10 times a year in a printed version, in a PDF file that we can email to you, and on our website.

The printed version is available at most HIV clinics in the UK and is available free by post.

HTB South

A quarterly bulletin based on HTB but with additional articles relevant to Southern Africa. HTB South is distributed in print format by the Southern African HIV Clinicians Society (www.sahivsoc.org) to over 20,000 doctors and healthcare workers. It is also available as a PDF file and is posted online to the i-Base website.

ARV4IDUs

An electronic publication, produced in English and Russian language editions, to provide an overview of research related to IV-drug use and antiretroviral treatment.

Treatment information request service - 0808 800 6013

i-Base offers specialised treatment information for individuals, based on the latest research.

We can provide information and advice over the phone, and we can mail or email copies of the latest research studies relevant to the caller.

For further details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm. All calls are in confidence and are free within the UK.

Online Q&A service

An online 'question and answer' service that now has over 1400 questions online. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).

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

Recent questions include:

- Can I take beta-blockers with my HIV drug combination?
- Will the new electronic NHS system disclose my status?
- Is ovarian cancer more common in people with HIV?
- My doctor disclosed my status to another specialist, what can be done to reverse this?
- Can my doctor force me to take treatment if I don't want it?
- Can I take Viagra with efavirenz and Truvada?

Order i-Base publications via the internet, post or fax

People with internet access can use our website to order and receive publications. You can access our publications online or subscribe to receive them by email or by post; and you can order single copies or bulk deliveries by using the forms at:

http://i-base.info/order

Copies of publications can also be ordered by post or fax using the form on the back page of HTB. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), HTB South, Treatment 'Passports' and all our guides to managing HIV and additional reports.

h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website: http://www.i-Base.info; by fax or post using the form on the back page by sending an email to: subscriptions@i-Base.org.uk

Editor: Simon Collins

Contributing Editor: Polly Clayden

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

HIV i-Base receives unconditional educational grants from Charitable Trusts, individual donors and pharmaceutical companies.All editorial policies are strictly independent of funding sources.

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All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it.

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