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EDITORIAL

Welcome to the first issue of HTB South for 2012, complete with a new design!

Our conference coverage in this issue comes from a meeting on HIV and women's health, another on HIV persistence and cure research, as well as the European AIDS Conference and ICAAC.

The possibility that the slow momentum from numerous research groups pursuing a cure for HIV is an exciting one and Richard Jefferys both summarises the state-of-the-art in this field and comments on the complexities of interpreting these early results in his report from the persistence workshop.

This issue also highlights serious concerns for treatment access and global health including changes at the Global Fund and responses to the suspension of round 11 grants – that became likely last year when donor pledges failed to meet even the minimum budget.

TB reports include the shocking state of TB in South African prisons, covered by Nathan Geffen who also reports encouraging results from the ZAMSTAR study and more news on two promising MDR TB drugs.

Southern African HIV Clinician's Society

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

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

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

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

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CONFERENCE REPORTS

2nd International Workshop on HIV & Women

9–10 January 2012, Bethesda, USA

Introduction

This was the second year for this new workshop focused on research into the impact of gender on HIV and related health issues.

It is very helpful that the meeting organisers have posted most of the slides for the oral presentations online, together with free access to the conference abstract book.

Abstracts and presentations are available at these links:

http://regist2.virology-education.com/abstractbook/2012_1.pdf

http://regist2.virology-education.com/2012/2ndHIV&Women/9_Jan.html

http://www.virology-education.com

Reports in this issue include:

- Similar efficacy and a few gender related differences in side effects with rilpivirine vs efavirenz at 96-weeks
- The effect of BMI on efficacy, safety and tolerability of lopinavir/r in women
- Hormonal contraception and higher risk of non-AIDS-defining events in Nashville cohort
- Poorer adherence and loss to follow up in Kenyan women who are pregnant when enrolled to ART programmes

Similar efficacy and a few gender related differences in side effects with rilpivirine vs efavirenz at 96-weeks

Polly Clayden, HIV i-Base

Rilpivirine (RPV) did not show teratogenicity risk in pre-clinical studies and is therefore FDA pregnancy category B, nor does it interact with the oral contraceptives norethindrone and ethinyl estradiol. For these reasons, it could be a useful option for women of child bearing potential.

RPV was non-inferior to efavirenz (EFV) when combined with a nucleos(ti)de backbone in the pooled 96-week analysis of the phase 3 ECHO and THRIVE trials but only for baseline viral load strata <500,000 copies/mL. The primary endpoint was viral suppression to <50 copies/mL at week 48 by TLOVR analysis, with non inferiority defined by 95% CI compared to control not crossing the lower margin of -12%.

An investigation was conducted to look at safety and efficacy outcomes in women participating in these trials specifically and in comparison to men. This analysis included data from 236 (22%) women and 860 men, of these, 121 women and 429 men were randomised to RPV, and 115 women and 431 men to EFV. The women and men had similar median age of about 35 years, baseline CD4 counts of 243 and 258 cells/mm3 and viral loads of 4.9 and 5.0 log10 copies/mL respectively. Of the participants, a greater proportion of women than men (45% vs 18%) were black, and a smaller proportion (33% vs 70%) were white and Latina/o (16% vs 28%).

At 96 weeks, CD4 increases were similar in women and men in the RPV and EFV groups (approximately 225 cells/mm3).

Overall, 14% vs 6.1% of women failed virologically and/or discontinued treatment in the RPV and EFV arms respectively. The difference between the two arms was greater in the first year of treatment with 11.6% vs 3.5% failing compared to 2.5% vs 2.6% in the second year. These proportions were similar for men participating in the study: overall 14.2% vs 7%, year one 11.4% vs 4.4%, and year two 2.8% vs 2.6%, in the RPV and EFV arms respectively.

Stratification by baseline viral load showed similar rates of virological suppression for women and men with ≤100, 000 copies/mL receiving RPV or EFV (approximately 80%). Between >100,000 and 500,000 copies/mL, women in the RPV arm did slightly better than those receiving EFV, respectively 81% and 73% had viral loads <50 copies/mL at 96 weeks. The results for men in this viral load stratum were similar across the two arms, 72% and 73% for RPV and EFV. Above 500,000 copies/mL only 30% of women in the RPV arm had viral loads <50 copies/mL but this percentage relied on results for 3/10 women. For women receiving EFV the proportion was 57% (8/140). Of the men 67% (29/43) and 79% (46/58) in the RPV and EFV arms had viral loads <50 copies/mL at 96 weeks.

Of women who reported adherence >95%, both those receiving RPV (n=94) and EFV (n=92) had 78% rates of virological suppression <50 copies/mL. For those reporting <95% adherence suppression rates were lower, 67% and 64% for RPV (n=18) and EFV (n=14) respectively.

For men who reported >95% adherence, 96-week suppression rates with RPV (n=364) and EFV (n= 336) were 82% and 85%. Rates for those reporting <95% adherence were 52% with RPV (n=50) and 68% with EFV (n=59).

Resistance was analysed in a very small subset of women, RPV (n=15) and EFV (n=5). This revealed 20% of virologic failures with wild-type virus and 60% of with NNRTI resistance. There were more NRTI mutations in the women receiving RPV than EFV, 47% vs 0% and the most common were E138K (33%) and M184I (27%).

At week 96, rates of adverse events (AEs) leading to discontinuation of treatment were similar across treatment arms and genders. Incidence of grade 2 to 4 adverse events was significantly lower with RPV than EFV in women, 15.7% vs 34.8% and men, 17.5% vs 32.7%, both p<0.001.

Nausea occurred more frequently in women than men receiving both RPV and EFV, 19% vs 11.2%, 18.3% vs 9.7%, both p<0.05. But the incidence of treatment-related psychiatric adverse events was significantly lower in women than men receiving RPV, 9.1% vs 18.2%, p<0.05). Both these rates were lower than those in women and men receiving efavirenz, 16.5% vs 29.5%, p<0.05).

There were lower rates of abnormal dreams and nightmares in women than men receiving RPV 4.1% versus 11.4%, p<0.05. Women also experienced less of these events than men with EFV,

8.7% vs 17.4%, p<0.05. Rates of diarrhoea were similar in women and men receiving RPV, 13.2% versus 16.3%, but lower in women than men receiving efavirenz, 9.6% vs 18.6%, p< 0.05.

Women and men receiving RPV reported lower incidence of neurologic AEs compared to those receiving EFV, 15.7% vs 34.8%, p<0.05, and 17.5% vs 32.7%, p<0.001, for men and women respectively. There was also lower incidence of dizziness, 12.4% vs 27.8%, p<0.05 and 8.8% vs 28.8%, p<0.0001; and rash, 5.8% vs 16.5%, p<0.05 and 6.8% vs 12.5%, p<0.05.

Women and men receiving RPV had less grade 3 or 4 laboratory abnormalities 7.4% vs 11.5% and 10% vs 18.7% but this only reached statistical significance in men, p<0.05.

There were less grade 1 to 3 elevations in LDL cholesterol with RPV than EFV in women 19.9% vs 49.6%, p< 0.05, and men 19.6% vs 43.1%, p<0.001.

For all groups, there were significant increases from baseline in limb fat at week 96 with no statistical differences between treatment groups. Women receiving RPV appeared to have greater increase than the EFV group, median 1592g vs 641g. For men the two groups had similar median increases 828g vs 835g.

There was a trend towards greater BMD changes in women for both arms, but this was in a small sample size (n=30).

Ref: Short W et al. Sustained efficacy and safety observed for RPV vs EFV plus FTC/TF and with a few gender differences in pooled 96-week ECHO and THRIVE analysis. 2nd International Workshop on HIV and Women. 9–10 January 2012, Bethesda, MD. Oral abstract O_14A.

The effect of BMI on efficacy, safety and tolerability of lopinavir/r in women

Polly Clayden, HIV i-Base

Body mass index (BMI) can lead to alterations in pharmacokinetics and pharmacodynamics. Data describing the relationship between BMI and clinical outcomes of ART in women are limited.

Investigators from Abbott conducted a meta-analysis in women taking lopinavir/ritonavir (LPV/r)-based regimens in order to look at the effect of BMI on efficacy, safety, and tolerability. Ashwaq Hermes presented findings from this study.

All prospective randomised controlled trials (RCTs) in the company database in adults receiving LPV/r in regimens with two NRTIs, having BMI data, and baseline to week 48 efficacy, safety, and tolerability data were included.

Women were stratified by baseline BMI (kg/m2) into <18.5, ≥18.5-<25, ≥25-<30 and ≥30 groups. As the number of women with BMI <18.5 was low (n=28), the investigators selected categories of <25 (normal), ≥25-<30 (overweight) and ≥30 (obese) for the analyses.

The meta-analysis included 485 women from seven RCTs, 258 with normal BMI, 130 were overweight women, and 97 categorised as obese. There were statistically significant differences (p<0.05) among the normal, overweight, and obese groups in baseline demographic characteristics: percentage of white women, 53.9%, 36.9% and 25.8% respectively; percentage of Latina women, 17.4%, 33.8%, and 20.6%, respectively and rate of hepatitis C co-infection, 17.2%, 10.8%, 6.2%, respectively.

There were also statistically significant differences in the three groups in baseline disease characteristics: mean viral load, 4.6, 4.4, and 4.3 log10 copies/mL, respectively, and mean CD4 counts 214, 244, and 278 cells/mm3, respectively.

Efficacy was similar across the groups at week 48. Similar proportions of women had viral load <50 copies/mL, 65.1%, 57.7% and 57.7%, respectively (ITT analysis). Mean increases in CD4 counts were also similar across the normal, overweight, and obese groups, 197, 158, and 172 cells/mm3, respectively.

Incidence of grade 3 and above adverse events (AEs) was also similar across the groups, 29.5%, 29.2%, and 41.2%, respectively, p=0.087. Differences were seen in the incidence of moderate/severe abdominal pain, 0.8%, 0%, 7.2%, respectively and diarrhea 9.3%, 10.8%, and 22.7%, respectively in the normal, overweight and obese groups, both p<0.05. These AEs were significantly higher, p<0.05, in the obese women compared with the other two groups. There was no significant difference in the incidence of nausea and vomiting among the three groups.

The investigators noted that increasing BMI is associated with a greater prevalence of diarrhea and abdominal pain, but not nausea or vomiting, in the general population. Also dietary differences among the BMI groups could be confounding, and this information was not collected or controlled for in the meta-analysis. Furthermore people with high BMI have elevated incidence of non-alcoholic fatty liver disease, which is associated with liver fibrosis and changes in drug metabolism.

They concluded that direct comparisons of dose safety and efficacy by BMI groups are needed to increase the understanding of obesity related changes and the impact on treatment.

C O M M E N T

As reported in other studies, increased weight did not lead to higher rates of virological failure, suggesting that pharmockinetics for lopinavir do not have a direct association with higher weight, even though the PK data were not available or analysed.

However, although the results were not significantly different, it is unclear whether a formal test of equivalence was performed. There is >7% difference between the normal group and the other two groups and response rates appear lower in heavier groups. It would be interesting to see the confidence intervals for the differences which would have to be to conclude equivalence. The CD4 count increases also seem to be lower.

It would also have been interesting to see whether lopinavir/ritonavir has an impact on BMI in relation to baseline BMI.

Reference

Hermes A et al. A meta-analysis of the effect of BMI on efficacy, safety, and tolerability of lopinavir/ritonavir in HIV-infected women in randomised clinical trials. 2nd International Workshop on HIV and Women. 9–10 January 2012, Bethesda, MD. Oral abstract O_15.

Hormonal contraception and higher risk of non-AIDS-defining events in Nashville cohort

Polly Clayden, HIV i-Base

Studies evaluating the effect of hormonal contraceptives (HC) on HIV disease progression have shown conflicting results. Previous findings have been from resource limited settings (RLS) and have not looked at the effect of HC on non-AIDS defining events (non-ADE).

Mainly observational data from Africa and Asia has shown both higher and lower rates of HIV disease progression in women receiving HC. Observational data in HIV negative women has shown an association between HC and metabolic complications.

Vlada Melekhin presented findings from a retrospective cohort study of HIV-positive women attending the Comprehensive Care Center (Nashville, TN) between 1998-2008. The study investigated the association between HC (oral and injectable methods used >28 days) and AIDS-defining events (ADE), non-ADE (ie cardiovascular, renal, liver, and metabolic diseases and non-AIDS associated malignancies) and death.

Eligible women were <55 years old with no history of pulmonary or deep venous thromboembolism, breast cancer, hysterectomy, or bilateral tubal ligation and not pregnant at first clinic visit. Women with no HC were evaluated from their first clinic visit and those using HC at HC start.

Logistic regression analysis included age, race, baseline CD4 count, viral load, and haemoglobin, CD4 nadir, history of ADE, non-ADE, HCV, antiretroviral (ART and non-ART) use, smoking status, IV and non-IV drug use, year of study start, and year of HC start.

Of 467 HC-eligible women, 112 (24%) were on HC at any time during the follow up. At baseline women on HC were younger, median 28.6 vs 35.6 years. They had higher CD4 count 523 vs 364 cells/mm3 and nadir, 340 vs 280 cells/mm3, and lower median viral load, 3.1 vs 4.1 log10 copies/mL. They were less likely to be coinfected with HCV, 5% vs 15% or inject drugs, 16% vs 27%, both p<0.03.

There was no statistical difference in ART use between the HC and no HC groups, 30.4% vs 26.8%, respectively, nor in prior ADE or non-ADE.

Of the 112 women using HC, 51 used oral and the remaining 61 used injectable for a median duration of 7.6 and 13 months respectively, p=0.26.

HC users had longer follow-up compared to non HC users, median 2.8 vs 1.5 years for ADE, 2.8 vs 1.6 years for non-ADE and 3.8 vs 2.1 years for death.

The investigators reported a lower proportion of deaths in the HC group, 6% vs. 15%, p=0.01. But these women had more new cardiovascular non-ADEs, 12% vs. 5%, p=0.02.

In the adjusted analyses, HC use was associated with a statistically significantly higher risk of non-ADE HR 2.0, (95% CI 1.28, 3.1), p=0.02 and non-ADE/death HR 1.89, (95% CI 1.25, 2.87), p=0.03). Risks of ADE and ADE/death were also higher among HC users but did not reach statistical significance: HR 1.51 (95% CI 0.59, 3.85), p=0.39 and 1.49 (95% CI 0.72, 3.11), p=0.29, respectively. Women using injectable HC were at a higher risk of non-ADE and non-ADE/death, HR 2.0 and 1.9 respectively, both p=0.03 and those using oral HC only non-ADE, HR 1.9, p=0.02.

The investigators plan further analyses from this cohort including looking at the effect of ART and suggested as the number of women with HIV who are of child-bearing age increases, it is important to better understand any negative effect of HC on their health.

C O M M E N T

Investigations into the use of hormonal contraceptive methods and its effect on disease progression in HIV positive women have led to conflicting results,

One randomised controlled trial conducted in Zambia showed risk of CD4 decline or death with hormonal contraception, compared to use of the copper IUD. [2] But the study was designed to look at the incidence of pregnancy and pelvic inflammatory disease in the IUD users and there was considerable discontinuation and switching between methods. Data from several observational studies do not confirm this effect.

The association with non-AIDS events found by Melekin are interesting but should be interpreted cautiously given that two large trials have reached very different conclusions. Observational data is vulnerable to unmeasured confounding and (as they are in the general population) lifestyles are very different between those that use hormonal contraception and those that do not. These differences could (feasibly) explain differences in incidence of some of these serious events. For example, even smoking and alcohol use may be different in the groups. Whille the researchers may have used propensity scores, these do nothing to tackle unmeasured confounding (and are arguably little better than standard multivariable logistic regression models).

The WHO recently held a stakeholders meeting to review the evidence on hormonal contraception and HIV, not only to consider the effect on disease progression but also female to male HIV transmission and HIV acquisition by negative women. The organisation and partners are producing three systematic reviews and there will be a statement from the consultation.

Currently the WHO medical eligibility criteria for contraceptive use defines hormonal contraceptives as category 1 – ie no restriction on the use of the methods for women with HIV (including AIDS).

References

1. Melekin V et al. Hormonal contraceptive use is associated with a higher risk of non-AIDS-defining events in HIV-1-infected women. 2nd International Workshop on HIV and Women. 9–10 January 2012, Bethesda, MD. Oral abstract O_13.
2. Stringer EM et al. A randomised trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human immunodeficiency virus. Am J Obstet Gynecol 2007 August; 197 (2):144-148. Free full text: http://www.ajog.org/article/S0002-9378(07)00399-7/fulltext

Poorer adherence and loss to follow up in Kenyan women who are pregnant when enrolled to ART programmes

Polly Clayden, HIV i-Base

There are concerns that women diagnosed with HIV during pregnancy may have greater difficulty with adherence to ART than those who are already aware of their status. This may lead to increased rates of vertical transmission and the development of drug resistance.

April Bell showed findings from a retrospective analysis of data collected from January 2006 to July 2011 by the United States Agency for International Development-Academic Model Providing Access to Healthcare (USAID-AMPATH) programme in Western Kenya.

The study compared adherence rates and pregnancy outcomes between women enrolled in the programme during pregnancy and those who became pregnant after they were already enrolled. Women from both groups were ART-naïve when their pregnancy was identified. Those meeting the eligibility criteria for treatment in Kenya at the time - CD4 <200 cells/mm3 - started ART immediately and those with CD4 >200 cells/mm3 started at 28 weeks gestation.

The women enrolled during pregnancy were younger, with a median age of 27 (IQR 23.2-31.7) years (n=8926), compared to 30.8 (IQR 26.6–35.1) years in the group already enrolled (n=5108). At enrollment a higher proportion were married, 69.6% compared to 52% and had a higher median CD4 count 371.5 (IQR 222 – 543) cells /mm3 compared to 282 (IQR 133-461) cells/mm3 for women who became pregnant when they were already enrolled in the programme. All comparisons, p<0.0001.

The women who were pregnant at enrollment were less adherent, 89.7% compared to 93.2% with perfect adherence, and were more likely to be lost to follow up before delivery, 29.6% compared to 3.4%, both p<0.0001.

Among the women who remained in the programme post-partum, there was no difference in the rate of mother-to-child transmission, 7% compared to 8.8%, p=0.0053, or early infant death, 3.2% compared to 4.2%, p=0.032, in those enrolled during pregnancy or became pregnant after enrollment respectively.

Although this study was limited by incomplete data, the investigators were able to conclude that women who are pregnant at enrollment into an HIV care programme are at higher risk for loss to follow up and poor adherence than those already enrolled in care at the time of pregnancy.

They suggested, "Interventions targeting women newly diagnosed with HIV infection during pregnancy are necessary to improve retention and adherence to therapy".

Reference

Bell A et al. Adherence and retention rates: a comparison of women enrolled in an ART programme during pregnancy and those who become pregnant after enrollment. 2nd International Workshop on HIV and women. 9—10 January 2012, Bethesda, MD. Oral abstract O_17.

CONFERENCE REPORTS

5th HIV Persistence Workshop on HIV Reservoirs

6–9 December 2011, West Indies

Richard Jefferys, TAG

Introduction

This meeting had a limited numbers of attendees and brought together an impressive group of leading researchers.

The abstract book and late breaker abstracts are available in PDF format from the conference website and links:

http://www.hiv-workshop.com/workshop-2011.htm

http://www.hiv-reservoir.net/index.php/the-news/189-abstract-book-2011-hiv-persistence-workshop.html

The site also contains daily rapid summaries of the workshop that will be followed in the next few weeks by more detailed reports.

Workshop report and commentary

Inaugurated in 2003, the bi-annual International Workshop on HIV Persistence during Therapy (aka "the persistence workshop") is the brainchild of researcher Alain Lafeuillade. The meeting presaged the recent explosion of interest in pursuing a cure for HIV infection, a pursuit many had considered quixotic until the case of Timothy Brown came to light in 2008.

As has been extensively documented, Brown's apparent cure resulted from a debilitating odyssey of treatments required for the grim diagnosis of acute myelogenous leukemia, enhanced with a mix of insight and good fortune on the part of his doctor Gero Hutter, who was able to provide a stem cell transplant from a donor lacking the major HIV co-receptor CCR5.

The sea change wrought by this fortuitous "proof of concept" was much in evidence at the 2011 persistence workshop this past December; the tentative forays into basic science that were once emblematic of the field are now mixed together with more ambitious plans for advancing ideas into the clinic. Perhaps most strikingly, two large pharmaceutical companies—Gilead and Janssen/Tibotec—described their use of industrial scale screening to search for compounds that are active against latent HIV; this represents an unprecedented expansion of efforts once confined to under-resourced academic labs.

A number of online resources are available with information on presentations at the 2011 persistence workshop: Lafeuillade runs a website called the Reference Portal on HIV Reservoirs & Eradication Strategies which includes an expanding number of reports, video interviews and commentary. [1]

David Margolis from the University of North Carolina has written a comprehensive report for Jules Levin's National AIDS Treatment Advocacy Project (NATAP) website. [2] Jon Cohen also covered one the most notable presentations in the journal Science. [3]

This report and commentary represents my subjective take on events.

To try and briefly summarise the top-line stories that emerged from the 2011 meeting:

- A triumvirate of researchers—Courtney Fletcher, Mario Stevenson and Tim Schacker—presented data suggesting that sporadic, very limited rounds of HIV replication may occur in some individuals on ART due to poor penetration of certain drugs into the lymphoid tissues. However, preliminary data were only available from a small number of participants (~4-5) so the implications are still uncertain. According to the clinicaltrials.gov entry for the study, it is now expanding from the original enrollment target of 12 to 40 so additional information should soon be forthcoming. [4] Alain Lafeuillade has posted an interview with Mario Stevenson about the findings, and these presentations were the subject of Jon Cohen's story in Science. [5]
- An Italian research group led by Andrea Savarino described a retrospective analysis involving 18 rhesus macaques infected with SIVmac251 that participated in various studies combining ART with drugs targeting the viral reservoir. The analysis found an association between the number of "anti-reservoir" drugs animals received and the likelihood of controlling SIV to undetectable levels after ART was interrupted; however only three macaques controlled SIV to this degree so the findings should be considered very preliminary. The workshop organisers issued a press release about the data suggesting that for the first time they show that anti-reservoir drugs may be able to contribute to what is now frequently referred to as a "functional cure" (control of viral load in the absence of ART). In an interview with Alain Lafeuillade, Savarino is careful to note that the findings require confirmation in human studies because they could relate to unknown factors specific to the three macaques that controlled SIV in the experiment. [6] This caveat is underscored by the fact that there are relatively few studies involving ART treatment of SIVmac251 in macaques to provide context, and in those that have been published there appear to be some examples of animals that spontaneously controlled viral load after ART interruption (both in control groups and in recipients of a DNA-based therapeutic SIV vaccine).
- David Margolis from the University of North Carolina presented the first data on the use of a histone deacetylase (HDAC) inhibitor named SAHA (aka vorinostat) in individuals with HIV. HDAC inhibitors are at the forefront of efforts to pharmaceutically urge HIV out of latency, so news from Margolis's trial has been eagerly awaited. While very preliminary, and derived from just four participants, the results so far suggest that the approach is able to increase HIV expression by latently infected cells. It took Margolis many years to get the trial started due to concerns about the safety of HDAC inhibitors (which are used as cancer treatments and can cause serious toxicities) but no serious side effects have occurred to date. As Margolis stressed, much more work is needed before any conclusions can be drawn about the promise of the approach.
- The burgeoning involvement of the pharmaceutical industry in cure-related research—represented by presentations from Romas Geleziunas from Gilead and Roger Sutmuller from Janssen/Tibotec—was important news because it promises to transform the drug discovery effort by increasing the number of compounds that are being screened by many orders of magnitude.

The workshop agenda was divided into discrete topic areas spread over three days. The first session addressed the subject of animal models, and was led off by Jeff Lifson from the National Cancer Institute (NCI) at Frederick who has nearly two decades of experience studying SIV infection in rhesus macaques. Lifson outlined some of the considerations in developing an appropriate model for cure-related studies, which include mimicking the degree of viral suppression achieved with ART in humans and developing tools to comprehensively assess the impact of additional interventions on SIV reservoirs.

The models currently in use include:

- Macaques infected with hybrid SIV/HIV viruses encoding HIV reverse transcriptase (SHIV-RT), treated with efavirenz, emtricitabine and tenofovir
- Macaques infected with SIVmac251 or SIVmac239 treated with multi-drug regimens (e.g. tenofovir, emtricitabine, raltegravir and ritonavir-boosted darunavir +/– maraviroc)
- Pigtailed macaques infected with SIV/17E-Fr and SIV/Delta B670 treated with tenofovir, integrase inhibitor, saquinavir, atazanavir (this model is primarily being used to assess issues relating to viral activity in the brain)

Lifson described a study conducted by his laboratory in which macaques were infected with the highly virulent challenge virus SIVmac239 and, after sixteen weeks, treated with a multi-drug antiretroviral regimen comprising an integrase inhibitor, tenofovir, emtricitabine, and ritonavir-boosted darunavir. Suppression of viral load to less than 30 copies/mL was eventually achieved, but Lifson noted that it took longer than is seen with HIV in humans. Like the vast majority of macaque studies, the experiment involved Indian rhesus macaques, and Lifson suggested that viral load suppression might be easier to achieve in Chinese rhesus macaques (this subspecies has been shown to control SIV somewhat better in the absence of ART). Lifson acknowledged that refinement of the SIV/macaque model for cure-related research is ongoing, and he cautioned against the premature adoption of any one approach as a standard. As an example of the pitfalls of premature standardisation, he cited the HIV vaccine field's mistake in adopting a SHIV89.6p challenge model that turned out to have essentially no relevance to human HIV infection.

One potentially important new technology that Lifson highlighted is called digital PCR, which is vastly superior to traditional PCR for measuring small quantities of nucleic acid in samples. PCR amplifies nucleic acid sequences from a single sample by inducing rounds of copying of the original sequence, then back-calculating how many were originally present using a formula that takes into account the number of rounds of copying; however these calculations can be imprecise for a number of reasons. Digital PCR divides a sample into many discrete "microfluidic" wells and then uses PCR to look for the nucleic acid sequence of interest in each well, providing a readout as to whether the sequence is absent (0) or present (1). The total amount of nucleic acid sequence that was present is then calculated based on the number of negative and positive wells, using an approach called a Poisson distribution. Digital PCR assays have only recently been commercialised and a number of laboratories are now busy using them to measure SIV and HIV in research studies.

The presentations following Lifson illustrated the diversity of animal models in use, and the uncertainties associated with them. Andrea Savarino from the Istituto Superiore di Sanità in Rome provided an update on experiments conducted by his group involving macaques

infected with SIVmac251. In a paper published in AIDS last year, Savarino and colleagues reported that the gold-based rheumatoid arthritis drug auranofin reduced the reservoir of SIV-infected cells in animals treated with combination ART. [7]

At the workshop, Savarino presented results of a retrospective analysis of 18 macaques (including those included in the experiments reported in the paper) that have received various combinations of antiretrovirals and "anti-reservoir" drugs including auranofin and buthionine sulfoximine (BSO). The breakdown of the antiretroviral regimens employed was as follows:

- ART: tenofovir, emtricabine, raltegravir
- Intensified ART (iART): tenofovir, emtricabine, raltegravir, ritonavir-boosted darunavir
- Mega-ART: tenofovir, emtricabine, raltegravir, ritonavir-boosted darunavir, maraviroc

Three of the 18 macaques have controlled SIVmac251 to undetectable (<40 copies/mL) levels after interruption of all treatment for several months, and Savarino reported that there was a significant correlation between the number of "anti-reservoir" drugs received and this salutary outcome (for the purposes of this analysis, the CCR5 inhibitor maraviroc was counted as an anti-reservoir drug due to evidence that it reduced the amount of SIV DNA when added to intensified ART and preliminary results from a human study suggesting it may impact reservoirs). Some macaques also received the HDAC inhibitor SAHA, but an impact on the SIV reservoir could not be demonstrated.

The complicated sequence of treatments and outcomes in the three macaques that have controlled viral load off ART can be roughly summarised as follows:

- Macaque P252: ART, ART+auranofin, iART+auranofin, iART+SAHA, iART+auranofin, treatment interruption, viral load control to limit of detection, viral load rebound, Mega-ART, treatment interruption, viral load control, viral load rebound, viral load control, viral load rebound, Mega-ART, viral load control, viral load rebound, Mega-ART+BSO, viral load control (100+ days)
- Macaque P157: ART, iART, Mega-ART+auranofin+BSO, treatment interruption, viral load rebound, viral load control (~60 days), viral load blip, viral load control (~50+ days)
- Macaque P177: ART, iART, Mega-ART, Mega-ART+auranofin, treatment interruption, viral load rebound, Mega-ART, treatment interruption, viral load rebound, viral load control, viral load rebound, viral load control (~50+ days)

The data appear encouraging but there are some potential caveats:

- The model of SIVmac251 infection treated with combination ART (the drugs used in the study included tenofovir, emtricabine, raltegravir, ritonavir-boosted darunavir and maraviroc) is not well characterised, at least in terms of the published literature
- There were very few control animals, and the results are not from a single study but rather from multiple experiments, sometimes involving the same macaques being rolled over from prior experiments
- As can be seen from the sequence of events in the three controlling macaques, the treatments were complex and there was variability between animals in terms of exactly when different interventions were administered

As Savarino stresses in his video interview with Alain Lafeuillade, human trials are now required to ascertain if the macaque results can be translated to HIV.

Paul Luciw presented results of an experiment in which macaques infected with SHIV-RT had prostratin and valproic acid added to long-term ART (efavirenz, emtricitabine and tenofovir) prior to an interruption. Luciw showed evidence of reduced viral RNA and DNA in tissues but when treatment was interrupted there was no significant difference in viral load rebound compared to macaques treated with ART alone. Daria Hazuda from Merck has included several of Luciw's slides in her recent presentations on cure research so the main findings can be viewed online, however note that prostratin is only referenced as a "protein kinase C activator" and valproic acid as an "HDAC inhibitor". [8]

Luciw also mentioned that he repeated the experiment adding raltegravir to the ART regimen and in that case there was no additional viral RNA and DNA reduction in tissues resulting from the anti-reservoir drugs, but he was running out of time and was unable to give any details; this finding is perhaps a reminder of how much uncertainty still surrounds macaque models for cure research.

Jerome Zack is trying to make drug-delivery nanoparticles out of weird cellular particles called "vaults" made of three proteins and a bit of RNA. [9] Zack presented some preliminary evidence that they can be engineered to deliver potential latency activators prostratin and bryostatin, Zack is also working with Paul Wender at Stanford to develop better analogues of these drugs to use. The goal is to come up with some lead vault-delivered anti-latency compounds to test in the BLT humanised mouse model.

Shifting topics to the virological aspects of HIV persistence, Sarah Palmer from the Karolinska Institute reported results of an intensive evaluation of viral genetics pre-ART and on long-term ART (up to >12 yearrs) in 12 people (seven treated at acute infection, five during chronic infection) to look for evidence of viral evolution that would be indicative of ongoing replication. No evidence suggestive of HIV replication was found in various CD4 subsets and other cell types in blood, lymph tissue, bone marrow and gut. Palmer noted that no hematopoetic progenitor cells (HPCs) containing HIV DNA could be found; occasional positive signals from HPC samples turned out to be due to low-level contamination with CD4 cells. This finding was recently echoed in a paper from Bob Siliciano's group at Johns Hopkins. [10]

Palmer drew attention to one case where a large amount of HIV DNA containing a huge deletion encompassing all of the protease gene was discovered. Since HIV can't replicate without protease, this demonstrates that the division of CD4 T cells carrying integrated, non-functional proviral HIV DNA can contribute to what may appear to be an HIV reservoir by some measures (but really isn't because the virus is defective). Mario Stevenson coined the term "junkyard DNA" for these non-functional proviruses, and it was quickly adopted at the workshop.

Tae-Wook Chun from the National Institute of Allergy and Infectious Diseases (NIAID) offered some data suggesting HDAC inhibitors may not be all they're cracked up to be in terms of reversing HIV latency, in the hands of his lab they didn't induce a significant amount of viral RNA from latently infected cells compared to prostratin (which is a potent activator generally considered too toxic for human use). Chun also said that the latently infected cells induced to produce viral RNA don't seem to die ("we haven't seen any evidence of cell death"), suggesting that induction using HDACs might have little

effect in the absence of an immune response capable of killing the infected cell.

Day two

Day two of the persistence workshop featured the presentations from industry, with Romas Geleziunas from Gilead and Roger Sutmuller from Janssen/Tibotec talking back-to-back about the ongoing work at their companies.

Gilead is looking at both virus activators and immune modulators, with Romas Geleziunas seemingly already having taken on board what Tae-Wook Chun had suggested the previous day: reactivating latent infection may not be enough to kill a cell, hence immune mechanisms may need to be induced to deliver the coup de grace. Geleziunas described Gilead's high throughput primary cell screening assay, which is a modified version of an assay developed by Vincente Planelles and Alberto Bosque. [11]

So far they've identified three HDAC inhibitors from the Gilead drug library, imaginatively named 001, 002 and 003. 001 is 10-fold more potent than SAHA but inhibits all classes of HDACs (which I think is a bit of a worry from a toxicity perspective) while 002 is of interest because while less potent it doesn't score positive on the AMES test (the standard test for assessing mutagenic potential). 001 and 003 were both AMES positive. Rats tolerated 3 weeks of 002 in a preliminary safety study. Romas noted that HDAC inhibitors only activate a fraction of the virus expression seen with pan-activating CD4 T cell stimulation using CD3 and CD28 antibodies, raising the question of whether the HDAC inhibitors are only activating a proportion of the latently infected CD4 cells, or rather causing less virus expression per cell. This question remains to be resolved.

High throughput screening of a Gilead library and a commercially available drug library produced a 1% hit rate, identifying 89 compounds that could be grouped into 15 clusters based on their structures. One was a calcium pump inhibitor named thapsigargin, possibly after a character from Lord of the Rings. It was a "robust activator" of latency in cells from 6 out of 6 donors. Romas didn't say anything more about it and Wikipedia offers an explanation as to why: "It is a tumor promoter in mammalian cells". Another was a "broad spectrum nonspecific tyrosine kinase inhibitor" called tyrphostin A which worked on cells from 3/6 donors. Since they hadn't expected to find kinase inhibitors, they then tried screening a library of those and got a 20% hit rate. Evidence of activity at low concentrations and dose responses were seen. Next steps are to confirm activity with more selective kinase inhibitors and explore the signaling pathways that are causing these compounds to work.

Switching to the topic of bolstering immunity, Romas said Gilead is looking at a TLR7 agonist it has in development for hepatitis B. It's been tested in chimps and woodchucks, where it has shown antiviral activity and dose-dependent induction of alpha interferon production and T cell and B cell activation. In woodchucks, it led to induction of antibodies against the hepatitis B surface protein. A small phase I human study has been safely conducted, also showing evidence of some T cell and B cell activation. Next step is to study the impact on HIV-infected cells and potentially test it in animal models in combination with HDAC inhibitors.

Meanwhile the overarching goals of Gilead's program continue to be:

- More high throughput screening
- Uncover novel mechanisms (e.g. as may happen as a result of the identification of kinase inhibitors)
- Discover new chemical entities (NCEs).

Roger Sutmuller from Janssen/Tibotec then described his company's efforts which have not been discussed publically before. He outlined the basic goal of discovering safe and effective compounds to reactivate latent HIV i.e. those that cause little or no cell activation and ideally have the potential to be combined. Unlike Gilead, Tibotec starts with a Jurkat cell line assay to identify compounds, after which they have a preplanned set of steps involving evaluation of:

- Toxicity/immune stimulation
- Virus reactivation in primary T cell assays
- Virus reactivation in latently infected cells from HIV+ individuals ex vivo
- Medicinal chemistry selection of lead compounds
- Testing in a humanised mouse model developed by Roberto Speck
- Testing of the pathways involved in drug activity eg using microarrays, HIV mutants with various signaling elements disabled, short-interfering RNAs etc.

Using the Jurkat cell line assay, 35,000 compounds have been screened to date, and the next step is to screen 480,000 compounds from a Johnson & Johnson "diversity library." Of those screened to date, 800 HDAC inhibitors have popped out (a 20% hit rate), 25 protein kinase C agonists (a family prostratin belongs to) and 600 unknowns that can be grouped into 11 different "chemotypes."

Sutmuller went on to describe their in-house primary T cell assay, which involves fresh cells expanded in the lab and infected with an HIV encoding green fluorescent protein (GFP). Cells are rested to create latency and then drug activity is measured based on the extent to which the cells light up green. They're using this assay to screen medium sized libraries; it can handle about 2,000 compounds per week. He showed some data from one compound "229," which induced virus at about half the level of pan-stimulator PMA, and worked even better in combination with SAHA. The next step is to study these and other compounds in Roberto Speck's humanised mouse model, which involves 3TC and TDF given in food pellets and a long-acting version of TMC 278 that is delivered by weekly injection. They have seen good viral suppression and can recover latently infected CD4 cells using this system.

Among the other highlights from day two, Una O'Doherty from the University of Pennsylvania showed that CD8 T cells from elite controllers can kill what appear to be latently infected CD4 cells because they express the HIV Gag protein, just with much slower kinetics than seen with activated CD4 cells (and without causing spreading infection). O'Doherty suggested that perhaps this means latently infected CD4 cells aren't as invisible to the immune system as has been thought, which provoked some controversy because—as she happily acknowledged—it is not yet known whether the same holds true for latently infected CD4 cells from individuals on ART.

In an effort to hone in on which elements of the Berlin patient's treatment were necessary to achieving the apparent cure of HIV infection, the ever-curmudgeonly John Mellors (University of Pittsburgh) presented an analysis of ten people who had undergone myeloablative chemotherapy and autologous stem cell transplants for lymphoma. None of these individuals were cured of HIV infection, leading Mellors to conclude that in the case of Timothy Brown, the CCR5-negative transplant was important, possibly along with the

graft-versus-host disease Brown experienced. In the Q&A afterwards, workshop attendee Mike McCune from UCSF suggested that total body irradiation (TBI) might also have played a role.

Santiago Moreno (Hospital Ramon Y Cajal, Madrid, Spain) presented some preliminary evidence that the CCR5 inhibitor maraviroc may activate a protein complex named NF-kappaB when the drug binds to the CCR5 receptor. Because NF-kappaB activation can stimulate latent HIV, Moreno suggested that maraviroc might have anti-reservoir activity, as was previously suggested by a small uncontrolled pilot study conducted by Moreno's laboratory and reported at a symposium prior to the 2010 International AIDS Conference in Vienna. However, results from a randomised trial of ART intensification with maraviroc were debuted at the persistence workshop by Maria Puertas, and this study was unable to document any additional declines in HIV reservoirs associated with receipt of the drug (HIV DNA levels fell by ~8-fold in both arms).

In a session on acute HIV infection, Marty Markowitz from Aaron Diamond AIDS Research Center presented 96-week results from a 3-drug vs. 5-drug treatment study, showing essentially no significant differences in a variety of reservoir and immunological measures in blood and gut. There was a slight reduction in cell-associated HIV RNA levels at week 96 in the 5-drug group but Markowitz felt this was unlikely to be meaningful. Jintanat Ananworanich (HIV Netherlands Australia Thailand Research Collaboration) described a study involving treatment of people with very, very early HIV infection, in which 60 people have so far been enrolled, with an average time from screening to enrollment of just 3 days. This would not seem like much time for someone to process the news that they have become HIV infected and make a decision to enter a trial involving a multiple treatments and sampling from the peripheral blood, CNS and GI tract, but Ananworanich said "acceptance rates are quite high." Individuals were in what in the following Fiebig stages of seroconversion:

- 34% stage I: within 5 days of infection
- 9% stage II: within 10 days of infection
- 48% stage III: within 13 days of infection
- 9% stage IV: within 19 days of infection

24-week results on a subset of participants indicated significantly smaller reservoirs in blood and gut of stage I vs. III or IV, with total and integrated HIV DNA being undetectable in a proportion of the earliest-treated individuals.

The very last presentations of day two involved the tag team of Timothy Schacker (University of Minnesota), Courtney Fletcher (University of Nebraska) and Mario Stevenson (University of Miami) outlining very preliminary results from their small study of viral replication in anatomical and cellular reservoirs. A total of 12 individuals are enrolled, ART naive at baseline but then treated (mostly with TDF, FTC and ritonavir boosted atazanavir) and analysed regularly up to six months. Not all individuals have data available yet, and the number of individuals from whom data were reported varied between the different presenters. Courtney Fletcher looked at drug levels in nine people, finding that some drugs (particularly atazanavir, FTC and efavirenz) may not reach adequate levels in lymph nodes and gut. Mario Stevenson then showed that in some study participants, 2-LTR circles increased in lymph tissue after starting ART, in one case along with a rise in proviral DNA. In one other individual, levels of both 2-LTR circles and proviral DNA went down. Stevenson stated: "this does not necessarily denote ongoing replication" but proposed an alternative model in which a population of long-lived cells can generate virions that infect one more cell and that's it – just one cycle of replication, in other words. He stated this would not lead to viral evolution but could replenish the latent reservoir. In the Q&A, John Coffin from the NCI got up to the microphone and noted that since latency is a rare event in infected cells, and since Stevenson was saying these were single-cycle rounds of infection, the number of times latency would be created is not known, and may well not be often enough replenish the reservoir.

Timothy Shacker closed out the talks with a description of his efforts to correlate Fletcher's and Stevenson's results with measurements of viral RNA on the follicular dendritic cell (FDC) network in lymph tissue (using in situ hybridisation). Schacker created 3D graphs for several participants that included 2-LTR circle levels, DNA levels, levels of viral RNA on FDCs and, lastly, drug levels. There appeared to be correlations between the various measures, but how many people had evidence of ongoing HIV replication cycles was unclear. Schacker noted that there was a significant inverse correlation between levels of FTC diphosphate in lymph tissue and viral RNA on FDCs. Additional results from the expanded version of this study are needed in order to understand if this is a broadly applicable phenomenon, and whether poor tissue penetration of antiretrovirals represents an under-appreciated obstacle to curing HIV infection.

Day three: Margolis reaches a milestone, the crowd thins for functional cures

The major news on day three of the workshop was the presentation by David Margolis (University of North Carolina) of very preliminary results from the phase I/II study of the HDAC inhibitor vorinostat (SAHA). The trial has a complicated schema, largely due to the safety concerns of the FDA regarding the drug, which scores positive on the AMES mutagenic test (a red flag for regulators even though the significance is not fully understood).

The first step of the protocol involved screening potential participants to assess whether vorinostat could reactivate latent HIV from their CD4 T cells ex vivo. Thirteen individuals had ~4 billion lymphocytes extracted by leukopheresis, then sorted into discrete pools of 1 million purified resting CD4 cells each (ending up with 24-36 pools per participant). These pools were exposed to either vorinostat or no drug, and a mean level of HIV RNA per million cells (and a standard deviation) was calculated for each person (the assay used can measure down to 10 copies per million cells). Margolis noted that the statistical approach used to calculate the mean RNA levels is robust but complicated, and a paper explaining it is currently in press at an unnamed statistics journal.

Four of the thirteen people screened showed a statistically significant upregulation of HIV RNA expression in this analysis and were therefore recruited into the next step of the trial. A 200mg dose of vorinostat was given first for safety, followed by a 400mg dose to study pharmacokinetics and for analyses of histone acetylation and acetylation of the p21 gene (in other words, analyses of the effects of the drug on cellular genetic machinery and not HIV). The pharmacokinetic data mirrored that reported in cancer studies and cellular acetylation (both total and p21 gene) was maximal by 8 hours then trended down by 24 hours.

A final 400 mg dose of vorinostat was then administered with leukopheresis performed 4-6 hours afterward based on the

pharmacokinetic data indicating this would be around the time of maximum activity. No grade 1 or greater toxicities were seen, and HIV RNA expression increased compared to baseline in all four individuals by a mean of 4.4-fold (range: 3-6.6 fold). HIV RNA in peripheral blood was also assessed using a single copy assay but no change was detected, perhaps not surprisingly given that this was a single dose study.

Margolis was obviously very encouraged by the data and stated that they had successfully "demonstrated induction of full length HIV RNA expression within a window of time after a single vorinostat exposure." He concluded that obstacles to HIV RNA expression can overcome "at least in some cells." But he stressed that many questions remain, including:

- Is there an equal effect to multiple doses or does it become attenuated?
- How much exposure is needed?
- Should drug be administered continuously or pulsed?
- Will toxicities emerge?
- What number of cells is needed to measure relatively rare reactivation events?
- Does RNA expression lead to virion production or clearance of cell?
- Are additional inducers needed?
- Are additional interventions needed to clear the latently cells that have been induced to express HIV RNA?

The final session of the meeting was on functional cures. Dishearteningly, the crowd of attendees thinned noticeably but the first presenter, Paula Cannon, was undeterred. "This is the first time people are going to be talking about functional cures," she opened sunnily. "I know you're all very obsessed with the reservoirs but we don't really care about the reservoir - if there's a little bit of virus left in the body, so what?" Having stuck fear into the hearts of any remaining reservoir obsessives, she then outlined what she meant, highlighting three key goals for those in pursuit of a functional cure:

- Reducing the pool of HIV target cells and thereby reducing the harmful immune activation and inflammation that is central to pathogenesis.
- Creating HIV-resistant HIV-specific CD4 T cells.
- Taking advantage of HIV as a selection agent to drive the expansion of resistant cells.

Cannon went on to review the Sangamo zinc finger nuclease (ZFN) approach to deleting CCR5, the work conducted by her laboratory to adapt it to modify hematopoietic stem cells (HSCs), and the efficacy demonstrated in a published experiment in which humanised mice were engrafted with the CCR5-deleted stem cells and challenged with HIV. Work is now underway to advance the approach into HIV positive people who need stem cell transplants as treatment for lymphoma, in collaboration with John Zaia and David DeGusto from City of Hope who have previous experience of studying gene-modified HSCs in this setting. Cannon explained that preparation for the trial has involved switching from relatively easy-to-use HSCs obtained from fetal cord blood to rather more uncooperative adult stem cells. These cells are called mobilised peripheral blood stem precursor cells (mPSCs) and sampling involves giving G-CSF for four days then conducting apheresis to extract white blood cells, followed by ex vivo purification of CD34+ cells. This procedure has now been performed on 13 donors, obtaining 42 billion white blood cells of which around 0.5% were CD34+ cells; Cannon estimates that around 1% of the CD34+ cells are "true" stem cells. These mPSCs are now being used in mouse studies to address a number of issues prior to human testing.

One such experiment assessed whether pre-existing immunity to adenovirus might be problematic, because an adenovirus vector is used to deliver the zinc finger nuclease into the mPSCs. Mice were given a high titer of anti-adenovirus antibodies prior to delivery of the mPSCs and, encouragingly, no difference was seen in the extent of engraftment compared to controls given phosphate buffered saline (PBS).

Next steps include large scale tumorigenicity studies in "NOD scid gamma" (NSG) mice and evaluation of modified mPSC under "maximising" conditions to test the upper limit of on and off target effects (there is some evidence that ZFNs can disrupt genes other than the CCR5 target, particularly a similar region of the CCR2 gene). Mice given the maximised mPSCs will be kept for many months and extensively analysed for safety.

Following Paula Cannon, Carl June gave an update on the use of the same technology to modify CD4 T cells that are extracted from individuals with HIV using apheresis, expanded and modified in the laboratory, and reinfused into the same individual. Previous presentations of data from these phase I trials has generated considerable excitement, because the proportion of modified CD4 T cells persisting in the blood and gut of participants far exceeds the extremely modest levels obtained with prior gene therapies delivered using the same approach. Significant CD4 T cell count increases have also been documented out to nine months of follow up. Unusually, CD4:CD8 ratios have also significantly improved from an average of 0.5 at baseline to 1.5 at last analysis; this type of improvement is rarely observed as a result of ART, and may have implications in terms of improving long-term health because inverted CD4:CD8 ratios are a well-documented risk factor for illness in the HIV-uninfected elderly.

Most intriguing, however, is a trial involving a 12-week analytical treatment interruption (ATI). Data is now available from six individuals who have undergone the ATI and while all experienced a viral load rebound, levels began falling prior to the reinitiation of ART, which June noted was not the case in a prior gene therapy study involving an ATI (an evaluation of a candidate named VRX496).

One notable individual controlled viral load to below the level of detection (<50 copies/mL) before ART was restarted. This person turned out to be heterozygous for the delta32 CCR5 deletion, which means that the ZFNs could work more efficiently because only one CCR5 gene in each cell had to be disrupted in order for CCR5 expression to be completely abrogated (instead of two as is normally the case). Importantly, June found a significant correlation between the proportion of modified CD4 T cells and viral load control during the ATI. This suggests that an antiretroviral effect is achievable with the approach, and that the potency of the effect may be boosted if the proportion of modified cells can be increased.

In the Q&A period, June was asked if he had assessed whether gene-modified HIV-specific CD4 T cells may have contributed the viral load results; he replied that HIV-specific CD4 T cell responses have not yet been analyzed in the ATI trial.

The last two talks in the final workshop session addressed the development of methods that attempt to specifically target latent HIV and excise it from the DNA of infected cells (or damage the provirus in order to render it non-functional). On paper, at least, these approaches sound very appealing but it was clear that significant hurdles remain. Jan van Lunzen (University Medical Centre Hamburg-Eppendorf) discussed the modification of an enzyme called Cre recombinase to target HIV DNA. The modified version, dubbed Tre recombinase, has successfully excised proviral DNA from cells in vitro and work is now underway to study how it might be delivered. Next steps involve studies in humanised mice using a lentiviral vector to deliver the Tre recombinase to CD34+ stem cells; the vector is designed to be "self-inactivating" in cells that do not contain HIV DNA. As an aside, Jan van Lunzen also mentioned a patient of his who started ART during early infection, was treated for five years, then stopped six years ago, had a small viral load blip and has been undetectable ever since. HIV RNA cannot be found in blood, gut or CNS. According to van Lunzen, the individual has a "very strong HIV-specific CD4 response," and he highlighted the case as being similar to Christine Rouzioux's report of five individuals treated very early who have controlled viral load to undetectable levels off ART for an average of around five years. [12] These case reports may bode well for prospects for a functional cure, van Lunzen suggested.

Keith Jerome from the Fred Hutchinson Cancer Research Center recounted the efforts of his group to employ different enzymes, endonucleases, to target latent HIV. The idea in this case is to induce mutations in the HIV provirus in order to render it non-functional. Some success has been achieved in vitro but considerable challenges remain in terms of improving the efficiency of targeting and developing delivery methods that might be able to get the endonucleases to where they are needed. Jerome's work is now being supported by a Martin Delaney Collaboratory grant from NIH.

The last word at the 2011 persistence workshop was given to Nobel laureate Françoise Barré-Sinoussi, who outlined the International AIDS Society's development of a Global Scientific Strategy "Towards an HIV Cure" and encouraged audience members to attend an IAS symposium on the subject that will take place in Washington DC immediately ahead of the 2012 International AIDS Conference. Barré-Sinoussi also stressed the importance of the work and the need to continue the momentum which has placed curing HIV infection back at the top of the research agenda.

The 6th International Workshop on HIV Persistence, Reservoirs & Eradication Strategies is scheduled for 2013 in Miami.

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CONFERENCE REPORTS

13th European AIDS Conference (EACS)

12–15 October 2011, Belgrade, Serbia

Introduction

The 13th European AIDS Conference was held in Belgrade from 12-15 October.

Unfortunately abstracts are not yet available online, and although webcasts, podcasts and PowerPoint slides are available these require a login name and password (obtainable by email from the EACS secretariat).

The same login details can also be used to access training resources from a pre-meeting training for doctors and other resources. iPhone and iPad versions are accessible using the free Talks On The Go App.

http://www.europeanaidsclinicalsociety.org/

The following reports are included in this issue.

- Raltegravir achieves superiority over efavirenz after four years
- Higher plasma levels of tenofovir and darunavir but not efavirenz in older patients
- Ritonavir levels reduced with high fat meal (900 kcal)
- Transplacental transfer of raltegravir and delayed plasma clearance in preterm neonates

Raltegravir achieves superiority over efavirenz after four years

Simon Collins, HIV i-Base

Four year results from a five year, double-blind, randomised, non-inferiority study comparing raltegravir to efavirenz (each with tenofovir plus FTC) in treatment-naïve patients were presented by Jurgen Rockstroh.

The study design, matched baseline characteristics and safety and efficacy results from earlier analyses have already been presented at earlier meetings. The new subgroup analyses (including baseline CD4 <200 copies/mm3, viral load >100,000 copies/mL, hepatitis and demographic responses) focused on virological efficacy with discontinuations related to viral failure included but discontinuations for other reasons excluded and using an observed failure approach.

From approximately 280 patients in each arm at baseline, 223 (79%) and 197 (70%) completed the 192 week analysis, in the raltegravir and efavirenz arms respectively. Discontinuations were all less frequent in the raltegravir arm: virological failure (n=5 vs 8); side effects (n=13 vs 26); and loss to follow-up (n=8 vs 17)

At 192 weeks, the primary analysis of viral suppression to <50 copies/mL (non-completer=failure) saw raltegravir achieve statistical superiority compared to efavirenz [76% vs 67% (difference = +9.0; 95%CI 1.6, 16.4, p < 0.001: with the lower limit for non-inferiority set at –12% and superiority being achieved when both confidence intervals became greater than 1.0].

CD4 increases were + 60 cells/mm3 higher in the raltegravir arm (95%CI 24, 95).

Overall clinical events (96% vs 98%, p = 0.16), discontinuations due to drug-related events (5% vs 8%, p = 0.173) and serious adverse events (18% in each arm, p = 0.91) were similar between the two study groups, raltegravir was associated with significantly fewer drug-related events (50% vs 80%, p < 0.001).

There were no statistically significant differences in response between groups by gender, age, race/ethnicity, viral load >100,000 c/mL, CD4 > 200 cells/mm3, hepatitis coinfection or HIV sub-type. Raltegravir showed a significantly stronger virological response in the <100,000 c/mL group (93% vs 81%; difference +12; 95% CI 3, 22). Interpretation of a difference in favour of raltegravir when baseline CD4 was 50-<200 cells/mm3 is complicated by a trend to favour efairenz when CD4 counts were <50 cells/mm3.

C O M M E N T

These results support durability and safety of raltegravir. they also show that after week 192 raltegravir achieves superiority compared to efavirenz with the difference largely driven by efavirenz-related side effects.

The CD4 difference may also be important for patients with sub-optimal CD4 responses on other HAART combinations.

Ref: Rockstroh JK et al. Long-term efficacy of raltegravir or efavirenz combined with TDF/FTC in treatment-naïve HIV-1-infected patients: week-192 subgroup analyses from STARTMRK. 13th EACS, 12–15 October 2011, Belgrade. Abstract PS 1/1.

Higher plasma levels of tenofovir and darunavir but not efavirenz in older patients

Simon Collins, HIV i-Base

Several studies looked at the association between older age and antiretroviral pharmacokinetics (PK).

Tenofovir

Muge Cevik from the Chelsea and Westminster Hospital London reported results from a PK study suggesting that tenofovir clearance is significantly reduced with increasing age and resulting in higher drug levels (AUC and Ctrough). [1]

This included steady-state plasma levels from 52 men and 2 women (12 of whom were on PI/r-based combinations). Median age was 54 years (range 40–81 years) with only two people younger than 50. Samples were drawn randomly and population pharmacokinetics applied to predict values.

Tenofovir median clearance (CL/F), AUC (24hr) and Ctrough (C24) were 110.0 L/r (27.4–248.3). 2.2 mg.hr/L (1.0–9.0), and 0.06 mg/L (0.01–0.3) respectively.

Increasing age was significantly associated with slower clearance (p=0.0012), higher AUC (p=0.0012) and higher Ctrough (p=0.0017).

People older than 60 had significantly lower clearances (p=0.0447) and higher AUC (p=0.0457) than those younger than 60.

No PK differences were seen between PI and NNRTI based combinations (p=0.08).

Efavirenz and darunavir/ritonavir

A similar analysis was presented by Ahmed and colleagues from the same group at Chelsea and Westminster on the PK of efavirenz or darunavir/ritonavir used by older patients (median age was 54 years (range 27-77) and 56 years (28-76), respectively). [2]

In 70 men and 7 women taking efavirenz, no differences were seen in any PK parameter when comparisons were made between people older and younger than 50 (all p-values >0.05 for between age comparisons).

In 33 men and one woman taking darunavir/ritonavir (23 using once-daily) oral clearance was significantly lower in people over 50 years old (10.3 vs 13.0 L/h; p=0.027) with higher AUC (80.9 vs 61.6 mg.h/L; p=0.021) and Ctrough levels (1.9 vs 1.2 mg/L; p=0.008) than those younger than 50.

Once-daily vs twice-daily could not be assessed because of unequal age distribution between the two dosing regimens.

References

1. Cevik M et al. Tenofovir (TFV) pharmacokinetics (PK) in HIV infected individuals over 40 years of age. 13th EACS, 12–15 October 2011, Belgrade. Abstract PS 6/1.
2. Ahmed A et al. Efavirenz and Darunavir Plasma Concentrations in HIV-infected Patients Aged 50 Years or over. 13th EACS, 12–15 October 2011, Belgrade. Abstract PE6.2/1.

Ritonavir levels reduced with high fat meal

Simon Collins, HIV i-Base

Researchers at Makerere University, Kampala and the pharmocology group at Liverpool University reported a significant interaction between high fat meals and ritonavir as a booster in lopinavir/r (Kaletra).

Three meal conditions were studied in an open-label, three part, cross over study in 12 HIV positive people (6 men, 6 women) using lopinavir/r (2 x 400/100 mg tablets) as second-line therapy. Median (IQR) age and weight of patients was 48 (44 - 49) years and 62 (59-68) kgs.

Intensive PK sampling after a moderate (20 g fat) and high (36 g) fat meal (on Day 1 and 8 respectively) were compared to fasted state on Day 15.

Compared to the fasting, administration with a high fat meal resulted in 29% lower ritonavir AUC (geometric mean ratio 0.71; 90%CI 0.61-0.84) and 29% lower Cmax (GM 0.71; 90%CI 0.60-0.84) while C12 increased non-significantly by 12% (GM 1.12 (90%CI 0.94-1.33).

Ref: Lamorde M et al. - Steady-state exposure of ritonavir is reduced by a high fat meal in Ugandan patients receiving lopinavir plus ritonavir co-formulated tablets. 13th EACS, 12–15 October 2011, Belgrade. Abstract PE6.6/1 (BPD1/1).

Transplacental transfer of raltegravir and delayed plasma clearance in preterm neonates

Polly Clayden, HIV i-Base

Preterm birth is common in infants born to HIV positive mothers and is associated with an increased risk of mother to child transmission. Oral drug absorption in infants is unpredictable due to the immaturity of the gastro intestinal tract at this age. Preloading the foetus with maternal nevirapine (NVP) is common in these cases.

Raltegravir (RAL) is pregnancy category C and data to guide its use in pregnancy are limited. However, it has been used to achieve a rapid reduction in viral load before delivery, for preloading the foetus where poor oral absorption is anticipated and in cases where there is resistance or intolerance to other antiretrovirals.

RAL is absorbed rapidly (with a T max of about three hours) it takes two days to reach steady state concentrations and has an elimination terminal half-life of 9 hours. It uses the UGT 1A1 metabolic pathway. About half of the oral dose is excreted unchanged in the stool and 30% in the urine (about a third of which is as unchanged RAL and the remainder as the metabolite). There is considerable inter patient variability in its metabolism.

In an oral presentation, Aseel Hegazi from St Georges University Hospital, London showed three maternal infant case studies in which pregnant mothers of preterm neonates received RAL as part of their prevention of mother to child transmission (PMTCT) regimens. [1] The investigators looked at transplacental transfer of the drug and plasma clearance in the infants.

The same group has previously described the use of RAL in PMTCT regimens in mothers of three term infants. In these cases they found good transplacental transfer with higher concentrations in the infants than the mothers approximately three hours after delivery. [2] They also reported persistence of neonatal concentrations at three days (although below the therapeutic range). They suggested that poor neonatal and foetal maturity of the UGT-dependent pathways could account for this. And that it is possible that increased activity of UGT1A1, associated with progesterone, observed in pregnant women contributed to the disparity.

In the three cases of RAL use in preterm delivery, paired blood samples were taken as close as possible to delivery and then post partum. Maternal and neonatal RAL plasma concentrations were measured using liquid chromatography and mass spectrometry. Table 1 summarises these cases.

Dr Hegazi concluded that therapeutic RAL plasma concentrations (> 15ng/mL) might be persistent for up to five days in preterm neonates. She noted that this is longer than that observed in term infants and is probably linked to immature UGT1A1 mediated gluronidation. She suggested that maternal RAL preloading might be a good alternative to NVP where oral absorption is unreliable (particularly with preterm infants) and maternal options are limited

Table 1. Three cases of maternal RAL use in preterm delivery

	Case 1	Case 2	Case 3
Background ART and clinical context	NNRTI and 3TC resistance. Ritonavir intolerance. Poor adherence. Preeclampsia. Placenta praevia. Small for gestational age. Emergency Caesarean section.	Poor adherence. Small for gestational age. Emergency Caesarean section.	ART naïve. Started on ABC+AZT+3TC in 2nd trimester. Spontaneous rupture of membranes. Multiple fibroids. Emergency Caesarean section.
Time of RAL initiation	22 weeks gestation	14 hours pre-delivery. No repeat dose due to advanced labour and obstetric complications).	25.5 hours pre-delivery. Dose repeated 10.5 hours pre-delivery.
Viral load at RAL initiation (copies/mL)	5030	100	Undetectable
Background regimen	TDF + ATV	ATV/r + TDF + FTC (NVP + IV AZT at delivery)	EFV + TDF + 3TC (NVP + IV AZT at delivery)
Gestation at delivery	33 weeks + 2 days	30 weeks + 3 days	29 weeks + 5 days
Infant birth weight	1510 g	920 g	1365 g
Viral load at delivery (copies/mL)	Undetectable	55	Undetectable
Maternal RAL plasma concentrations (ng/mL)	2318 (6 hours post dose at delivery)	4870 (3.5 hours post dose, 11 hours pre-delivery) 64 (3 hours post dose, 1 hour post delivery)	300 (10.5 hours post dose at delivery)
Neonatal RAL plasma concentrations (ng/mL)	3781 (7 hours post maternal dose, 1 hour post delivery)	120 (16 hours post maternal dose, 2 hours post delivery) 67 (65 hours post maternal dose, 63 hours post delivery)	602 (11 hours post maternal dose, 0.5 hours post delivery)
Neonatal:maternal RAL plasma concentrations	1.6	1.9	2.0

C O M M E N T

These case studies are interesting and this use of RAL could prove important. RAL used this way is likely to be mentioned in the next BHIVA guidelines (although data is very sparse so evidence will be weak).

IMPAACT 1097 is a washout (passive) PK and safety study designed to investigate this phenomenon in neontates. It is the first clinical trial of an investigational drug to look at neonatal PK. It is recruiting mothers already receiving RAL in pregnancy and the infants will be sampled at intervals up to 30 to 36 hours after dosing.

After a review of PK and safety data from this and IMPAACT1060 – which is investigating this drug in children in de-escalated age bands with those below two years, receiving a granule formulation, now being studied – the company is planning a study of infants born to HIV positive mothers from immediately after birth until their status has been confirmed.

References

1. Hegazi A et al. Raltegravir in the prevention of mother to child transmission of HIV: effective transplacental transfer and delayed plasma clearance observed in preterm neonates. 13th EACS, 12–15 October 2011, Belgrade. Oral abstract PS 6/7.
2. Mckeown D A et al. High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women AIDS. 24 September 2010. Volume 24. Issue 15. p 2416–2418.

CONFERENCE REPORTS

51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

17–20 September 2011, Chicago

Introduction

The annual ICAAC conference in recent years has had a reduced focus on HIV research but still includes studies that are interesting to highlight.

Unfortunately the conference restricts public access to this research. Although abstracts available online (for a short time) the database to access abstracts is not very user friendly and the long URLs often change, making referencing problematic.

Also, few, if any studies are supported by webcasts or the option to view slides or full PDF posters.

The following studies are largely thanks to natap.org.

- Monitoring kidney function change with cobicistat
- Intracellular raltegravir concentrations better with twice-daily than once-daily dosing

Monitoring kidney function change with cobicistat

Simon Collins, HIV i-Base

Cobicistat is a pharmacokinetic (PK) booster currently in phase 3 studies that unlike ritonavir has no direct antiretroviral activity. This Gilead booster might facilitate a wider range of coformulated boosted medicines: with elvitegravir and Quad (boosted elvitegravir plus Truvada) and with products developed by other companies (darunavir and atazanavir).

An early caution is that cobicistat produces significant reductions in estimated glomerular filtration rate (eGFR). These do not indicate clinically significant changes but will pose a problem for interpretation of routine monitoring tests where clinical changes in eGFR are a concern.

If average actual GFR (aGFR) is used to monitor cobicistat, determined by iohexol clearance (a probe drug excreted almost exclusively by glomerular filtration), no changes are observed.

At ICAAC, Gilead researchers presented results from a placebo controlled study in 36 HIV negative participants with normal renal function (eGFR >80 mL/min) and 18 HV negative participants with mildly impaired renal function (eGFR 50-79 mL/min).

Participants with normal function were randomised (12 per group) to one of three groups: 150 mg cobicistat + placebo; 100 mg ritonavir + placebo; or double placebo for 7 days, with both eGFR and aGFR measured at baseline, day 7 and day 14 (following a 7 day washout). All participants with reduced renal function took cobicistat for seven days with similar monitoring.

Independent of baseline eGFR, volunteers taking cobicistat experienced significant average reductions in eGFR by day seven which resolved seven days after discontinuation, with but showed no significant changes in aGFR (see Table 1). Similar changes were seen using either Cockcroft-Gault or MDRD to calculate eGFR. Participants taking ritonavir or placebo showed no significant changes in either measure.

Table 1: Changes in aGRF and aGFR (mL/min) in HIV negative people using cobicistat for 7 days

	aGFR		eGFR (Cockcroft-Gault)	
Baseline eGFR	day 7	day 14	day 7	day 14
>80 mL/min	-2.7 (NS)	-2.5 (NS)	-9.9 ($p<0.05$)	+1.4 (NS)
50-79 mL/min	-3.6 (NS)	-5.8 (NS)	-11.9, $p<0.05$	-2.2 (NS)

The researchers interpret these findings to show that true GFR is not affected by cobicistat which affects proximal tubular secretion of creatinine.

While these results are reassuring in terms of clinical impact of cobicistat it is unclear how patients using other medications that affect eGFR would be managed in order not to misinterpret a genuine impact on real GFR.

Source: Mascolini M. Kidney Function Change With Cobicistat Calculated in HIV-Negative Volunteers. NATAP.org

http://www.natap.org/2011/ICAAC/ICAAC_66.htm

References

1. German P et al. Effect of cobicistat on glomerular filtration rate (GFR) in subjects with normal and impaired renal function. 51st ICAAC, 17-20 September 2011, Chicago. Abstract H2-804.

Intracellular raltegravir concentrations better with twice-daily than once-daily dosing

Mark Mascolini, NATAP.org

Intracellular concentrations of raltegravir stayed above the 95% effective concentration (EC95) in higher proportions of people taking this integrase inhibitor twice daily than in those taking it once daily, according to results of a 13-person study [1]. The average intracellular-to-plasma ratio was 0.37.

Raltegravir is licensed for adults at a dose of 400 mg twice daily with or without food. A randomised trial of twice- versus once-daily raltegravir for antiretroviral-naive people found that 318 of 382 (83%) in the once-daily group versus 343 of 386 (89%) in the twice-daily group had a viral load below 50 copies/mL after 48 weeks, a significant difference (-5.7%, 95% confidence interval -10.7 to -0.83, P = 0.044) [2]. The investigators concluded that “despite high response rates

with both regimens, once-daily raltegravir cannot be recommended in place of twice-daily dosing."

The study of plasma and intracellular raltegravir concentrations involved 12 people taking 400 mg of raltegravir twice daily and 1 taking 800 mg once daily for more than 1 week [1]. People on the twice-daily dose who had a viral load below 50 copies were offered a switch to once-daily dosing for at least 3 days so the investigators could assess raltegravir after once-daily dosing. Six people agreed.

In the twice-daily group, the researchers collected 26 paired samples of plasma and peripheral blood mononuclear cells (PBMCs) 2, 4 or 6, and 12 hours after dosing. In the once-daily group they collected 12 paired samples over the 24-hour dosing interval. Among people taking raltegravir twice daily, 3 had a detectable viral load; 2 of these were considered blips, and one load of 2649 copies came during the first 6 weeks of treatment.

No one taking raltegravir twice daily had a plasma trough concentration below the EC95 (14 ng/mL). Three of 12 had an intracellular trough below the EC95, at 7, 11.1, and 13.3 ng/mL.

Two of 6 people taking raltegravir once daily had a plasma trough below the EC95, at 7 and 13.8 ng/mL. Three of these 6 had an intracellular trough below the EC95, at 1.56, 4.06, and 6.56 ng/mL.

The mean ratio of intracellular-to-plasma concentrations was 0.37 and did not change over time. The ratio was higher than reported previously, probably because cell-wash steps in older methods flushed out some intracellular drug.

The researchers proposed that the high plasma and intracellular troughs with twice-daily raltegravir "may contribute to the efficacy observed with this regimen."

UK researchers just published results of a 24-person study comparing plasma and intracellular raltegravir concentrations with once- and twice-daily dosing, with or without darunavir/ritonavir [3]. Study participants were taking 400 mg of raltegravir twice daily for at least 21 days. They added 800/100 mg of darunavir/ritonavir once daily for 14 days. During that 14-day period, people were randomised to continue twice-daily raltegravir (group 1) or to switch to 800 mg once daily (group 2).

Geometric mean ratios (and 90% confidence intervals) of raltegravir area under the concentration-time curve without and with darunavir/ritonavir for group 1 were 0.90 (0.73 to 1.44) in plasma and 1.02 (0.81 to 1.67) in cells and for group 2 were 1.21 (1.03 to 1.77) in plasma and 1.27 (1.07 to 1.94) in cells. These researchers concluded that "no remarkable interactions between darunavir/ritonavir and raltegravir in plasma or cells were seen."

References

1. Sandkovsky US, Swindells S, Robbins BL, Nelson SR, Acosta EP, Fletcher CV. Measurement Of plasma and intracellular concentrations of raltegravir in patients with HIV infection. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). September 17-20, 2011. Chicago. Abstract A1-1738b.
2. Eron JJ Jr, Rockstroh JK, Reynes J, et al. Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial. Lancet Infect Dis. 2011 Sep 19. http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(11)70196-7/fulltext
3. Jackson A, Watson V, Back D, et al. Plasma and intracellular pharmacokinetics of darunavir/ritonavir once daily and raltegravir once and twice daily in HIV-infected individuals. J Acquir Immune Defic Syndr. 2011 Sep 15. Epub ahead of print. http://www.ncbi.nlm.nih.gov/pubmed/21926632

ANTIRETROVIRALS

Tenofovir label extended to paediatric indication

On 18 January 2012, the FDA extended the product indication for tenofovir disoproxil fumarate (Viread) to include dosing information in paediatric patients 2 to less than 18 years of age.

An oral powder (40 mg per 1 gram of oral powder) formulation and 150 mg, 200 mg and 250 mg tablets were also approved to support dosing in paediatric patients.

The major changes to the product labeling include information on dosing plus efficacy and safety concerns based on clinical studies.

These include:

DOSING

- Recommended dose in paediatric patients 2 years of age and older is 8 mg of tenofovir DF per kilogram of body weight (up to a maximum of 300 mg) once daily administered as oral powder or tablets. Tables 1 and 2 of the product labeling contain dosing recommendations for tenofovir oral powder and tablets based on body weight. Weight should be monitored periodically and the tenofovir dose adjusted accordingly.
- Tenofovir oral powder should be measured only with the supplied dosing scoop. One level scoop delivers 1 g of powder, which contains 40 mg of tenofovir DF. Tenofovir oral powder should be mixed in a container with 2 to 4 ounces of soft food not requiring chewing (e.g. applesauce, baby food, yogurt). The entire mixture should be ingested immediately to avoid a bitter taste. Do not administer tenofovir oral powder in a liquid as the powder may float on top of the liquid even after stirring. Further patient instructions on how to administer tenofovir oral powder with the supplied dosing scoop are provided in the FDA-approved patient labeling.
- Tenofovir is also available as tablets in 150, 200, 250 and 300 mg strengths for paediatric patients who weigh >/=17 kg and who are able to reliably swallow intact tablets. The dose is one tablet once daily taken orally, without regard to food.
- There are no data to recommend use of tenofovir tablets 150, 200 or 250 mg or tenofovir oral powder in patients with renal impairment.

SAFETY AND EFFICACY

The safety and efficacy data of tenofovir in paediatric patients is supported by data from two randomised trials (Studies 352 and 321). This involved only 184 treatment-experienced children (aged 2 to <18 years), only half of who received tenofovir and half received d4T or AZT. Tenofovir was later provided to these children.

Bone Mineral Density (BMD)

Bone effects were similar to those observed in adult subjects. Under normal circumstances BMD increases rapidly in paediatric patients. In Study 352 (2 to less than 12 years), the mean rate of BMD gain in lumbar spine at Week 48 was similar between the tenofovir and the d4T or AZT treatment groups. Total body BMD gain was less in the tenofovir compared to the d4T or AZT treatment group. One

tenofovir-treated subject and none of the d4T or AZT-treated subjects experienced significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline in BMD Z-scores were -0.012 for lumbar spine and -0.338 for total body in the 64 subjects who were treated with tenofovir for 96 weeks. In Study 321 (12 to less than 18 years), the mean rate of BMD gain at Week 48 was less in the tenofovir compared to the placebo treatment group. Six tenofovir treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were -0.341 for lumbar spine and -0.458 for total body in the 28 subjects who were treated with tenofovir for 96 weeks. In both trials, skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir-treated paediatric subjects suggest increased bone turnover, consistent with the effects observed in adults.

Eighty-nine paediatric subjects received tenofovir in Study 352 (48 who were initially randomised to tenofovir and 41 who were initially randomised to continue stavudine or zidovudine and then received tenofovir in the extension phase) for a median exposure of 104 weeks. Of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these four subjects presented with hypophosphatemia and also had decreases in total body or spine BMD Z score.

For full details please refer to the new label:

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

FDA approve US paediatric dose for raltegravir

On 21 December 2011, the FDA approved dosing recommendations for raltegravir (Isentress) for paediatric patients ages 2 to 18 years and weighing at least 10 kg.

In addition a 100 mg scored chewable tablet and 25 mg chewable tablet was approved for use in paediatric patients.

Safety, efficacy and formulation data were from the IMPAACT P1066 Phase I/II study in 126 treatment experienced children (age 2 to 18 years) who received either the 400 mg film-coated tablet formulation (6 to 18 years of age) or the chewable tablet formulation (2 to less than 12 years of age). Raltegravir was administered with an optimised background regimen.

The Dosage and Administration section includes the following dosing recommendations and dosing recommendations for pediatrics. Main changes to the product label are also included below.

General Dosing Recommendations

- Raltegravir Film-Coated Tablets and Chewable Tablets can be administered with or without food
- Maximum dose of chewable tablets is 300 mg twice daily.
- Raltegravir Chewable Tablets may be chewed or swallowed whole.
- Raltegravir Film-Coated Tablets must be swallowed whole.
- Because the formulations are not bioequivalent, the chewable tablets should NOT be substituted for the 400 mg film-coated tablet.
- During coadministration of raltegravir 400 mg film-coated tablets with rifampin, the recommended dosage of raltegravir is 800 mg twice daily in adults. There are no data to guide co-administration of raltegravir with rifampin in patients below 18 years of age. All interaction studies were performed in adults

PAEDIATRIC DOSING

Dosing is recommended based on age and weight:

- 12 years of age and older: One 400 mg film-coated tablet orally, twice daily
- 6 to less than 12 years of age:

If at least 25 kg in weight:

- One 400 mg film-coated tablet orally, twice daily **OR**
- Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1 – please refer to prescribing information for details.

If less than 25 kg in weight:

- Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1 - Please refer to prescribing information for details.

- 2 to less than 6 years of age:

If at least 10 kg in weight:

- Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1 - Please refer to prescribing information for details.

WARNINGS AND PRECAUTIONS

Raltegravir chewable tablets contain phenylalanine, a component of aspartame. Each 25 mg raltegravir chewable tablet contains approximately 0.05 mg phenylalanine. Each 100 mg raltegravir chewable tablet contains approximately 0.10 mg phenylalanine. Phenylalanine can be harmful to patients with phenylketonuria.

ADVERSE REACTIONS

In the IMPAACT P1066, frequency, type and severity of drug related adverse reactions through week 24 were comparable to those observed in adults.

One patient experienced drug related clinical adverse reactions of Grade 3 psychomotor hyperactivity, abnormal behavior and insomnia; one patient experienced a Grade 2 serious drug related allergic rash.

One patient experienced drug related laboratory abnormalities, Grade 4 AST and Grade 3 ALT, which were considered serious.

The following information was added to Section 12.3 Pharmacokinetics:

- Under Absorption: Based on a formulation comparison study in healthy adult volunteers, the chewable tablet has higher oral bioavailability than the film-coated tablet
- Under Effect of Food on Oral Absorption: Administration of chewable tablet with high fat meal led to an average 6% decrease in AUC, 62% decrease in Cmax and 188% increase in C12hr compared to administration in the fasted state. Administration of the chewable tablet with a high fat meal does not affect raltegravir pharmacokinetics to a clinically meaningful degree

and the chewable tablet can be administered without regard to food

- Special Populations: The doses recommended for HIV-infected children and adolescents 2 to 18 years of age resulted in a pharmacokinetic profile of raltegravir similar to that observed in adults receiving 400 mg twice daily. A Table was added to the package insert to display the raltegravir steady state pharmacokinetic parameters in paediatric patients.

CLINICAL STUDIES

The median age of the 96 study participants in IMPAACT P106 receiving the recommended raltegravir dose was 13 (range 2 to 18) years, 51% female, 34% Caucasian, and 59% Black. At baseline, mean plasma HIV-1 RNA was 4.3 $\log_{10}$ copies/mL, median CD4 cell count was 481 cells/mm3 (range: 0 – 2361) and median CD4% was 23.3% (range: 0 – 44). Overall, 8% had baseline plasma HIV-1 RNA >100,000 copies/mL and 59% had a CDC HIV clinical classification of category B or C. Most subjects had previously used at least one NNRTI (78%) or one PI (83%).

Ninety-three (97%) subjects completed 24 weeks of treatment (3 discontinued due to non-compliance). At Week 24, 54% achieved HIV RNA <50 copies/mL; 72% achieved HIV RNA <400 copies/mL or =1 $\log_{10}$ HIV RNA drop from baseline. The mean CD4 count (percent) increase from baseline to Week 24 was 119 cells/mm3 (3.8%).

Source: FDA HIV/AIDS Update (21 December 2011).

For full details please refer to the updated prescribing information:

http://dailymed.nlm.nih.gov/dailymed/about.cfm

FDA approve paediatric dose for darunavir

On December 16, 2011, The Food and Drug Administration approved an oral suspension formulation of darunavir (Prezista). Darunavir is now available as a 100 mg/mL oral suspension.

Additionally, the product labeling was updated to provide dosing recommendations for paediatric patients ages 3 to less than 6 years of age and for adult and paediatric patients greater than 6 years of age who can not swallow darunavir tablets.

Treatment-naïve adults and treatment experienced adults with no darunavir resistance associated substitutions can take darunavir 8 ml once daily with 1.25 ml of ritonavir once daily with food. The 8 mL dose should be taken as two 4 mL administrations with the included oral dosing syringe.

For treatment-experienced adults with at least one darunavir resistance associated substitution the dose for oral suspension is 6 mL twice daily with 1.25 mL ritonavir twice daily with food.

For paediatric patients, dosing with oral suspension or tablets is based on weight. Please refer to full prescribing information for details. Do not use darunavir/ritonavir in paediatric patients below 3 years of age.

Section 6 Adverse Reactions (ADRs) was updated as follows:

- ADRs to darunavir/ritonavir (all grades, >/= 3%), excluding lab abnormalities, were diarrhea (19%), vomiting (14%), rash (10%).
- There were no Grade 3 or 4 laboratory abnormalities considered as ADRs in this study.

Section 14: Clinical Studies was updated to reflect the results from the paediatric trial as follows:

Study TMC114-C228

Treatment-experienced paediatric subjects between the ages of 3 and less than 6 years and weighing greater than or equal to 10 kg to less than 20 kg received darunavir oral suspension with ritonavir oral solution plus background therapy consisting of at least two active non-protease inhibitor antiretroviral drugs. Twenty-one subjects received at least one dose of darunavir/ritonavir.

The 21 subjects had a median age of 4.4 years (range 3 to less than 6 years), and were 48% male, 57% Black, 29%, Caucasian and 14% other. The mean baseline plasma HIV-1 was 4.34 $\log_{10}$ copies/mL, the median baseline CD4+ cell count was 927 x 10^6 cells/l (range: 209 to 2,429 x 10^6 cells/l) and the median baseline CD4+ percentage was 27.7% (range: 15.6% to 51.1%). Overall, 24% of subjects had a baseline plasma HIV-1 RNA greater than or equal to 100,000 copies/mL. All subjects had used greater than or equal to 2 nucleoside reverse transcriptase inhibitors (NRTIs), 62% of subjects had used greater than or equal to 1 non-nucleoside reverse transcriptase inhibitors (NNRTI) and 76% had previously used at least one HIV protease inhibitor (PI).

Twenty subjects (95%) completed the 24 week period. One subject prematurely discontinued treatment due to vomiting assessed as related to ritonavir.

The proportion of subjects with HIV-1 RNA less than 50 copies/mL and less than 400 copies/mL was -57% and 81%, respectively. The mean change in CD4+ percentage from baseline was 4%. The mean change in CD4+ cell count from baseline was 109 x 10^6 cells/L.

Dose recommendations from the two studies were based on the following:

- Similar darunavir plasma exposures in children compared to adults, and
- Similar virologic response rates and safety profile in children compared to adults

Source: FDA HIV/AIDS Update (16 December 2011).

For full details please refer to the updated prescribing information:

http://dailymed.nlm.nih.gov/dailymed/about.cfm

Efavirenz dose increase to 800 mg QD with rifampin in patients >50 kg

On 6 January the FDA approved revisions to the efavirenz (Sustiva) package insert to include dosing with efavirenz and rifampin. The Dosage and Administration and Drug Interaction sections of the package insert were updated to include the following:

If Sustiva is coadministered with rifampin to patients weighing 50 kg or more, an increase in the dose of Sustiva to 800 mg once daily is recommended.

The recommendation to increase the dose of efavirenz to 800 mg in patients weighing 50 kg or more when efavirenz is co-administered with rifampin is based on empirical data from two drug-drug interaction trials (one trial in healthy volunteers and one trial in HIV-1 infected patients) and semi-mechanistic population pharmacokinetic modeling. The population pharmacokinetic model was constructed using data collected in the drug-drug interaction trials and single- and multiple dose pharmacokinetic data of efavirenz from other healthy volunteer trials.

The data from the drug-drug interaction trials showed that rifampin decreased the exposure of efavirenz 600 mg once daily. Further, the systemic exposure of efavirenz, when efavirenz 800 mg was coadministered with rifampin, was similar to the systemic exposure of efavirenz when efavirenz 600 mg once daily was given alone. The results from the population pharmacokinetic analysis were consistent with the empirical data.

Source: FDA HIV/AIDS Update (06 January 2012).

For full details please refer to the updated prescribing information:

http://dailymed.nlm.nih.gov/dailymed/about.cfm

FDA updates US label for darunavir for serious rash

On 19 October 2011 the FDA approved updates to the darunavir (Prezista) package insert to include 192-week results from the Phase 3 registrational studies.

In addition, section 5.3 Severe Skin Reactions now includes the following text about combinations that include darunavir/ritonavir plus raltegravir:

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing darunavir/ritonavir + raltegravir compared to subjects receiving darunavir /ritonavir without raltegravir or raltegravir without darunavir /ritonavir. However, rash that was considered drug related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

Source: FDA HIV/AIDS Update - Prezista label update includes 192-week safety, resistance and efficacy data (21 October 2011).

FDA updates US label for raltegravir due to serious rash

On 2 November 2001 the US Food and Drug Administration (FDA) approved updates to the package information and patient leaflet for raltegravir (Isentress).

Postmarketing reports have included cases of severe, potentially life-threatening, and fatal skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure.

Patients should be advised to immediately contact their healthcare provider if they develop rash. They should discontinue raltegravir (with medical supervision) and other suspect agents immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema).

Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping raltegravir treatment or other suspect agents after the onset of severe rash may result in a life-threatening reaction.

Cerebellar ataxia and drug rash with eosinophilia and systemic symptoms have been added as side effects.

Patients should understand that if severe rash occurs, they will be closely monitored, laboratory tests will be ordered and appropriate therapy will be initiated.

Source: FDA HIV/AIDS Update - Isentress (raltegravir) package insert updated, (02 November 2011).

Lopinavir concentrations suboptimal at reduced dose of lopinavir/ritonavir 200/50 mg twice daily

Polly Clayden HIV i-Base

An article published online ahead of print in JAIDS, November 2011, shows findings from a pharmacokinetic (PK) study to evaluate a lower dose of lopinavir/ritonavir (LPV/r) than that currently approved.

Reshmie A Ramautarsing and HIV-NAT colleagues from Thailand and the Netherlands performed a two-arm crossover study including 20 HIV-positive Thai patients. Participants receiving a PI-containing regimen (virlogically suppressed <50 copies/mL for at least 4 weeks at enrollment) were randomised receive branded or generic LPV/r dosed at 200/50mg twice daily, in addition to an NRTI backbone.

Due to a compulsory license, Abbott only markets the paediatric formulation (100/25 mg) of LPV/r in Thailand. The Indian generic company, Matrix, has developed a 200/50 mg tablet formulation of LPV/r, which is currently used at the standard dose (400/100 mg twice daily).

Following sampling for PK analysis at week 2, all participants crossed over from their initial study arm to the other. A second sampling was performed at week 4. Participants continued with their study regimen until week 12, when they resumed their pre-study regimen.

There were 10 participants in each arm with a median age, weight and CD4 count of 38.6 (IQR 34.4 – 47.5) years, 59.8 (52.9 – 62.0) kg and 578 (476 – 795) cells/mm3, respectively. The majority (n=17) received standard dose LPV/r and the remainder saquinavir containing regimens prior to the study. None were lost or discontinued their medication during follow up.

The investigators reported comparable bioequivalence for the generic and branded formulations, with point estimates and 90% CI of the geometric mean ratios of 1.00 (0.92-1.09), 1.01(0.90-1.07) and 0.87 (0.76-1.31) for the AUC0-12, Cmax and Ctrough respectively.

Overall 10/40 (25%) samples had subtherapeutic (<1.0 mg/L) plasma concentrations of LPV. These were detected in 8 patients: 2 had subtherapeutic levels measured with both branded and generic

formulations, 4 with branded and 2 generic. The lowest concentration was 0.25 mg/L. The investigators noted that all participants reported >90% rates of adherence and 7/8 reported 100% at the time that subtherapeutic plasma concentrations were found.

A comparison of PK parameters for different doses and formulations of LPV/r, using historical data from the same research group, revealed decreased concentrations at lower doses. When compared to LPV/r soft gel capsule (SGC) 400/100 mg twice daily, a dose of LPV/r SGC 266/66 twice daily resulted in 44.1%, 36.0% and 49.1% decreases in LPV concentrations for AUC0-12, Cmax and Ctrough respectively. Using LPV/r generic tablets 200/50mg twice daily decreased the same parameters by 63.5%, 56.6% and 70.2% respectively.

At week 12 all participants remained virologically supressed <50 copies/mL.

The researchers noted that LPV plasma concentrations are dependent on the RTV dose to a greater extent than some other PIs and in this study they had reduced both the LPV and RTV dose, which may explain the subtherapeutic LPV concentrations. They wrote that other dose reduction studies suggest that 200 mg of LPV is sufficient if there is a sufficient boosting dose of RTV (100 mg).

The researchers also noted that this bio-equivalence analysis of LPV/r, although not using the approved 400/100 mg twice-daily dose, demonstrated that the generic and branded tablets result in comparable PK parameters. They wrote: "These data are particularly important for clinicians working in settings where the branded tablets are not available due to compulsory licensing or cost. The availability of safe and effective generic alternatives to branded second line treatment will play an important role in the scaling up of second line treatment in low- and middle-income countries."

C O M M E N T

That the generic and originator products are bioequivalent is important.

Previous PK trials have shown that the dose of ritonavir affects LPV levels. In the first dose-ranging trial by Abbott, the dose with the best efficacy and safety profile was 200/100 mg twice daily. If we had 50 mg ritonavir tablets (see below), we could get back to this dose and it may be worth doing more studies.

However, the WHO and Clinton Foundation are more interested in ATV/r and DRV/r, which showed better efficacy and safety profiles than LPV/r (in the CASTLE and ARTEMIS trials, respectively).

Ref: Ramautarsing RA et al. Neither branded nor generic lopinavir/ritonavir produces adequate lopinavir concentrations at a reduced dose of 200/50mg BID. J Aquir Immune Defic Syndr. Publish ahead of print. DOI: 10.1097/QAI.0b013e3182ba736.

Switching to 50mg ritonavir dose for selected protease inhibitors

Polly Clayden HIV i-Base

Although not appropriate for LPV (see previous article), a 50mg boosting dose of RTV may be sufficient for selected PIs, argue researchers from the University of Liverpool and Chelsea and Westminster in a letter to the editor published in the December 15 2011 edition of JAIDS.

Lower doses of RTV may be better tolerated, cheaper and easier to co-formulate with PIs than the current dose.

Andrew Hill and colleagues identified four crossover PK studies evaluating 50 vs 100mg of RTV. These included boosting once daily atazanavir (ATV), 300/50 vs 300/100mg and once daily darunavir (DRV) 800/50 vs 800/100mg. The other two studies indentified by the researchers were with saquinavir and amprenavir, which are less commonly used PIs and not preferred options, particularly in resource-limited settings.

These small PK studies – conducted with 13 and 18 participants for ATV and DRV respectively – showed bioequivalent AUC and Cmax concentrations of both drugs using the lower and higher RTV doses. But Cmin concentrations were slightly lower when boosted with the 50 mg dose of RTV. See Table 1: PK parameters of ATV and DRV boosted with 50 and 100mg of RTV.

Table 1: PK parameters of ATV and DRV boosted with 50 and 100mg of RTV

PI (Ref)/dose	Cmax mg/L	AUC mg.h.L	Cmin mg/L
ATV 300/50 mg	5.07	47.1	0.59
ATV 300/100 mg	5.19	50.6	0.79
DRV 800/50 mg	6.14 (1.32)	68.5 (20.5)	1.67 (0.64)
DRV 800/100 mg	6.17 (1.27)	77.2 (23.5)	2.12 (0.80)

Mean PKs of boosted PI (SD)

The researchers explained that the clinical significance of the lower Cmin levels was not known and this would need to be investigated in larger studies including efficacy endpoints. They added that small differences in RTV boosting doses might have different consequences in treatment naïve and experienced patients.

They noted that as RTV is only marketed as a 100 mg tablet, these studies were conducted using the liquid formulation. If a 50mg heat stable tablet of RTV could be manufactured or 50 mg coformulated with either PI, new bioequivalence trials would be needed to ensure the boosting effects were similar to those achieved with the liquid.

A 50mg RTV tablet would also be very useful for paediatric dosing, as the liquid is expensive, impractical (particularly for resource limited settings) and tastes dreadful.

They concluded that if lower doses of RTV are able to achieve bioequivalence there is a strong justification for the development of a 50mg tablet and/or coformulations of RTV with these PIs.

C O M M E N T

Once again, the 50 mg RTV tablet really would be useful in paediatrics.

The generic companies should be able to make 50 mg tablets and get approval by showing that 2 x 50 mg tablets are bioequivalent to an Abbott 100 mg tablet.

Ref: Hill A et al. Should we switch to a 50mg boosting dose of ritonavir for selected protease inhibitors? J Acquir Immune Defic Syndr. Volume 58. Number 5. December 15, 2011.

http://journals.lww.com/jaids/Citation/2011/12150/Should_We_Switch_to_a_50_mg_Boosting_Dose_of.18.aspx

New formulations, acquisitions and company announcements

Simon Collins, HIV i-Base

The last two months have been a lively time for pharmaceutical industry announcements concerning Fixed Dose Combinations (FDCs) and new compounds in the HIV and hepatitis pipelines.

Integrase FDC Quad submitted to the FDA

At the end of October, Gilead submitted a new drug application (NDA) to the US regulatory agency (FDA) for its four-drug formulation of elvitegravir, cobicistat, tenofovir and FTC (Quad). This is based on 48-week data from two Phase 3 studies.

Three weeks later Quad was also filed with the European Medicines Agency (EMA).

If these applications are given a fast track review a decision will be made by both agencies within six months.

Reference: Gilead press release: Gilead Submits New Drug Application to U.S. FDA for Once-Daily, Single-Tablet "Quad" HIV Regimen (27 October 2011).

Planned co-formulations of cobicistat with atazanavir, darunavir and darunavir/FTC/GS7340

On 26 October, Bristol-Myers Squibb (BMS) announced that it has entered an agreement to develop and market an FDC of its protease inhibitor atazanavir (Reyataz) with a pharmacokinetic booster cobicistat, currently in development with Gilead. [1]

Phase 2 and 3 studies of atazanavir using cobicistat boosting are ongoing in treatment-naïve patients.

Cobicistat has a similar inhibitory impact on cytochrome P450 3A (CYP3A) and similar side effect profile to ritonavir.

Earlier this year a similar agreement was reached between Gilead and Tibotect to produce an FDC of darunavir with cobicistat. [2]

The press release also referred a further collaborate to produce an FDC of darunavir plus FTC together with cobicistat plus the new tenofovir prodrug (GS7340).

References

1. Press release: Bristol-Myers Squibb and Gilead Sciences announce licensing agreement for development and commercialisation of new Fixed Dose Combination pill for People Living with HIV. (26 October 2011).
2. Press release: Gilead Sciences announces agreement with tibotec Pharmaceuticals to develop and commercialise a new fixed-dose combination of cobicistat and darunavir (Prezista). (28 June 2011).

Gilead license integrase inhibitor compounds from Boehringer Ingelheim

Gilead acquired a license for exclusive worldwide rights for the research, development and commercialisation of its novel non-catalytic site integrase inhibitors (NCINIs) for HIV. This includes the lead compound BI 224436, which has been evaluated in a Phase 1a dose-escalation study to assess bioavailability and pharmacokinetics in healthy volunteers.

NCINIs inhibit HIV integrase by binding to a novel site, distinct from the catalytic site used by the current class of integrase inhibitors, and therefore may possess a differentiated resistance profile from raltegravir or elvitegravir.

Ref: Press statement: Gilead and Boehringer Ingelheim Sign License Agreement for Novel HIV Non-Catalytic Integrase Inhibitors. (05 October 2011).

Gilead spends $11 billion to buy Pharmasset

Finally, on 21 November 2011, Gilead announced that it would acquire Pharmasset for the not insignificant cost of $11 billion from 'cash on hand, bank debt and senior unsecured notes'.

Pharmasset currently has three clinical-stage product candidates for the treatment of chronic hepatitis C virus (HCV) advancing in trials in various populations.

- The lead product compound, PSI-7977, an unpartnered uracil nucleotide analogue, has recently been advanced into two Phase 3 studies in genotype 2 and 3 patients. Both studies use 12 weeks of treatment with PSI-7977 in combination with ribavirin. Comparitor arms include pegylated : 'interferon/ribavirin in treatment-naïve patients, and placebo in interferon- intolerant/ ineligible patients. A third Phase 3 study in genotype 1 patients will be initiated in the second half of 2012.
- PSI-938, an unpartnered guanosine nucleotide analogue, is being tested in a Phase 2b interferon-free trial as monotherapy and in combination with PSI-7977 in subjects with HCV of all viral genotypes.
- Mericitabine (RG7128), a cytidine nucleoside analogue, is partnered with Roche and is being evaluated in three Phase 2b trials. Roche is responsible for all aspects of the development of mericitabine.

Ref: Press statement: 'Gilead Sciences to acquire Parmasset Inc for $11 billion'. (21 November 2011).

Abbott to separate treatment from medicinal products in company split

Abbott, the research-based company responsible for developing lopinavir/ritonavir (Kaletra) and ritonavir (Norvir) which has a annual revenue close to $18 billion dollars announced that it plans to divide into two separate companies: one focused on research and treatment and the other on diversified medical products.

The press statement listed immunology, Multiple Sclerosis, chronic kidney disease, Hepatitis C, women's health and oncology, but not HIV, as future research priorities.

Ref: Press statement: 'Abbott to Separate into Two Leading Companies in Diversified Medical Products and Research-Based Pharmaceuticals'. (19 October 2011).

BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011

Simon Collins, HIV i-Base

New guidelines for routine management of HIV are now posted to the BHIVA website and are published in the January 2012 edition of HIV Medicine (with free access). [1]

The comprehensive 40-page document includes a detailed review of the most important routine monitoring. It is an essential reference for understanding the current recommended minimum standard of care.

These guidelines include suggestions for audited targets and cover each stage of the treatment pathway from initial diagnosis, through to naïve and experienced management, and includes the case of transferred care.

It is also important for highlighting simple and inexpensive aspects of care that are important but if overlooked have the potential to greatly impact on patient quality of life. These include full patient history, psychological assessment (including depression, anxiety and social support), sexual history (including sexual health), support for evaluating adherence, baseline evaluations (including physical examination, waist circumference, blood pressure and BMI). Mental health has a separate consideration.

Recommendations for CD4 and viral load monitoring are similar to earlier guidelines. In naïve patients, as long as CD4 count remains 100 cells higher than the threshold for starting treatment (currently this would be 450), CD4 monitoring should be every 4-6 months, and 3-4 monthly if it falls below this. CD4 count should still be monitored four weeks after starting therapy (with viral load). In people who maintain an undetectable viral load for more than one year and whose CD4 count is greater than 200, CD4 monitoring can be reduced to six-monthly.

Viral load should still be a factor when deciding to initiate HAART, needing at least two results for patients in chronic infection to establish a reliable set point, six monthly thereafter and repeated within one month prior to treatment. Short term efficacy needs to be confirmed by a drop of at least I log, four weeks after starting treatment, and further tests at 3 and 6 months. Undetectable (<40 or <50 copies/mL) should be achieved by 4-6 months. Subsequent monitoring should be 3-4 monthly, and six-monthly viral load can be considered in a strictly adherent patients on stable treatment. Viral rebound to >50 copies/mL needs to be conformed with a new sample.

The cut-off for switching treatment is only briefly mentioned but blips are described as transient increases to between 50 and 1000 copies/mL (subsequent test being < 50 copies/mL) and multiple blips a signal to review drug potency, adherence, tolerability, resistance and potential modifications to the combination.

Resistance testing is still strongly recommended for all newly diagnosed patients and again prior to starting treatment if reinfection is possible, or in patients without results from first diagnosis, at week four of treatment if viral suppression is less than 1 log copies/mL, in all patients with confirmed viraemia (while on the failing combination) recognising that specialised labs are able to work with samples where viral load is 'just over' 50 copies/mL.

The guidelines also address laboratory monitoring for renal, hepatic, cardiovascular, bone and biomarkers, other infections including sexual health and for specific patient groups (women, older patients, injecting drug users and late presenters.

References and links

British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011

BHIVA site link:

http://www.bhiva.org/Monitoring.aspx

HIV Medicine, January 2012 Volume 13, Issue 1 Pages 1–88.

http://onlinelibrary.wiley.com/doi/10.1111/hiv.2011.13.issue-1/issuetoc

Draft BHIVA ARV treatment guidelines online for comment until 5 March

The British HIV Association (BHIVA) guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012 are now online in draft.

The scope of this document includes guidance on the initiation of ART in those previously naïve to therapy, support of patients on treatment, management of patients experiencing virological failure and recommendations in specific patient populations where other factors need to be taken into consideration.

Comments can be made online at the same URL for the draft document:

http://www.bhiva.org/treatmentguidelinesconsultation.aspx

C O M M E N T

These guidelines have been produced based using a new methodology and grading system compared to earlier documents, and are clearly the result of considerable additional work. The evidence base is published in a separate 270 page appendix.

Of note, some of the recommendations in the current draft include differences between the BHIVA writing committee and current prescribing by the London consortium. Readers have until 5 March to comment.

Draft BHIVA pregnancy guidelines online for comment until 5 March

The British HIV Association (BHIVA) Guidelines for the management of HIV infection in pregnant women 2012 are now online in draft.

The overall purpose of these guidelines is to provide guidance on best clinical practice in the treatment and management of HIV-infected pregnant women. The scope includes guidance on the use of ART therapy both to prevent HIV mother-to-child transmission (MTCT) and

for the welfare of the mother herself, guidance on mode of delivery and recommendations in specific patient populations where other factors need to be taken into consideration such as co infection with other agents.

Comments can be made online at the same URL for the draft document:

http://www.bhiva.org/PregnancyGuidelinesConsultation.aspx

US guidelines (DHHS) update recommendations for first-line combinations (October 2011)

In October the US Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents were updated and posted online to the AIDSinfo web site.

This revision to the guidelines is focused on What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient. Additions and key changes to the section are outlined below. More detailed discussion of the rationale for changes can be found in the updated section. Related tables have also been updated.

Table 1: Key changes to DHHS guidelines (October 2011)

NNRTI-based combinations	
Rilpivirine	Added as an alternative NNRTI option for initial therapy in treatment-naive patients.
Nevirapine-based combinations (NVP)	All reclassified as acceptable for naive patients (women with CD4 count <250 cells/mm3 or men with CD4 count <400 cells/mm3). Previously, NVP+ AZT/3TC was an alternative regimen and NVP + abacavir/3TC and NVP + tenofovir/FTC were 'acceptable but should be used with caution'.
PI-based combinations	
Darunavir/ritonavir + abacavir/3TC	Reclassified as an alternative regimen (BIII) - was 'acceptable but needed more data (CIII)'.
Unboosted fosamprenavir	Removed as a PI option for naive patients (inferior potency and potential for cross-resistance to darunavir).
Raltegravir-based combinations	
Raltegravir + abacavir/3TC	Reclassified as an alternative regimen (BIII) - was 'acceptable but needed more data (CIII)'.
Dual NRTI options	
AZT/3TC	Reclassified to 'acceptable' from 'alternative' because of greater toxicities compared with tenofovir/FTC and abacavir/3TC and twice-daily dosing. However, AZT+3TC remains as the preferred dual-NRTI during pregnancy.
ddI/3TC	Removed for initial therapy due to poor data and higher toxicity.
abacavir	Discussion on the association between abacavir use and the risk of a cardiovascular event updated.

In addition to the changes highlighted above, the following tables are updated with information relevant to rilpivirine:

- Tables 14, 15b, and 16b – Drug interaction tables
- Appendix B, Table 2 – Drug characteristic table
- Appendix B, Table 7 – Dosing recommendation for patients with renal or hepatic insufficiency

The DHHS guidelines are online in PDF and html page formats. The PDF file helpful highlight all recent changes in yellow.

http://www.aidsinfo.nih.gov/guidelines/

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
tenofovir/FTC 300 mg/200 mg tablets	Hetero Labs, India	22 December 2011
abacavir/3TC 60 mg/30 mg tablet paediatric (> 3 months and >5 kg)	Mylan Pharmaceuticals, India	31 January 2012
abacavir/3TC 600 mg/300 mg adult tablet	Cipla, India	31 January 2012

FDC: Fixed Dose Combination

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

Fixed Dose Combinations are reviewed for PEPFAR under the FDA guidance titled "Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously approved Antiretrovirals for the Treatment of HIV". This document was developed to clarify what regulatory requirements apply to such applications, what issues might be of concern, and how these issues should be addressed. The guidance is intended to encourage sponsors to submit applications for combination and co-packaged products, and to facilitate submission of such applications to FDA.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079742.pdf

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 (now at 140) 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

Disastrous warning for global HIV programmes in 2012

Simon Collins, HIV i-Base

Some of the first indications that the economic debt crisis in Europe will contribute to 2012 being a disastrous year for global health came in articles from the corporate financial institution Bloomberg Businessweek (not known for it's focus on HIV news) and the mainstream scientific journal Nature.

This year will not be business as usual for anyone, and those most dependent on international aid are most vulnerable.

The impact of the suspension of Round 11 of Global Fund grants, reported in both this and the previous issue of HTB is causing global concern. The Bloomberg article includes MSF data on 28,000 people in the Democratic Republic of the Congo who will not now be able to start treatment. This seems likely to be an underestimate. Similar reports and concerns – often with a greater human impact – are likely to apply to every country with limited access to HIV treatment.

For example, in a report on the implications of the funding crisis for Malawi, which currently has no funding past 2013, an estimated 200,000 people currently in need of treatment will not be able to access antiretrovirals.

Both reports focus on the impact that unfulfilled pledges from 2008 from leading European countries has had on the Global Fund. According to the Fund's website, outstanding pledges include $168 million from Italy (from 2009) and $116 million from Spain (from 2010). Five countries - Italy, Spain, Greece, Iceland and Portugal - also made no pledges last year. Holland has cut the proportion of GDP allocated to development assistance from 0.8 to 0.7%. While the US increased funding by 1.6% to $7.6 billion and the UK and Germany (the second and third largest donors after the US) increased pledges by 14%, global donor commitments that had increased to $8.7 billion in 2008, flat-lined in 2009 and dropped by 10% in 2010. The budget available for treatment in the PEPFAR fell by 17% and was accompanied by a shift from adult care exclusively to a mother and child programme. In countries where funding programmes has made treatment is available – and over six million people now access ARVs - it remains largely based on archaic use of d4T (stavudine) despite alternatives such at tenofovir being cost effective. The funding uncertainty will clearly also undermine key WHO recommendations to switch away from use of d4T and earlier treatment using a CD4 threshold of 350 rather than 200 cells/mm3.

Access to treatment has always provided the incentive for people to come forward to test. Whether this was for AZT in 1987 or HAART in 1997 in Western countries or in any of the global access programmes rolled out since 2000. Without the hope of any intervention to improve a person's individual health it has always been difficult to argue that learning you are HIV positive is going to improve your quality of life. Even with treatment, diagnosis is currently late for the majority of people, when defined as a CD4 count lower than the threshold recommended for starting treatment. But without it, HIV will be driven back underground, testing programmes will falter, and the progress from the last ten years will slowly be lost.

It is spectacularly short sighted for this to be occurring at exactly the time when effective treatment is not only cheaper than every before but also proven to be the most effective method of preventing further transmission.

References

Bennett S. Financial crisis may kill in Congo as global health aid stalls. Bloomberg Buisnessweek. 17 January 2012

http://www.businessweek.com/news/2012-01-18/financial-crisis-may-kill-in-congo-as-global-health-aid-stalls.html

MSF press statement: DRC: Majority of people living with HIV denied treatment. (25 January 2012).

http://www.doctorswithoutborders.org/press/release.cfm?id=5742&cat=press-release

Farquhar D et al. Breaking promises to the poor: the donor retreat puts Malawi's AIDS programme in peril (unpub).

Wadman M. Cutbacks threaten HIV gains. Nature; 480; 159–160. (08 December 2011).

http://www.nature.com/news/cutbacks-threaten-hiv-gains-1.9581

Michel Kazatchkine resigns from Global Fund: Gabriel Jaramillo, Brazilian banker, to serve as general manager

Global Fund Observer

On 24 January 2012, Michel Kazatchkine announced that he will "step down" as Executive Director of the Global Fund by mid-March. He said that his planned resignation resulted from a decision by the Global Fund Board two months ago to appoint a General Manager who will supervise many Global Fund activities and who will report direct to the Board. GFO understands that this decision by the Board to transfer many of Dr Kazatchkine's responsibilities to someone else arose from the Board's concern that the Fund's managerial leadership was not sufficiently effective.

"For the last ten years, the Global Fund has been my passion and my most important undertaking," Prof. Kazatchkine said in a statement to staff. Simon Bland, Global Fund Board Chair, responded by saying, "Few individuals have played a more central role in the creation and evolution of the Global Fund than Michel."

The Global Fund also announced today that the General Manager will be Gabriel Jaramillo, a prominent banker from Latin America who was one of the members of the High Level Panel that extensively evaluated the work of the Global Fund during 2011. Mr Jaramillo spent three days last week meeting senior staff at the Global Fund.

The Global Fund said that Mr Jaramillo will take up a 12-month appointment on 1 February. The Fund did not specify whether Mr Jaramillo will serve as Acting Executive Director once Dr Kazatchkine leaves, but it implied that he will when it said, in a Q&A document sent to Board delegation members, that Mr Jaramillo will "take over all of the management responsibilities of the Global Fund Secretariat." A spokesman told GFO that the Global Fund will launch a search for a new Executive Director "in due time."

Mr. Jaramillo, a native of Colombia and a citizen of Brazil, is a former Chairman and Chief Executive Officer of Sovereign Bank. Since he retired a year ago, he has served as a Special Advisor to the Office of the Special Envoy for Malaria of the Secretary General of the United Nations. Mr Bland said in a press release that Mr Jaramillo "is an outstanding choice, and exactly what we need at this time: an excellent manager and a proven financial leader who can direct change and improve performance in a large institution during a time of transition."

Source: Global Fund Observer (GFO) Issue 174: 24 January 2012.

http://www.aidspan.org.gfo

http://www.theglobalfund.org/en/mediacenter/pressreleases/2012-01-24_The_Global_Fund_Executive_Director_to_step_down_in_March/

Janssen block Patent Pool access to darunavir, rilpivirine and etravrine

In a press release on 19 December 2011, the Medicine Patent Pool announced that Johnson and Johnson, the parent company for Janssen/Tibotec, have decided not to allow licensing of its antiretroviral products as part of the international collaboration to enable sustained and affordable access to latest HIV medicines in poor countries.

The Medicine Patent Pool, founded and financed by UNITAID, seeks to increase access to HIV medicines by negotiating with pharmaceutical companies for voluntary licenses for ARVs that are still covered by patents. The work of the Pool has received support from the World Health Organization, UNAIDS, the Global Fund to Fight HIV, TB, and Malaria, and the G8.

Licensing agreements have already been developed with Gilead Sciences and the US National Institutes of Health, with ongoing negotiations with Boehringer-Ingelheim, Bristol-Myers Squibb, F. Hoffman LaRoche, Sequoia Pharmaceuticals, and ViiV Healthcare (GSK/Pfizer).

Generic companies contribute a royalty to make lower cost versions of new HIV treatments for use in developing countries.

Source: Patent Pool press release. Johnson & Johnson says "no" to joining the Medicines Patent Pool. (19 December 2011).

http://www.medicinespatentpool.org/NEWS-ROOM/News-from-the-Pool/JandJ-Says-No

UNITAID continues funding the Patent Pool, paediatric HIV medicines and malaria

On 14 December, UNITAID Executive Board announced its continued commitment to scaling up access for HIV/AIDS and malaria by allocating an extra US$ 138 million to HIV and malaria.

This included support for four years for the Medicines Patent Pool to negotiate voluntary licenses from brand companies to generic manufacturers to facilitate affordable access to HIV/AIDS medicines in developing countries.

"Precisely because funding for AIDS is threatened by the economic crisis, we need to leverage all the tools at our disposal to ensure

staunch commitment to increase treatment coverage," said Philippe Douste-Blazy, Chairman of the UNITAID Executive Board. "Innovative mechanisms that can increase treatment availability and decrease prices, such as the Pool, are critical components of UNITAID's strategy to address the funding gap… The Pool has achieved promising results in its first year and we urge all pharmaceutical companies to enter into licensing agreements to breach the gap of 15 million people who need treatment."

The UNITAID Board committed US$ 62 million to continue supporting the scale-up of HIV/AIDS treatment for children in partnership with the Clinton Health Access Initiative. US$ 50 million was committed to the Global Fund to increase access to artemisinin-based combination therapy in the eight African countries that bear the largest malaria burden.

Source: UNITAID press release: UNITAID continues funding the Patent Pool and paediatric HIV medicines: Additional US$ 50 Million Allotted to Malaria. (14 December 2012).

http://www.unitaid.eu/en/component/content/article/3-press/380-additional-us-50-million-allotted-to-malaria

We need the Patent Pool to work

Joint statement by TAC, TAG, HIV i-Base, EATG and SECTION27

The exorbitant price of AIDS medicines, especially antiretrovirals, has been one of the main barriers to people with HIV accessing them, especially in developing countries. As activist organisations we have been at the forefront of many of the struggles to make medicines affordable.

A patent gives a pharmaceutical company the exclusive right to manufacture and market a medicine. The patent lasts for 20 years from the date of filing the patent application. Companies typically patent medicines that they develop, they buy patents from other companies or they enter into exclusive licensing arrangements with universities or small companies that have developed medicines but do not have the capacity to bring them to market.

The purpose of patents is to encourage research and development into new medicines. The problem is that patents ordinarily create monopoly conditions which allow companies to charge exorbitant prices. Over the last 15 years, some developing world governments and activists have battled pharmaceutical companies to reduce medicine prices. They have won many hard-fought concessions that have brought down the prices of life-saving drugs and allowed millions of people to go onto antiretroviral treatment. But new generation patented drugs that have fewer side effects, are easier to take or offer treatment alternatives to people resistant to current regimens, are mostly unaffordable. Yet they will soon be needed by millions of people. Furthermore, the struggles for lower medicine prices have to a large degree depended on country-specific laws and the capacity of activists in those countries to organise. Crucially, it is not sustainable to fight drug-by-drug, country-by-country for concessions from the pharmaceutical industry.

One of the initiatives that has resulted from these struggles is the Patent Pool. This is an initiative by activists and UNITAID [1] to negotiate concessions from the pharmaceutical companies on an international scale to license their products through the patent pool. Multiple generic producers will then be able to access these licenses, stimulating sufficient competition between generic producers to drive down prices. The pool also aims to spur the production of generic combinations of medicines, where patents on medicines are held by a number of different companies.

There is no guarantee the Patent Pool concept will work. It ultimately depends on pharmaceutical companies entering into voluntary agreements that dilute the monopolies that patents give them. Getting pharmaceutical companies to the negotiating table requires ongoing activist pressure and protests. It requires co-ordinated strategies to monitor prices and patents, pressure governments to use the powers they have under TRIPS [2] to license essential medicines and campaigns to expose profiteering from health.

The Patent Pool has not been without teething problems and this has led to questions and criticism from activists around the world. It needs to improve its consultation mechanisms. We are pleased that it has begun to do so by meeting with key HIV civil society organisations around the world and by putting together an expert advisory group that will recognise the expertise and experience that members of civil society may bring.

So far only one antiretroviral patent-holding company, Gilead has signed an agreement with the Patent Pool. Gilead has agreed that the Patent Pool can license some of its antiretrovirals to generic companies in over 100 countries. The drugs include tenofovir (TDF), cobicistat (COBI), elvitegravir (EVG), and the Quad, a fixed-dose combination of TDF-COBI-EVG-emtricitabine. Gilead has also committed to not enforcing its exclusive rights on emtricitabine (FTC). It will also not stop companies from making fixed-dose combinations involving these compounds. [3]

The Gilead agreement has shortcomings. For example, Brazil, Thailand, China, Botswana, Namibia and Ukraine, all countries with significant numbers of people with HIV, and many other middle-income countries are excluded from part or all the agreement. Botswana, Thailand and Namibia are included in the TDF license, but excluded from the COBI one. The current agreement also unnecessarily restricts the sub-licensees to Indian generic manufacturers only.

Nonetheless these licenses are the most far-reaching of the concessions obtained from pharmaceutical companies on AIDS drugs. Millions of people can benefit and we must keep up pressure to ensure that all people do. That is why we demand that Gilead re-open negotiations with the Patent Pool to extend the licenses to include all the above countries and others in all aspects of the agreement. Also, the excluded countries can still access products produced by licensed companies if they make use of their TRIPS flexibilities; we therefore call upon them to do so.

We also demand that other pharmaceutical companies join the Patent Pool and make their essential HIV medicines available for voluntary licensing. In particular, we call on ViiV, Merck, Johnson & Johnson and Abbott to conclude agreements with the pool so that the antiretrovirals dolutegravir (still in clinical trials), raltegravir, darunavir, etravirine, rilpivirine and lopinavir and ritonavir become more accessible.

If these companies join the Patent Pool, the prices of these drugs are likely to drop substantially. Hundreds of thousands, perhaps millions, more people with HIV will therefore have access to these life-saving medicines.

Today six million people are alive and receiving antiretrovirals. Nine million more are in need. In some countries however, access to treatment is reducing rather than increasing. The unaffordable

price of medicines is one of the reasons for this. We maintain the view that patents should not be used to make essential medicines unaffordable and that governments should play a much greater role in research and development of medicines. Access to essential medicines cannot be left to the market and the private sector; these cannot meet people's needs.

We call on activists globally to unite and once again build powerful campaigns against pharmaceutical company profiteering so that access to antiretrovirals as part of the human right to the highest attainable standard of health, can be universally realised.

Joint Statement by Treatment Action Campaign, Treatment Action Group, HIV i-Base, European AIDS Treatment Group and SECTION27, 16 November 2011.

Notes

1. UNITAID is a WHO initiative. Its mission is "to contribute to scaling up access to treatment for HIV/AIDS, malaria and tuberculosis, primarily for people in low-income countries, by leveraging price reductions for quality diagnostics and medicines and accelerating the pace at which these are made available."
2. The WTO's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) was negotiated in the 1986-94 Uruguay Round. While imposing intellectual property regimes on countries that did not previously have them, it does contain some flexibilities.
3. TDF is an important drug because it can be used for first-line antiretroviral treatment instead of an older drug called stavudine which has much worse side-effects. Cobicistat, which is not yet approved, is potentially important because there is currently only one other drug that serves a similar purpose, i.e. to boost other antiretrovirals. The Quad is a four-in-one once daily pill that is not yet approved, but is hopefully going to be an excellent first-line antiretroviral regimen. Elvitegravir is also being tested. It will likely be useful for people who are resistant to other antiretrovirals.

Call to Action on Global Fund restriction to new funding to 2014

Organisations and individuals are being urged to sign a Call for Action demanding that the Global Fund and its Board mobilise the necessary resources to create a new funding opportunity in 2012 in the amount of $2 billion.

Organised by civil society activists at the World AIDS Campaign they state that the cancellation by the Global Fund of all new programming until 2014 will cost lives and cripple international efforts to deliver on health-related goals, and that it breaks promises made to some of the world's most vulnerable people.

The Call to Action demands that the Global Fund hold an emergency donor conference and issue a new call for proposals before the International AIDS Conference in July 2012. The Call says, "This is 200 days from 1 January. 200 days to save the Global Fund."

Further information:

http://www.worldaidscampaign.org/2011/12/global-fund-call-to-action/

Source: Global Fund Observer (GFO) Issue 169: 5 December 2011.

http://www.aidspan.org.gfo

Analysis of why the Global Fund cancelled Round 11

Global Fund Observer

At its meeting in December 2010, the Global Fund Board approved the launching of Round 11. At its meeting in May 2011, the Board discussed but did not change this decision.

Therefore, in August 2011, Round 11 was launched, and many CCMs devoted enormous amounts of work to preparing their proposals. Then last month, in November 2011, the Board cancelled Round 11.

Why was Round 11 launched and then cancelled? And what does the decision to cancel Round 11 tell us about the Global Fund's financial condition?

In a nutshell, the answer is...

Unlike what some news reports have suggested, the Global Fund has billions of dollars in the bank, with billions more expected to arrive during the next two years. The problem is that most of that money is needed for the current and renewal phases of existing grants. In addition, the Fund has introduced a more cautious methodology for estimating how much funding it will receive in future. Primarily because of these two factors, the Global Fund now estimates that until 2014, it will have almost no money for new grants. Hence, the need to cancel Round 11. It is not accurate to say that Round 11 was cancelled because of decisions by donors since May to cancel, reduce or delay their pledges, because that is not happening.

In somewhat more detail, the answer is....

As Simon Bland, Global Fund Chair, said, recently, the Global Fund disbursed $8 billion during the three-year period 2008-2010, and the Fund forecasts that it will have enough money to be able to disburse $10 billion during 2011-2013. This is a 25% increase from one period to the next.

Unfortunately, however, the $10 billion that the Global Fund expects to be able to disburse in 2011-2013 is about $1 billion less than the Fund had forecast in May 2011. Almost all of the $10 billion will be needed to fund existing grants and the renewals of existing grants. Grants are normally approved for a two-year Phase 1 followed by a three-year Phase 2. The Global Fund's policies require that priority be given to Phase 2 renewals of existing grants, over the funding of new grants.

In May 2011, when the Global Fund was forecasting that it would be able to disburse about $11 billion in 2011-2013, the Fund estimated that $1.55 billion of that would be available for Round 11 grants. By the time of the Board meeting in November, that estimate went down to minus $0.6 billion. That meant that not only was there no money for Round 11, but also the Global Fund was short of money to pay for grant renewals and probably also for some unsigned Round 10 grants.

The decisions that were made during the Board meeting - decisions that achieved savings by reducing the amount of money required for future grant renewals - increased the estimate of available money from minus $0.6 billion to plus $0.6 billion. However, this amount was not deemed to be enough to permit the launching of Round 11 before 2014. Rather, the money has to be used primarily for funding those Round 10 grants for which grant agreements have not yet been signed, and for funding transitional arrangements (i.e., essential services) for grants that will end soon.

Thus, new grants now cannot be approved until 2014, though the Fund may decide to invite applicants to start preparing proposals during 2013.

In the last few years, the Global Fund has had some serious problems with certain donors, particularly the following:

- Italy has not yet pledged any money for 2011-2013, and has not delivered any of the $347 million it pledged for 2009-2010.
- Spain has not yet pledged any money for 2011-2013, and has not delivered $116 million of the $250 million it pledged for 2010.
- Ireland has not yet pledged any money for 2011-2013, and has not delivered $35 million of the $46 million it pledged for 2010.
- Netherlands has not paid $37 million of the $119 million it pledged for 2010.

However, those problems were all known when the Board agreed in May 2011 to launch Round 11. They are not new. The main factors that last month caused the Global Fund to reduce its revenue projections from the May 2011 levels, and therefore to cancel Round 11, were as follows:

- Many donors make their pledges in Euros and other non-dollar currencies. Between May and November, those currencies, on average, weakened against the dollar, so the anticipated dollar value of those pledges decreased by about $100 million.
- Some of the $4.0 billion that the U.S. announced last year for 2011-2013 will not be received until 2014, because U.S. legislation specifies that not all of each year's money can be handed over until the U.S. government can certify to Congress that a number of conditions have been met.
- There has been a reduction in estimated interest earnings from the Fund's money in the bank.
- Most significant by far: The Global Fund has developed a new and more cautious forecasting methodology regarding future income from donors. (The Global Fund refers to this as producing "risk-adjusted" forecasts.) The new methodology was introduced because the negative economic situation and the challenging political environment create uncertainties that are difficult to reflect in a multi-year forecast. In its new risk-adjusted forecasts, the Global Fund no longer automatically assumes that all countries will give the exact amount they pledged or that the funds will arrive equally distributed across the years to which the pledge applied. For example, the amount announced by the U.S. for the fiscal years 2011-2013 ($4.0 billion) is subject to Congressional approval each year. The Global Fund hopes - but cannot be certain - that the U.S. Congress will approve the full amount each year.

It is important to point out that only one country has formally cancelled or reduced the pledge that it originally made for 2011-2013. This is Denmark, which reduced its pledge by approximately $10 million; this represents well under one percent of what would have been needed for Round 11.

At the Accra Board meeting, the Executive Director said that the problems which then led the Board to cancel Round 11 represented a "perfect storm" of factors. Some participants privately blamed the Secretariat for not taking the possibility of those factors into consideration when it launched Round 11. Others blamed the Board for accepting the Secretariat's May projections.

Source: Global Fund Observer (GFO) Issue 170: 9 December 2011.

http://www.aidspan.org.gfo

Reaction to the Global Fund's decisions on Round 11 and grant renewals

Global Fund Observer

The following reactions from key organisations to the Global Fund's decision to do away with Round 11 were highlighted in a GFO article.

Health GAP

"The funding window that was cancelled today would have enabled scale-up of lifesaving treatment and prevention services for HIV, tuberculosis and malaria to millions of poor people in developing countries.

"What is particularly scandalous about this cancellation is that donors didn't have to do it. The amounts of money we're talking about are barely a rounding error in donor budgets."

MSF

"There's a shocking incongruence between both the new HIV science and political promises on one hand, and the funding reality that is now hitting the ground on the other. Donors are really pulling the rug out from under people living with HIV/AIDS at precisely the time when we need to move full steam ahead and get life-saving treatment to more people."

ITPC

"The lack of political and financial commitment to the AIDS response is deeply worrisome. The millions of people living with and fighting against these deadly diseases will pay an enormous price. Rather than building on the new evidence that AIDS treatment saves lives and prevents new infections, and scaling up treatment programs to try to end this epidemic, donor governments are now implicitly supporting a policy of triage, determining who lives and who dies."

"The shortfall in funding for the Global Fund is an insignificant amount in comparison to the bank bailouts made by the U.S. and European governments, or even the bonuses set aside for Goldman Sachs executives this year."

International HIV/AIDS Alliance

"The news that the Global Fund Board had decided to cancel Round 11 has devastated civil society organisations across the Alliance global partnership. We should not be shy in saying this decision and the financial situation of the Global Fund at this moment is a disaster for Africa."

"International solidarity, perhaps the most precious resource needed to reach the Millennium Development Goals, is in dangerously short supply. A few days ago at the Fund's meeting, tensions were high among representatives of implementer countries: They were fighting to be granted the dubious recognition of being the poorest among the poor in order to guarantee their access to the few resources still left. During these discussions, we tend to forget that people have a right to live regardless of where they were born."

Coalition of AIDS activist organisations in Southern Africa

"It is a disaster for Zimbabwe as a country. More than 86,000 people will be left without treatment and about 5,000 children will be affected. The situation in Swaziland, where approximately 26 percent of the population of 1.2 million live with HIV, is dire, with stockpiles of ARVs already dwindling".

The Guardian

The Global Fund has been "staring at a financial black hole ever since its big replenishment meeting in New York a year ago failed to deliver the sums it hoped for. It wanted $20bn. It got $11.7bn. That was in spite of exhortations to donors to pledge money from the U.N. Secretary General, Ban Ki-moon, who warned that the stakes were high and that lives would be lost if pressure on the big killer diseases was not maintained."

New Statesman

"it reveals just how precarious daily life has become for the global 99 per cent: those whose very health, as much as their job security, is pegged to the rise and fall of the money markets. The politics of austerity we are going through has not even begun to be properly costed. This is the real lesson of the Global Fund's demise and it will require much more than simply getting wealthy donors back on board to address it."

Source: Adapted from Global Fund Observer (GFO) Issue 169: 5 Dec. 2011.

http://www.aidspan.org.gfo

PAEDIATRIC CARE

Delaying ART in childhood can reduce long-term CD4 count in adulthood

Polly Clayden, HIV i-Base

The decision to start ART in children is made with guidance based on age and CD4 percentage or count. Guideline recommendations are based on observed short-term risk of morbidity and mortality. ART can be delayed in children with CD4 values above the recommended thresholds for initiation to avoid toxicities, resistance and some of the practical considerations associated with giving ART to children.

Investigators from ICH and the PENTA group suggest that current guidance assumes such a delay in treatment initiation is without detrimental long-term consequences. In a paper published ahead of print in JID, 28 December they write that evidence suggests differences between children and adults in the level of T-cell repopulation due to children's greater thymic activity. A number of paediatric studies show poorer recovery of CD4 count on ART is associated with older age and lower CD4 count at initiation. Using longitudinal data from the PENTA 5 study and non-linear mixed-effects models, the group investigated the relationships between age, CD4 count at start of treatment, and CD4 repopulation. As well as confirming the associations previously described, their findings illustrate the importance of the naïve subpopulation for this recovery and they explore the consequences for ART naïve children of different age groups and with different CD4 counts.

The PENTA 5 trial assessed different ARV regimens in perinatally infected, treatment-naïve children. Among the 127 children starting treatment, the median age at initiation was 5.3 (IQR 2.4 to 8.6) years; CD4 count was 620 (IQR 343 to 912) cells/mm3; z-score (indicating the rank of a recorded CD4 count within the expected distribution for HIV-negative children of the same age, born to HIV-positive mothers expressed in terms of the standard, normal distribution) was -2.3 (IQR -4.1 to -1.3) and follow-up was 5.7 (IQR 5.1 to 6.5) years.

In a multivariate model the investigators estimated the children's pre-treatment z-score to be -0.41 ± 0.07 (point estimate ±SE) lower for each year older at initiation and their long term z-score -0.5 ± 0.03 lower for each year older at initiation, both $p<0.001$. In addition to these effects, there was a strong positive association ($p<0.001$) between pre-treatment and long-term z-score – that is, children with z-scores below (or above) average for their age before treatment still had below (or above)-average scores in the long term.

Naïve and memory CD4 counts were recorded in a substudy of 26 children. This analysis revealed T-cell reconstitution in these children appeared to arise mainly from the naïve compartment with a comparatively small increase memory cell count, although on a faster timescale. However this potential for recovery via the naïve pool is apparently progressively reduced with age and/or duration of infection. The model illustrated suggests that the threshold currently recommended for initiating treatment in younger children results in a higher count in the long term than that for older children. Therefore guidelines for older children may not be optimal for maintaining CD4 counts in adulthood.

Ref: Lewis J et al. Age and CD4 count at initiation of antiretroviral therapy in HIV-infected children: effects on long-term T-cell reconstitution. JID. Published ahead of print 28 December 2011.

Efavirenz under-dosing in children

Polly Clayden HIV i-Base

An article in the December 1 2011 edition of JAIDS describes efavirenz (EFV) exposure in African children in the ARROW trial, dosed according to the 2006 WHO weight bands, which are similar to the manufacturer's recommendations (the current approved paediatric doses).

ARROW is an open label randomised trial comparing routine laboratory to clinical monitoring (a paediatric version of DART) in children in Uganda and Zimbabwe. It also compares different ART strategies. Quirine Fillekes and colleagues from the trial team conducted a pharmacokinetic (PK) sub study in Ugandan children aged 3-12 years. The children evaluated had received twice daily lamivudine plus abacavir (3TC+ABC) with once daily EFV and participated in a crossover study comparing twice to once daily 3TC+ABC.

EFV was dosed according to WHO 2006 weight bands. Doses were 200, 250, 300 and 350 mg for children weighing 10 to <15, 15 to <20, 20 to <25 and 25 to >30 kg respectively. The children received 200/50mg capsules or halved 600mg tablets.

At week 36 from initiating treatment (once daily EFV plus NRTIs), 12 hour PK sampling was performed, pre-dose and at 1, 2, 4, 6, 8 and 12 hours post dose. The children were switched to once daily NRTIs at 36 weeks. Intensive PK sampling was repeated at 40 weeks, including an extra PK sample at 24 hours post dose.

A total of 41 (24 girls and 17 boys) were enrolled in this sub study. Of these, 4 children increased weight bands between the first and second PK sampling but were included in the analyses and 2 were excluded due to implausible time concentration curves (believed to be labeling errors).

Eighteen of the children were age 3 to 6 years and 23 children were 7 to 12 years. The majority were moderately stunted and wasted. Five, 16, 17 and 3 children were in the 10 to <15, 15 to <20, 20 to <25 and 25 to >30 kg weight bands respectively, at the first PK sampling.

Doses in mg/kg were highest in the 15 to <20 kg (median 14.7 mg/kg) and lowest in the 20 to <25 kg (median 13.0 mg/kg) weight bands. The median dose received overall was 13.6mg/kg.

The geometric mean EFV plasma concentrations time curves obtained at the first and second samplings were similar. Six children at the first sampling and 7 children at the second had subtherapeutic (<1.0 mg/L) plasma concentrations at 8 hours and/or at 12 hours; 7/41 (17%) at either sampling. At the second sampling 15/39 (38%) of children had subtherapeutic levels at 24 hours. Ten (24%) children at the first sampling and 11 (28%) at the second had potentially toxic levels >4 mg/L at 8 hours and/or at 12 hours; 12/41 at either sampling.

Overall the EFV Cmax, Cmin and AUC0-24 were respectively 15%, 36% and 10% lower than those observed in adults receiving the 600mg tablet.

The authors observed wide intersubject but modest intrasubject variability across EFV PK parameters. There was no evidence of significant differences across the four weight bands for all PK parameters evaluated (suggesting no major effect of using divided tablets) however, with only 41 children in total the sub study was rather underpowered to show this.

They wrote that these data (and that of two previous studies) strongly suggest that children should receive EFV doses higher than the WHO 2006 recommendations or the manufacturers daily dose in the leaflet (50mg higher only for children weighing 14 to <15 kg and 30 to 32.5 kg).

More recent 2010 dosing guidelines have higher EFV doses than evaluated in this study for children weighing 14 to <20, 25 to <30 and 35 to <40 kg. The authors noted that these higher doses were not only selected in response to concerns about under doing but to remove the 50 mg tablets from dosing tables as these were being discontinued.

They expressed concern that although these data suggest that higher doses should lead to greater exposure and in turn better virological efficacy, the trade off is that more than one-third of children will be exposed to potentially toxic EFV levels.

Reference

Fillekes Q et al. pediatric underdosing of efavirenz: a pharmacokinetic study in Uganda. J Acquir Immune Defic Syndr. Volume 58. Number 4. December 1, 2011.

Treatment response and duration of first line treatment in European infants

Polly Clayden HIV i-Base

Investigators from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group in EuroCoord evaluated response to antiretroviral therapy (ART) and predictors of switching or interrupting treatment in children starting in infancy up to 5 years from treatment initiation. Findings from this study were reported in the 28 November 2011 edition of AIDS.

The study evaluated data from nine observational cohorts in 13 European countries. A total of 437 HIV-infected, ART naïve infants, less than 12 months of age, born between 1996 and 2008 were included.

The infants started ART at a median of 3.7 (IQR 2.1-5.8) months. About 40% were from UK/Ireland and 20% each from France and Italy. About half were black and half female. Just over a third had been exposed to maternal antiretrovirals in pregnancy and just under a third neonatal prophylaxis. One third were breast-fed.

The median duration of follow up after starting ART was 5.9 (IQR 2.3 – 7.6) years. During this time 20 children died and 32 were lost to follow up. The median CD4 percentage and viral load at treatment initiation of were 29% (IQR 17 - 39%) and 5.7(IQR 4.9 – 5.9) log10 copies/mL respectively.

The majority (76%) started ART before 6 months of age. Twenty four percent started on an NNRTI plus 2 NRTIs, the most common backbone being ddI/d4T from 1996 – 1999 and AZT/3TC from 2000 onwards. Four drug regimens, most frequently NNRTI plus 3NRTIs, were used more often in the later time period (18% compared to 3%) and in UK/Ireland. Boosted PIs were used only from 2001 onwards (34% 2004-2008). Nelfinavir use declined over calendar time.

Just over half (53%) the infants initiating ART in 1996 – 1999 had viral load <400 copies/mL by 12 months, this increased to 57% in 2000 – 2003 and 77% in 2004 – 2008, but the difference was not

statistically significant, p=0.09. Infants aged 6 -12 months at ART initiation were more likely to be suppressed than those aged <3 months AOR 1.98 (95% CI 0.92 – 4.25), but again, this difference did not reach statistical significance, p=0.06.

Four-drug NNRTI regimens were associated with significantly better viral load suppression; AOR 3.00 (95% CI 1.24 – 7.23) compared to three drug NNRTI (reference) regimens, p<0.001. But boosted PI plus 2 NRTI regimens performed similarly to the reference regimen, AOR 1.39 (0.62 – 3.13). Higher baseline viral load was associated with less likelihood of virological suppression, AOR 0.67 per log10 copies/mL (95%CI 0.50 – 0.89), p=0.01.

For infants with data available, median baseline and 12 month CD4 count, CD4 percentage and CD4 z-score were 520 (IQR 271 – 1340) cells/mm3, 6% (-6 to 16%) and 0.92 (-0.14 to 2.34), respectively. Median CD4 z-score increase was 2.29 in infants receiving four-drug NNRTI regimens compared to 0.65 in those receiving three-drug NNRTI regimens and 0.91 for boosted PI regimens, p=0.04.

Eighteen percent of infants switched to second line treatment. The cumulative incidence of switching was 10.2% (95% CI 7.5 – 13.4) and 16.7% (13.0 – 20.7%) by 2 and 5 years respectively. Children starting treatment with a four drug NNRTI or boosted PI-based regimen were slower to switch; AHR 0.41 (95% CI 0.15 – 1.14) and AHR 0.26 (95% CI 0.06 – 1.19) respectively, p=0.03. Although the investigators noted data were sparse.

Twenty eight percent of children experienced at least one treatment interruption of more than 14 days, no factors predicted interruption.

Sixty five percent of children remained on treatment without interruption at last follow-up. Of these 36% had been treated for at least 5 years. The estimated probability of remaining on first-line ART without interruption was 79.3% (95% CI 75.1 – 83.1%) and 63.8% (95% CI 58.7 – 68.9%) by 2 and 5 years from starting ART respectively.

C O M M E N T

That boosted PI-based regimens performed similarly to NNRTI-based is contradictory to findings from IMPAACT 1060 that showed 20% higher rates of failure at 24 weeks in children aged 2 months to 3 years receiving NNRTI-based regimens compared to PI-based (whether or not they had been NNRTI exposed through PMTCT). Although IMPAACT 1060 was an RCT and these are cohort data – the difference in length of follow up is considerable.

That four drug NNRTI-based regimens did well is notable and induction/maintenance strategies in young children remain under explored.

Ref: European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group in EuroCoord. Early antiretroviral in HIV-1 infected infants, 1996-2008; treatment response and duration of first-line regimens. AIDS: 25(18):2279-2287, 28 November 2011.

OIs AND COMPLICATIONS

No increased risk of non-AIDS deaths from cumulative use of ART in EuroSIDA cohort

Nathan Geffen, Centre for Social Science Research, UCT

Two ongoing concerns for HIV positive people on ART are (1) whether long-term side effects shorten life-expectancy? and (2) is premature ageing related to either ART or HIV?

While both short and medium term outcomes have so far been very good, data for these questions requires following large numbers of patients over many years. Since it is impossible to have randomised control groups, the interpretation of cohort results also needs to consider numerous confounding variables.

The second question is a particular focus for current research. But a new analysis from the EuroSIDA cohort comes close to answering the first. In an article published in the 21 January 2012 edition of AIDS, there was no evidence in this huge cohort that the risk of death, all-cause or AIDS, increased with length of time on ART. [1]

EuroSIDA is one of the largest prospective observational ART cohorts. It includes nearly 17,000 patients from Europe, Israel and Argentina. This cohort's researchers previously have published important papers showing the benefits of ART on life expectancy. The authors explain that this is the first study "to look into the association of non-AIDS deaths with duration of time spent on combination antiretroviral therapy (cART) and with a long-term perspective of exposure to treatment. The results are reassuring that so far prolonged use of cART does not appear to be leading to increased risk of death due to some previously identified cumulative effect or a drug effect whereby there is a long induction period before disease appears."

Just over 12,000 patients were followed from baseline, defined as the time of starting ART or enrolment into EuroSIDA after 1996. Three quarters of the cohort is male. About 40% acquired HIV homosexually, 22% from IDU and 30% heterosexually. Interestingly, nearly 60% of the cohort are current or previous smokers and smoking status was unknown in more than 20%. At baseline about 21% were confirmed hepatitis C positive and about 53% were confirmed negative. About 10% had confirmed hypertension and just over 2% confirmed diabetes.

The researchers calculated incidence rates of death, AIDS-related and non-AIDS-related, per 1000 person-years of follow-up stratified by time of exposure to cART (< 2 years, 2 to 3.99 years; 4 to 5.99 years; 6 to 7.99 years and > 8 years).

During 70,613 person years of follow-up, a total of 1,297 patients died. AIDS caused 413 and non-AIDS diseases caused 884 deaths. Incidence rates per 1,000 years of follow-up were 18.3 overall (95% CI: 17.4–19.4), 5.85 for AIDS deaths (95% CI: 5.28–6.41) and 12.5 for non-AIDS deaths (95% CI: 11.7–13.3).

For the non-AIDS related deaths, 121 were due to infections, 182 due to liver-disease, 125 due to cancer, 122 due to cardiovascular disease, 90 due to violence (including suicide) and 91 due to other causes.

The main analysis compared mortality over the predefined periods on ART. The researchers used 2 to 3.99 years on ART as reference. In a multivariate analysis controlling for sex, ethnic origin, region of Europe, hepatitis B and C status, diabetes, hypertension, smoking, viral load, CD4 cell count, prior AIDS and age, they found the following incidence rate ratios of all-cause, AIDS-related and non-AIDS related deaths (see Table 1).

Table 1: Incidence rate ratios (95% CI) for all-cause, AIDS-related and non-AIDS related deaths

Time on ART	all-cause death	AIDS deaths only	non-AIDS deaths only
< 2 years	1.02 (0.88-1.17)	1.43 (1.13–1.81)	0.81 (0.67–0.98)
4-5.99 years	0.78 (0.66-0.93)	0.55 (0.38–0.78)	0.89 (0.73–1.09)
6-7.99 years	0.87 (0.72–1.04)	0.61 (0.42–0.89)	0.98 (0.79–1.21)
> 8 years	0.69 (0.57–0.83)	0.37 (0.24–0.56)	0.84 (0.68–1.03)

Longer time on ART was associated with a reduction in the risk of liver-related death, violent, and unknown deaths. But longer time on ART was also associated with an increase in mortality attributed to non-AIDS-related cancers. The researchers suggest this "may reflect ageing of the HIV population, as the effect was no longer present after adjustment for time updated age ..."

C O M M E N T

This article is reassuring for people who are recently diagnosed, who have access to modern ARVs and a medical history that is uncomplicated by coinfections or prior drug resistance. It is important that there is no signal of additional risk from treatment that is otherwise stable and effective.

The risk of premature ageing is the focus for research into immune activation and inflammation. It is also dependent on HIV negative controls to understand the impact of residual inflammation in people suppressed on HAART. In an editorial in Current Opinion Infect Diseases, Martin Fisher and Vanessa Cooper suggest caution over links between HIV or ART and ageing. They conclude, "Although undoubtedly there are higher rates of comorbidities in the HIV-positive population [...] Further research is needed to explore the mechanisms by which HIV/HAART may contribute to age-related diseases, the contribution of other important and potentially modifiable risk factors including smoking, alcohol and drug use, and the role of comorbid disease." [2]

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TUBERCULOSIS

Need for expanded access to two promising MDR TB drugs

Nathan Geffen, Centre for Social Science Research, UCT

Two experimental drugs for the treatment of MDR TB have completed phase II clinical trials. While neither is ready yet to be registered with a regulatory authority, bedaquiline (formerly TMC207, manufactured by Tibotec) is already better tested than most second-line TB drugs and has a good side-effect profile. The results of a Phase II trial of delamanid (formerly OPC-67683, manufactured by Otsuka Pharmaceuticals) are expected to be published soon.

Bedaquiline

HTB previously reported the development of bedaquiline and Phase II trial results [1,2]. Tibotec reported further results at a Critical Path to TB Drug Regimens meeting in Arlington in November. In this trial of 160 MDR TB patients, that compared an optimised background regimen plus either placebo or bedaquiline, there was faster culture conversion in the bedaquiline arm by 24 weeks (p=0.003). This was the primary endpoint. In secondary analyses, median time to culture conversion was 12 weeks vs 18 weeks. And at 24 weeks 79% of bedaquiline patients vs 58% of placebo ones had converted to sputum-negative (p=0.008). Side effects were distributed evenly over the two groups. There were no serious study drug-related side effects nor were there clinically significant differences in laboratory results. QT prolongation was seen on the bedaquiline arm, but there were no adverse events associated with this nor were there any prolongations greater than 500 milliseconds. [3]

In an ongoing open-label study (C209) that is assessing safety, efficacy and tolerability over two years of bedaquiline in smear-positive MDR TB patients, there was an 80% response rate at 24 weeks. Resistance to more drugs was associated with poorer response rates (56% for XDR, 77% for pre-XDR and 87% for MDR; p=0.0006). Patients with no cavitations also responded better (p=0.0157), as did patients on three or more potentially active drugs (p=0.0376). The most frequent side effects were nausea (11%), arthralgia (12%) and hyperuricaemia (14%). About 2% of the patients stopped bedaquiline due to an adverse event.

Tibotec has planned a Phase III superiority study (C210) with 600 subjects. The primary endpoint is intended to be relapse free cure at 15 months and a final analysis will also be done at 21 months.

The company is also considering a paediatric trial of 60 children to examine PK and safety.

The company has a compassionate use/expanded access programme. In countries that have a mechanism to authorise pre-approval access of unregistered medicines, patients with pre-XDR or XDR TB at what the company describes as validated centres can obtain bedaquiline. In countries where this is not feasible, such as China, Russia and Lithuania, an expanded access trial is planned. But at the time of the Critical Path meeting when this was presented, fewer than 30 patients had accessed the drug via compassionate use or expanded access.

Delamanid

In a phase II trial (Trial 204), about 480 patients with MDR TB were divided into three arms, stratified by disease severity. All patients received optimised background regimens. The first group received placebo, the second delamanid 200mg/day and the third delamanid 400mg/day for eight weeks. Patients were followed for an additional four weeks for safety and to confirm sputum conversion. The trial took place at 15 sites in 9 countries. Those patients who successfully completed Trial 204 were eligible to enroll in a 26 week open label protocol. Those who participated in Trial 204 and received placebo therefore had 26 weeks exposure to delamanid and those who received delamanid in trial 204 had a total of 34 weeks exposure to delamanid. [4]

Otsuka is currently recruiting for a Phase 3 trial to test the safety and efficacy of delamanid 200mg daily. [5]

C O M M E N T

These two drugs are the furthest along in the pipeline to treat drug-resistant TB. It is essential that they soon be tested together, so that if or when they are approved clinicians do not have to grapple with whether or not to add a single drug to failing regimens.

TB drug development is painfully slow. Consider that rilpivirine (TMC278), an antiretroviral of minor importance, was presumably discovered after bedaquiline (given that TMC278 signifies a chronologically later drug than TMC207). Yet the rilpivirine phase III trial started in 2008 and the FDA approved the drug last year. In contrast, bedaquiline is not expected to be registered in the very near future. This is not to single out Tibotec: indeed their TB development is the most advance. But this example shows the comparative lack of resources invested in getting TB drugs to market. Regulatory hurdles specific to TB worsen the situation. For example, some regulators want to see two-year relapse rates before granting approval.

Pre-regulatory approval expanded access should be a priority. Tibotec has committed to this but because of regulatory hurdles, lack of knowledge about the programme and perhaps lack of urgency from the company, we remain far from significant expanded access. It is unclear what commitment Otsuka has to expanded access.

Activists and patients must increase the pressure on Otsuka, Tibotec, health ministries and service providers to make these drugs available more widely for pre-approval access. More pressure must be put on the entire industry to develop more drugs, though as recent TAG/i-Base pipeline reports show, this is starting to improve.

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ZAMSTAR study suggests active case finding in households reduces TB prevalence

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The event at the World Lung Conference in Lille that generated the most media was the ZAMSTAR study results, presented by Peter Godfrey-Faussett of the London School of Hygiene and Tropical Medicine. [1] [2]

Four interventions were randomly assigned to six communities each, from a pool of 24 communities. The randomisation was also balanced across two regions comprising the study - Zambia and the Western Cape in South Africa - and high versus low TST levels, drawn at baseline from a sample of children in grades one to three. There were just under a million people altogether in the communities. Each community had a minimum of 25,000 people and a TB notification rate of more than 400 per 100,000 per year.

The primary endpoint was prevalence of active TB in a randomised sample drawn from the population.

The four interventions were as follows:

- Clinic based TB and HIV interventions (clinic, or control arm), which included TB and HIV programme collaboration, testing TB clients for HIV and voluntary HIV counseling and testing for clients screened for TB.
- Enhanced case finding (ECF), which included using community-based interventions to improve awareness of TB and HIV, fast track sputum collection for smear microscopy at a nearby health centre, a schools education campaign and mobile sputum collection points with community advocacy using local youth drama groups. Guiding principles of this intervention were that every person should be able to give sputum within a 30 minute walk and sputum smear results would be available within 48 hours.
- Household interventions (HH) which included, households of people with active TB being visited for active case finding, IPT for asymptomatic HIV-positive people and children less than six years old in the household, access to HIV counseling and testing and discussion with households to try to reduce risk of HIV-negative people contracting HIV, as well as counseling and referral for care.
- All of the above.

The study was run from 2006 to 2009. The ECF intervention attracted TB cases. Overall, 4.6% of the communities in ECF sites gave a sputum sample through ECF and 24% of smear-positive cases (20,630 people, of whom 14,130 were in the Zambian sites and 6,500 in South Africa) were detected via ECF. Interestingly, the South

African sites, despite dealing with a smaller number of sputa, had far less efficient turnaround times on microscopy and more missing samples. The costs ranged from $17,137 to $24,455 per ECF site per year, which is equivalent to $0.31 to $0.71 per person per year.

In the HH sites, just over 9,350 households were visited, containing nearly 37,000 people, about 6% of the population. About 27,000 people experienced all three of the study's scheduled visits. The cost ranged from $24,126 to $34,661 per site per year, or $0.48-$0.8 per person per year. Nearly every household individual received HIV education and group counseling, 67% had HIV tests and 38% (7,029 people) were HIV-positive. Godfrey-Faussett noted that 4,000 people were accessing ART and he described IPT as challenging.

The sample sizes in the prevalence survey at the end of the study were designed on the assumptions that there was a TB prevalence of 1% in the control arm and that a reduction of 30% in arms two and three would be detected. This turned out to be optimistic. On the basis of these assumptions the sample size was 4000 adults per community in each of the 24 communities. Geographically based cluster sampling was used based on standard census enumeration areas. All households in randomly selected enumeration areas were visited. A total of 55,450 households were visited including 123,790 individuals. Of these 90,600 were present and consented to a questionnaire, respiratory sample, HIV test and blood sugar test. Of these, 64,430 had evaluable TB cultures, of which 884 were positive for active TB. Overall prevalence in the Zambian sites was 542/100,000 adults, ranging from 221 to 1,096. Overall prevalence in the South African sites was 2,319/100,000 adults, ranging from 1,489 to 3,054.

The primary outcome was that prevalence for communities with the HH intervention was 746/100,000 versus 883/100,000 in communities without HH. The adjusted risk ratio was 0.78 [95%CI: 0.61-1.00]. The presentation is not clear here but this result appears to be adjusted for age, sex, TST prevalence, HIV prevalence, socio-economic status, education, marital status and smoking. Prevalence for communities with ECF was 927/100,000 versus 711/100,000 without ECF. The adjusted risk ratio was 1.11 [95%CI: 0.87-1.42].

Some secondary endpoints were also presented in Lille. From the presentation it appears that a baseline TST study was done in kindergarten children and then repeated on the TST-negative children at the end of the study four years later, in order to calculate infection incidence. A new infection was defined as a change in induration from 0mm to 15mm. Incidence in the HH arms was 0.87 per 100 person years versus 1.71 for the non HH arms. The adjusted rate ratio was 0.45 but this was non-significant [95%CI: 0.20-1.05]. For ECF this was 1.41 versus 1.05 for non ECF communities, for an adjusted rate ratio of 1.36, also non-significant [95%CI: 0.59-3.14].

Interestingly, incidence in Zambia was 1.2 per 100 person years versus 4.5 per 100 person years in South Africa.

No statistically significant effects were found for any of the interventions on TB treatment outcomes for index cases, cumulative TB incidence or HIV prevalence or incidence.

C O M M E N T

The ZAMSTAR study has produced many interesting results, not least the differences between TB incidence and systems in Zambia and South Africa. Many interesting papers should come out of it.

Unfortunately there was only one statistically significant endpoint presented: a lower prevalence at the end of the study in communities, which had the household (HH) intervention. But even this effect was modest. With a longer time period, the effect might have been greater. Moreover, since no baseline prevalence survey was done we cannot be sure that the differences in prevalence did not exist at baseline, but perhaps this concern will be allayed when the study results are published in a journal.

The household intervention appears to be affordable and certainly not harmful, so it might be worth implementing on a larger scale.

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A court case and a model show how poor conditions are fueling a TB epidemic in prisons

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Simon Johnstone-Robertson and colleagues at Cape Town and Stellenbosch universities have published the results of a model that calculated a TB transmission probability of 90% per year for awaiting trial prisoners in a large South African prison. They found that by implementing the national cell occupancy recommendation, the transmission probability could be reduced by 30%. And by implementing international recommendations, transmission probability could come down by 50%. They also found that implementing any one of improved passive case finding, modest ventilation increases or decreased lock-up times according to national or international standards would have a minimal effect. But by implementing all of these measures together including reduced occupancy, transmission could be reduced by 50% if national guidelines were adhered to and by 94% if international guidelines were used. [1]

The authors explain that South Africa has the fourth highest global incarceration rate, with more than 165,000 prisoners in 237 prisons. There is rapid turnover of awaiting-trial prisoners with 79% being imprisoned for less than 12 months and the number of people passing through the system annually exceeding 368,000. There are at any time about 3,200 prisoners awaiting trial in Pollsmoor, the 3rd-largest facility with awaiting trial prisoners in the country. Awaiting trial prisoners are mostly kept in communal cells of 40 to 60 prisoners each.

The South African Constitution's Bill of Rights says "Everyone who is detained, including every sentenced prisoner, has the right … to conditions of detention that are consistent with human dignity, including at least exercise and the provision, at state expense, of adequate accommodation, nutrition, reading material and medical treatment". [2]

A 2011 court judgment showed how far the country is from attaining this right. From November 1999 to 27 September 2004 Dudley Lee was an awaiting trial prisoner in Pollsmoor prison complex in Cape

Town, except for a four month period in 2000 during which he was out on bail. In June 2003, while he was in prison, he became ill and was diagnosed with pulmonary TB. He later sued the Minister of Correctional Services because the state's conduct caused him to become ill with TB.

Conditions in Pollsmoor Prison

In his court action, Lee's legal team claimed that:

- It was common for prisoners in the prison, including Lee, to be in close proximity to one another and to be housed in mass cells;
- A considerable proportion of prisoners were infected with active TB and that it was inevitable that some of the prisoners with TB would infect non-infected prisoners in close proximity to them;
- The Department of Correctional Services was aware of the presence of TB in the prison and the risk of non-infected prisoners becoming infected;
- The Department failed to adhere to prisoners' requests for adequate treatment to prevent and/or treat and/or cure people;
- The Department could have eliminated or reduced the spread of TB by creating conditions in the prison which made it impossible or difficult for tuberculosis to be spread by separating prisoners sick with TB from healthy prisoners, regular and effective checkups of prisoners to see whether or not they were actively infected with tuberculosis, and by providing regular and effective treatment for the control and elimination of the disease;
- The defendant's actions towards the plaintiff were unlawful because the Department violated the Constitution and the Correctional Services Act 8 of 1959 including sections that deal with respect and protection of physical integrity.

The court judgment describes overcrowded cells in which inmates typically spend 23 hours a day and an hour in an overcrowded recreational area. The environment is engulfed in tobacco smoke and fumes and coughing. There is a chronic shortage of nurses and staff and so the DOTS system that is supposed to be used is implemented inconsistently at best. TB data in the prison is poorly kept and inconsistent. For example, one doctor testified that treatment cases had to be recorded in a treatment register, which was held in quadruplicate. One copy was to be sent off to the Medical Officer of Health but documents, which were supposed to have been forwarded to the Medical Officer, were still in the register. Another example: A schedule of TB cases covering the period 1998 to 2009 had been prepared by the prison but other records in the prison showed the schedule was wrong. The total number of TB cases for 2001, according to the register, was 177 but the schedule recorded 69 cases with no cases provided at all for April to October.

South Africa has an extraordinarily high crime rate and there is not much public sympathy for prisoners. Dostoevsky's comment that a "society should be judged not by how it treats its outstanding citizens but by how it treats its criminals," is not a widely held view, in spite of Constitutional guarantees and legislation protecting prisoner rights. It is therefore notable that Mr Lee was acquitted and therefore arguments lacking empathy for criminals are irrelevant to his case. Moreover, as Johnstone-Robertson and colleagues point out, high TB transmission rates in prison contribute to a high TB burden in the general population.

The judge explained the effect of prison conditions on Mr Lee's testimony, "Given that prisoners who were awaiting trial spent approximately 23 hours out of every 24 in their cells, there must clearly have been little to distinguish one day from another. Indeed, the plaintiff himself said that one day was much like the next. The plaintiff spent approximately four and a half years in prison awaiting trial and attended court on approximately 70 occasions during that time. In these circumstances it does not appear to me to be surprising that the plaintiff became confused at times."

The judgment describes a justice system that is under-resourced, cruel and careless.

It is difficult for current or former state employees to testify against the state. The South African state, both during and post-apartheid has a record of ostracising health workers who stand up for patient rights. During the Tshabalala-Msimang era, some doctors were dismissed for providing antiretroviral treatment. So it is worth mentioning that the judge depended on testimony by doctors Paul Theron and Craven, who had been employed as part-time district surgeons at the prison, as well as a male nurse, Frans Muller, formerly employed at the prison. The judge described their testimony of the problems at the facility and their attempts to bring these problems to the attention of authorities as reliable. All three described their frustrated attempts to get the authorities to improve prison conditions.

On the other hand, experts who provide dubious testimony to defend indefensible state policies act without concern for the consequences of their actions. Therefore it is also worth noting the judge's views of one such witness. Prof. Paul van Helden, who is described on the website of Stellenbosch University's Division of Molecular Biology and Human Genetics, as the 4th highest ranked scientist in the world in the field of tuberculosis, gave astonishing testimony for the state. He argued that the plaintiff's acquisition of TB was primarily a consequence of genetics and re-activation, not the prison environment. Dr Theron rebutted his testimony. The judge pointed out a salient problem with it:

"Prof Van Helden also appeared to fall into the trap of losing his objectivity. So, for example, he used statistical evidence which was obtained in lower socio-economic areas such as Ravensmead and Masiphumelele to justify his opinion that the plaintiff, who came from a middle class environment, had probably been infected with TB prior to coming into the prison, in circumstances where he himself had admitted that those statistics would not be applicable in middle and higher socio-economic areas. Indeed, Prof Van Helden went so far as to say that the plaintiff's chances of having been infected with TB prior to entering prison were 'exceptionally high'."

The judge concluded, "There is no doubt that Prof Van Helden is an expert is his field, but he is not a medical doctor and has had no experience in the diagnosis and treatment of TB. His experience relates to research. On the whole, Prof Van Helden's evidence was tainted with bias and misinformation. As a consequence, his evidence is, in my view, in many instances unreliable and inaccurate."

The judge drew several conclusions, "On the totality of the evidence, I am accordingly satisfied that it is more probable than not that the plaintiff contracted TB as a result of his incarceration in the maximum security prison at Pollsmoor."

She also found "that a reasonable person in the position of the defendant would have foreseen that the prevailing conditions in the maximum security prison at Pollsmoor would reasonably possibly spread TB amongst inmates and cause inmates, such as the plaintiff,

who had not previously been ill with TB, to succumb to the disease."

She further wrote, "… the crisp answer to the question as to whether the defendant took reasonable steps to guard against the spread of TB, or to curb its spread in the maximum security prison, is no. There is no evidence that the defendant … took any steps whatsoever to guard against the spread of TB in the maximum security prison".

And she found that "a reasonable person in the defendant's position would, in my view, have taken steps to guard against the spread of TB in the maximum security prison, because it is such a formidable disease which is easily spread. More particularly, a reasonable person would have ensured that sufficient numbers of nursing staff were employed to perform the various tasks involved in the control and prevention of TB in the said prison."

The judge found the state's actions unlawful. She found the Minister liable to the plaintiff for having become ill with TB and ordered the state to pay costs. The damages amount was scheduled for a separate hearing.

Technical aspects of the model

Johnstone-Robertson and colleagues used data presented in the court case to construct their model. The court record provided several inputs into the model including TB incidence rate (5.5/100 person prison years, derived from 177 cases in a prison population of 3,200), period of infectiousness (1 to 180 days), ventilation (one air change per hour in a cell of 195m3) and floor area per prisoner (1.42m2). Other input parameters were infectious particles produced (1 per hour, a conservative estimate) and respiratory volume (360 litres per hour). The model was also run using other ventilation values: 3 air changes per hour (minimum international recommended ventilation), 8 (intermediate ventilation); and 12 (optimal ventilation), as well as different cell dimensions and floor areas per prisoner (3.34m2, a Red Cross recommendation and 5.4m2, WHO recommendation). The floor space per prisoner parameter corresponds to cell occupancy levels of about 250% (situation in Pollsmoor), 100% (South African recommendation) and 50% (international recommendation).

The authors explain that the model's main equation is the number of TB infections (C) occurring in a prison cell with susceptible prisoners (S). This was assumed to be a function of the number of infectious cases (I), their infectivity (q, quanta of infectious particles produced per hour), time of exposure (t, minutes), respiration rate (p, litres per hour), and germ-free ventilation (Q, litres per hour):

$C = S (1-\exp(-Iptq/Q))$

This is known as the Wells-Riley equation.

The authors further explain that the prevalence (P) of infectious adults at any time is the annual smear-positive incidence rate (M, per cent) and the period of infectivity (D, days) as

$P = M/[365/D]$.

The risk of contact with an infectious adult was modeled using a Poisson distribution.

The model is restricted to calculating the risk of infection, not the risk of active disease. Calculating the latter is extremely complex.

Interpret the transmission rate with caution. It is the annual risk of transmission, but Johnstone-Robertson and colleagues explain that 79% of prisoners awaiting trial are incarcerated for less than a year. Also the Wells-Riley model averages the effect of several complex variables. The model is useful for showing that awaiting trial prisoners are at high risk of acquiring infection, but the 90% estimate is an approximation without a confidence interval and should not be cited as the definitive calculation of risk.

The annual risk of TB transmission in the Western Cape in poor communities is also extremely high. One of the authors has pointed out to me that reaching adulthood in the province carries a similar risk of TB acquisition as being incarcerated as an awaiting trial prisoner in Pollsmoor for a year.

Recommendations

The horrendous conditions are not confined to just one prison. We only have detailed information on the situation in Pollsmoor because of this court case.

Johnstone-Robertson and his colleagues explain that there are many strategies to deal with the high transmission rate. They suggest that ventilator grills should not be closed at night. Communal cells can be cross-ventilated by using barred rather than solid doors and using corridor ventilator extraction systems. Carbon dioxide monitoring should be implemented. There should be active case finding and new fast TB diagnosis methods, such as the Gene Xpert presumably, should be introduced. They also say that TB notification data for South African prisons should not be considered secret or restricted information and that accurate data should be made available to the Judicial Inspectorate of Prisons to include in the annual report on the state of our prisons.

The problem, acknowledged by the authors, is that sensible recommendations for improving the situation have been made repeatedly by the Judicial Inspectorate. These can be found in the annual reports. [4] Dr Theron, Dr Craven and Mr Muller testified about the efforts they made to get the authorities to act. In 2000 the Department of Health set up a special task team to deal with TB. But its recommendations were either followed only temporarily, too little or not at all.

A further problem apparent from the case and several cases that the Treatment Action Campaign has been involved in is the sheer inefficiency of the court system, which creates a bottleneck that results in large numbers of awaiting trial prisoners. This is evidenced by the large number of trial hearings Lee attended and that, despite being acquitted, he spent the amount of time in prison reserved for serious crimes.

There is clearly a lack of political will to address TB in South African prisons. The steps to address TB have been identified but are not being implemented. Perhaps more cases of infected prisoners or former prisoners suing the state, such as this one, and protests are the only way to address this ongoing public health crisis.

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Thank you to Alex Welte for advice.

DRUG INTERACTIONS

Interactions between nevirapine and antimalarials (artemether and lumefantrine)

www.hiv-druginteractions.org

Artemether-lumefantrine and nevirapine-based antiretroviral therapy (ART) are the most commonly recommended first-line treatments for malaria and HIV respectively in Africa.

However, there is the potential for drug interactions with this combination as artemether and lumefantrine are substrates of CYP3A4 and nevirapine is both a substrate and inducer of CYP3A4.

This parallel-design pharmacokinetic study, obtained concentration-time profiles for lumefantrine, artemether, dihydroartemisinin and nevirapine in two groups of HIV-infected patients: ART-naïve and those stable on nevirapine-based therapy. Both groups (n=18 per group) received the recommended artemether-lumefantrine dose (80/480 mg). The primary outcome was day-7 lumefantrine concentrations, as these are associated with therapeutic response in malaria.

Nevirapine decreased artemether ($p<0.0001$) and dihydroartemisinin ($p=0.01$) AUC, but unexpectedly increased lumefantrine exposure. Median (range) day 7 lumefantrine concentrations were 622 ng/mL (185-2040) and 336 ng/mL (29-934) in the nevirapine and ART-naïve groups, respectively ($p=0.0002$). In the ART-naïve group, 6/18 subjects had day 7 lumefantrine concentrations below target (280 ng/ml) compared with 1/18 in the nevirapine group (Odds Ratio=8.5, 95%CI 0.9 to 80.02, $p=0.061$). Adverse events were similar between groups, with no difference in electrocardiographic QTcF and PR intervals.

The mechanism of inhibition of lumefantrine remains to be elucidated. Studies investigating the interaction of nevirapine and artemether-lumefantrine in HIV-infected patients with malaria are urgently needed.

Source: hiv-druginteractions.org (16 November 2011).

http://www.hiv-druginteractions.org/LatestArticlesContent.aspx?ID=564

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http://www.ncbi.nlm.nih.gov/pubmed/21947399

Interactions between antiretrovirals and complementary and African traditional medicines

www.hiv-druginteractions.org

The use of traditional/complementary/alternate medicines in HIV/AIDS patients who reside in Southern Africa is quite common. This review looks at the mechanisms of pharmacokinetic interactions and summarises the published clinical studies and case reports of antiretroviral-herbal interactions. In vitro screening studies of several African traditional medicinal plants and extracts are described and details given in a very useful table.

The review highlights the lack of clinical studies - despite a high incidence of HIV/AIDS in the African region, only one clinical study (efavirenz and Hypoxis hemerocallidea) has been conducted. More studies on African traditional medicines are warranted in order for more meaningful data to be generated and the true potential for such interactions to be determined.

Source: hiv-druginteractions.org (24 November 2011).

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Drug interactions between sirolimus (rapamycin) and ARVs

www.hiv-druginteractions.org

This study aimed to i) evaluate the safety and toxicity of rapamycin (sirolimus) in HIV-infected individuals with KS receiving antiretroviral therapy, ii) investigate rapamycin interactions with both PI-containing and NNRTI-containing regimens, and iii) assess clinical and biological endpoints.

Seven participants, 4 on ritonavir-boosted PIs (2 lopinavir, 2 atazanavir) and 3 on NNRTI-based regimens (2 efavirenz, 1 nevirapine), had rapamycin titrated to achieve trough concentrations of 5-10 ng/mL. Patients were monitored for safety and KS response. Despite pharmacokinetic interactions resulting in >200-fold differences in cumulative weekly rapamycin doses between participants on PI-containing and NNRTI-containing regimens, treatment was well tolerated. Maintenance rapamycin doses in the PI subjects were 0.1 mg and 0.2 mg twice weekly with lopinavir and 0.2 mg twice weekly and 0.3 mg three times weekly for atazanavir; doses in the NNRTI subjects were 2.3 mg and 6.7 mg daily for efavirenz and 2.8 mg daily for nevirapine. There were no significant changes in viral loads or cytokine levels; modest initial decreases in CD4 counts occurred in some patients. Three participants, all on PI-containing regimens and with higher rapamycin exposure, showed partial KS responses.

Rapamycin appears safe in HIV-positive individuals with KS and can, in some cases, induce tumour regression and affect its molecular targets. Significant pharmacokinetic interactions require careful titration to achieve target drug trough concentrations, but may be exploited to achieve therapeutic benefit.

Source: hiv-druginteractions.org (29 November 2011).

http://www.hiv-druginteractions.org/LatestArticlesContent.aspx?ID=566

Ref: Krown SE et al. Rapamycin with antiretroviral therapy in AIDS-associated Kaposi sarcoma: an AIDS Malignancy Consortium Study. J Acquir Immune Defic Syndr, 2011, epub ahead of print.

http://www.ncbi.nlm.nih.gov/pubmed/22067664

TRANSMISSION & PREVENTION

International PrEP study (VOICE) discontinues use of tenofovir vaginal gel due to lack of efficacy

Simon Collins, HIV i-Base

On 17 November a large international Phase 2b study looking at interventions to reduce HIV sexual transmission announced that it will discontinue use of a 1% tenofovir vaginal gel and matched placebo gel due to the study's data and safety monitoring board (DSMB) finding no difference in efficacy between these two groups. [1]

In the latest review the DSMB found a 6% HIV incidence rate among participants in both the tenofovir gel group and the placebo gel group. No other safety concerns (other than efficacy) have been reported with any of the studied interventions.

This is the second major change in the US NIH funded VOICE study (Vaginal and Oral Interventions to Control the Epidemic) in two months. In September, we reported in HTB that the use of daily oral tenofovir was discontinued for a similar lack of efficacy. [2]

The study originally enrolled more than 5,000 HIV-negative women at 15 clinical research sites in Uganda, South Africa and Zimbabwe. The study randomised women to one of five groups: daily oral tenofovir, daily oral Truvada, daily oral placebo tablet, daily tenofovir gel or daily placebo gel.

Only the daily oral Truvada and oral placebo arms will continue to be studied, with results expected in 2013.

References:

1. NHI press statement: NIH discontinues tenofovir vaginal gel in 'VOICE' HIV prevention study: product safe but no more effective than placebo. (25 November 2011).
   http://www.niaid.nih.gov/news/newsreleases/2011/Pages/VOICEdiscontinued.aspx
2. DSMB stops oral tenofovir monotherapy arm of VOICE PrEP study due to lack of difference compared to placebo. HIV Treatment Bulletin (HTB), October 2011.
   http://i-base.info/htb/15779

Further information

Statement and Q&A from Microbicide Trials Network (MTN):
http://www.mtnstopshiv.org/node/3909

OTHER NEWS

Infant feeding: TAC's position

The Treatment Action Campaign (TAC) recently issued a position statement regarding infant feeding among HIV positive women in South Africa.

TAC notes that recommendations and practice have been divided between the promotion of exclusive breastfeeding (mainly in Kwazulu-Natal) and formula feeding (mainly in Western Cape and Guateng).

Following recent studies showing that the risk of transmitting HIV during breastfeeding can be reduced significantly with antiretroviral (ARV) treatment for the mother or prophylaxis for the infant, the South African government plans to implement a new infant feeding policy from April 1 2012. This policy recommends exclusive breast feeding for the first 6 months and then the introduction of complementary foods and continuing breastfeeding until the infant is 12 months old. This will be accompanied by the provision of ARV treatment for women so indicated and nevirapine prophylaxis for infants of HIV positive mothers not yet indicated for treatment in South Africa.

The TAC statement calls for the new policy to cater for women who are unable to exclusively breastfeed for various reasons. TAC also stresses the regional variation in risk from formula feeding in South Africa and the importance of responsible introduction of the new policy, with an emphasis on the provision of ARVs. They are concerned that the Department of Health intends to end formula milk provision by September 2012, which, they are concerned is far too abrupt.

They state that patient education and counselling and provision of ARVs at PMTCT sites are critical for the success of the policy. And, that there should not be a sudden withdrawal of formula milk.

For more information **info@tac.org.za**.

WHO upholds guidance on hormonal contraceptive use and HIV

Women living with HIV or at high risk of HIV can safely continue to use hormonal contraceptives to prevent pregnancy

16 FEBRUARY 2012 | GENEVA - WHO has concluded, on the advice of its Guidelines Review Committee, that women living with HIV or at high risk of HIV can safely continue to use hormonal contraceptives to prevent pregnancy. The recommendation follows a thorough review of evidence about links between hormonal contraceptive use and HIV acquisition.

Current WHO recommendations in the Medical eligibility criteria for contraceptive use (2009 edition) therefore remain: there are no restrictions on the use of any hormonal contraceptive method for women living with HIV or at high risk of HIV. Couples seeking to prevent both unintended pregnancy and HIV should be strongly advised to use dual protection – condoms and another effective contraceptive method, such as hormonal contraceptives.

A study published in Lancet Infectious Diseases in October 2011 suggested that hormonal contraceptives, such as the pill or injectable contraceptives, may increase a woman's risk of HIV infection. It also found that women living with HIV and using hormonal contraception may be more likely to transmit the virus to their partner than women who did not use hormonal contraception.

WHO convened a technical consultation from 31 January – 1 February 2012 to review findings from all recent epidemiological studies on the issue. The meeting brought together 75 experts from 18 countries to review existing WHO recommendations in the light of these findings.

The experts recommended that women living with HIV, or at high risk of HIV, continue to use hormonal contraceptives to prevent pregnancy, but emphasised the need to also use condoms to prevent HIV acquisition and transmission. They also stressed the need for further research on the issue and the importance of offering a wider choice of contraceptive options.

On 15 February 2012 WHO's Guidelines Review Committee upheld the recommendations.

Source WHO press release:

http://www.who.int/mediacentre/news/notes/2012/contraceptives_20120216/en/index.html

New York court rejects AIDS denialist case against leading HIV community activist and journalist

Simon Collins, HIV i-Base

It is with great pleasure, and considerable relief that we report that the New York State Supreme Court Justice Louis B. York granted summary judgment in favor of Richard Jefferys in a defamation lawsuit brought by an AIDS denialist named Celia Farber. [1] Jefferys was represented in the case by Joseph Evall of Gibson, Dunn & Crutcher.

The suit against Jefferys arose out of a May 12, 2008, comment he submitted via the now-defunct website for "Whistleblower Week," conference. [2]

Jefferys was responding to an announcement that one of the conference sponsors was planning invite the AIDS denialists Celia Farber and Peter Duesberg to testify before a "tribunal" (including several Congresspeople), in the guise of whistleblowers.

In his comment, Jefferys asserted that Farber and Duesberg "are not whistleblowers, they are simply liars who for many years have used fraud to argue for Duesberg's long-discredited theory that drug use and malnutrition - not HIV - cause AIDS."

Jefferys wrote that he could provide "many, many examples, including their altering of quotes from the scientific literature, false representations of published papers, etc." He stated that including Farber and Duesberg in this event "will, regrettably, discredit and demean your efforts to support the very real issues of recrimination against legitimate whistleblowers."

Justice York found Farber to be a "limited purpose public figure," which means that a defamation case can only be sustained if the alleged defamatory comments were malicious and knowingly false. Also, since HIV is a matter of public concern and debate, Jefferys would have to be shown to have been grossly negligent regarding the factual accuracy of his statements.

Justice York decided that Jefferys comments reflected his sincere and informed opinions and therefore met neither of these criteria. Justice York's full opinion, which is available on the New York Courts website [3], provides a potted history of the AIDS denialism controversy and Celia Farber's role within that controversy. But this decision is not a judicial verdict on AIDS denialism. Instead, it is a strong defense of freedom of speech on contested questions of public policy.

NY Law School Professor Arthur Leonard wrote: "In effect, Farber was contending that defamation law can be used to stifle criticism of a controversial position on a matter of great public importance."

This report is edited from Arthur S. Leonard's excellent detailed legal analysis of this case. [1]

References

1. New York Court Rejects Journalist's Defamation Claim Against AIDS Activist. (12 November 2011). http://newyorklawschool.typepad.com/leonardlink/2011/11/new-york-court-rejects-journalists-defamation-claim-against-aids-activist.html
2. Whistleblower Week In Washington (May 12-16 2008) http://web.archive.org/web/20080517225306/http://www.w3conference.org/contact.htm
3. Justice York, Supreme Court, New York. (09 November 2011). http://decisions.courts.state.ny.us/fcas/fcas_docs/2011NOV/300106399 2009001SCIV.pdf

FUTURE MEETINGS

Conference listing 2012

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.

19th Conference on Retroviruses and OIs (CROI)

5–8 March 2012, Seattle

http://retroconference.org

10th European HIV & Hepatitis Drug Resistance

28–30 March 2012, Barcelona, Spain

http://www.virology-education.com

13th Intl Workshop on Clinical Pharmacology of HIV Therapy

16–18 April 2012, Barcelona

http://www.virology-education.com

47th European Liver Conference (EASL)

16–18 April 2012, Barcelona

http://www.easl.eu

18th Annual BHIVA Conference

17–20 April 2012, Birmingham

http://www.bhiva.org

20th Intl HIV Drug Resistance Workshop

9–13 June 2012, venue tbc

http://www.informedhorizons.com/resistance2012

14th Intl Workshop on Co-morbidities and Adverse Drug Reactions (Lipodystrophy Workshop)

19–21 July 2012, Washington

http://www.intmedpress.com/comorbidities

7th Intl Workshop on HIV Transmission

19–20 July 2012, Washington

http://www.virology-education.com

4th Intl Workshop on HIV Paediatrics

20–21 July 2012, Washington

http://www.virology-education.com/

Towards a Cure: IAS pre-conference symposium

20–21 July 2012, Washington

http://www.iasociety.org/Default.aspx?pageId=606

19th IAS World AIDS Conference

22–25 July 2012, Washington

http://www.aids2012.org

11th Intl Congress on Drug Therapy in HIV

11–15 November 2012, Glasgow

http://www.hiv11.com

HIV i-BASE

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

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

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

All i-Base publications are available online.

http://www.i-base.info

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

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

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

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

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

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

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

HIV i-Base

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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