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CONTENTS

EDITORIAL 2
HTB SUPPLEMENT: 2
- i-Base Guide to HIV Testing and Risks of Sexual Transmission

CONFERENCE REPORTS 3
2nd International Workshop on HIV & Women, 9–10 January 2012, Bethesda, USA
- Introduction
- 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

CONFERENCE REPORTS 6
5th HIV Persistence Workshop on HIV Reservoirs, 6–9 December 2011, West Indies
- Introduction
- Workshop report and commentary

ANTIRETROVIRALS 13
- Nevirapine once-daily prolonged release (PR) formulation available in the UK
- Etravirine 200 mg formulation available in UK
- Tenofovir label extended to paediatric indication
- FDA approve US paediatric dose for raltegravir
- FDA approve paediatric dose for darunavir
- Efavirenz dose increase to 800 mg QD with rifampin in patients greater than 50 kg

TREATMENT ACCESS 16
- FDA approval of generic ARVs
- Disastrous warning for global HIV programmes in 2012
- Janssen block Patent Pool access to darunavir, rilpivirine and etravirine
- UNITAID continues funding the Patent Pool, paediatric HIV medicines and malaria
- Michel Kazatchkine resigns from Global Fund: Gabriel Jaramillo, Brazilian banker, to serve as general manager
- Call to Action on Global Fund restriction to new funding to 2014
- Analysis of why the Global Fund cancelled Round 11
- Reaction to the Global Fund's decisions on Round 11 and grant renewals
- Activists oppose Gates Foundation funding study using low dose d4T

PAEDIATRIC CARE 23
- Delaying ART in childhood can reduce long-term CD4 count in adulthood

OIs AND COMPLICATIONS 24
- No increased risk of non-AIDS deaths from cumulative use of ART in EuroSIDA cohort

TUBERCULOSIS 25
- Need for expanded access to two promising MDR TB drugs

DRUG INTERACTIONS 26
- Interactions between nevirapine and antimalarials (artemether and lumefantrine)
- Interactions between antiretrovirals and complementary and African traditional medicines
- Drug interactions between sirolimus (rapamycin) and ARVs
- Contraceptive failure with etonogestrel implants and efavirenz: case reports

GUIDELINES 28
- Draft BHIVA ARV treatment guidelines online for comment until 5 March
- BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011
- Draft BHIVA pregnancy guidelines online for comment until 5 March

TRANSMISSION & PREVENTION 29
- NICE guidance on increasing the uptake of HIV testing

OTHER NEWS 29
- London Commissioning: new announcements

BOOK REVIEW 30
- Testosterone: a man's guide: practical tips for boosting physical, mental and sexual vitality, by Nelson Vergel

ON THE WEB 30
FUTURE MEETINGS 31
PUBLICATIONS AND SERVICES FROM i-BASE 32
ORDER FORM 32

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EDITORIAL

Welcome to the first issue of HTB for 2012, which includes an updated design thanks to comments from last years survey.

The last issue of 2011 highlighted serious concerns for global health, and the Treatment Access news in this issue continues this theme, with an indication that funding uncertainties will continue throughout the year. This includes further changes at the Global Fund and responses to the suspension of Round 11 grants—an outcome that became likely when donor pledges last year failed to match even the minimum working budget.

Fortunately these sobering events are balanced by more positive news. The FDA recently approved new indications and formulations of three important antiretrovirals. Tenofovir is now available as an oral powder and lower dose pills for an indication in children of two years and older. Raltegravir is available in a 100 mg scored chewable tablet and a 25 mg chewable tablet for children older than 2 and weighing greater than 20 kg. Finally, an oral suspension of darunavir was approved with two bands of dosing recommendations (age 3 to 6 years; and, older than 6 years) that, as with adult dosing include separate recommendation for naïve and experienced patients.

Our conference coverage in this issue comes from a meeting on HIV and women's health, and from a biannual workshop on HIV persistence and cure research. This report from Richard Jefferys both summarises the latest state-of-the-art in this field and comments on the complexity of interpreting these early reports.

The excitement is that the slow momentum from numerous research groups carries our ultimate hope to for a future that may offer alternatives to our current life-long reliance on ARVs.

Finally, and closer to home, BHIVA have published both new monitoring guidelines and the draft for the 2012 UK treatment guidelines. As this is the first update since 2008, with only a few weeks to comment it is important that the writing committee receive feedback promptly if this to be considered for the final document.

HTB SUPPLEMENT

A new i-Base guide is included as a supplement to this issue of HTB.

HIV Testing and Risks of Sexual Transmission was produced in response to the growing number of testing and transmission questions that i-Base receives. This resource brings together research into the impact of treatment on transmission and explains aspects of transmission that are often missed from resources that focus almost exclusively on condoms to explain risk.

This guide, written in non-technical language, will hopefully be as useful for training as for general information.

The guide is also already online, together with further reading, appendices and references that are not included in the print edition.

Additional copies are free – please order in the usual way (online, by email or fax-back the back page of HTB).

We welcome feedback on this guide and this short online survey includes space for comment:

http://i-base.info/guides/testing/feedback

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.

References

1. Reference Portal on HIV Reservoirs and Eradication Strategies website.
http://www.hiv-reservoir.net/
2. Margolis D. HIV Persistence during Therapy 5th International Workshop. natap.org, 2011.
http://www.natap.org/2011/HIV/122111_01.htm
3. Cohen J. Tissue says blood Is misleading, confusing HIV cure efforts. Science 23 December 2011: Vol. 334 no. 6063 p. 1614.
http://www.sciencemag.org/content/334/6063/1614.summary
4. Clinical Trial. Tissue drug levels of HIV medications.
http://clinicaltrials.gov/ct2/show/NCT01490346
5. Mario Stevenson Interview. (9 December 2011).
http://www.youtube.com/watch?v=_fhb95p__9g
6. Andrea Savarino Interview on HIV Cure. (10 December 2011).
http://www.youtube.com/watch?v=xIqdDU_OEFU
7. Lewis MG et al. Gold drug auranofin restricts the viral reservoir in the monkey AIDS model and induces containment of viral load following ART suspension. AIDS. 25(11):1347-1356, July 17, 2011.
http://journals.lww.com/aidsonline/toc/2011/07170
8. Hazuda D. Powerpoint can be downloaded at the bottom of this page, Luciw's data is on slides 21-25):
http://www.iasociety.org/Default.aspx?pageid=416#session5
9. TEDxUCLA - Leonard Rome – online video. (29 August 2011).
http://tedxtalks.ted.com/video/TEDxUCLA-Leonard-Rome-Vaults-mo
10. HIV-1 DNA is detected in bone marrow populations containing CD4+ T cells but is not found in purified CD34+ hematopoietic progenitor cells in most patients on antiretroviral therapy. J Infect Dis. (2012). First published online: 24 January 2012.
http://jid.oxfordjournals.org/content/early/2012/01/24/infdis.jir884.abstract
11. Bosque A et al. Studies of HIV-1 latency in an ex vivo model that uses primary central memory T cells. 2011 Jan;53(1):54-61. Epub 2010 Oct 21.
http://www.ncbi.nlm.nih.gov/pubmed/20970502
12. Hocqueloux C et al. Long-term immunovirologic control following antiretroviral therapy interruption in patients treated at the time of primary HIV-1 infection. 19 June 2010 - Volume 24 - Issue 10 - p 1598–1601.
http://journals.lww.com/aidsonline/Fulltext/2010/06190/Long_term_immunovirologic_control_following.27.aspx

ANTIRETROVIRALS

Nevirapine prolonged release (PR) once-daily formulation available in the UK

Following the approval in Europe last year of a prolonged release (PR) formulation of nevirapine (called extended release/XR in the US), this 400 mg once-daily tablet is now available in the UK.

The lead in dose of 200 mg once daily (using the original formulation) is still required, with the same caution not to increase to the 400 mg daily dose if the patient shows rash at the end of these 14 days.

The daily price of nevirapine PR has been price matched to the price of the 200 mg formulation.

Reference:

Boehringer press release: Viramune (nevirapine) prolonged-release once-daily formulation receives approval in the EU. (Septemebr 2011).

http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2011/21_september_2011nevirapine.html

Etravirine 200 mg formulation available in UK

On 17 January 2012, Janssen announced the launch of a 200 mg formulation of the NNRTI etravirine (Intelence).

The recommended oral dose of 200 mg etravirine is one tablet taken twice daily following a meal. The previous formulation required 2 x 100 mg twice-daily.

These tablets are dispersible in a glass of water. This option may be important given the new pill is slightly larger than the 100 mg formulation (22 mm vs 19 mm long).

The monthly list price for the 200 mg formulation is matched to the current daily price for the 100 mg formulation at £301.27.

Source: Janssen PR: Janssen launches 200mg etravirine (Intelence) for anti-retroviral treatment-experienced adults with HIV-1. (17 January 2012).

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

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

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 Dec 2012).

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

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/

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

Activists oppose Gates Foundation funding study using low dose d4T

On 14 December 2011 a group of prominent treatment activists from South Africa, Europe and the USA took the unusual step of contacting funders of a proposed international study. [1]

In writing to the Bill and Melinda Gates Foundation, the group were advocating against the proposed financial support for continued research into the use of the nucleoside analogue d4T (stavudine), even at the proposed lower 20 mg dose. [2]

Stavudine has long been discontinued in Western countries due to an unacceptably high risk of serious side effects in comparison to alternative drugs in the same class.

The letter argues strongly against this research and was concerned that previous meetings with representatives from the Foundation had not been formally answered. It argues for a focus on increasing access to safer cost-saving alternatives to d4T, not on seeking a comeback for a drug virtually abandoned in rich countries.

The objections, summarised from the letter, include:

d4T's significantly worse side effects are well documented

In 2004, d4T was removed from the list of preferred first-line antiretroviral drugs recommended by the US Department of Health and Human Services (DHHS). [3]

Starting in 2006, the WHO recommended that countries start moving away from d4T, and in 2009 recommended that the drug be phased out in first-line antiretroviral treatment (ART) programmes. [4]

In 2011, the European Medicines Agency (EMA) revised the indication for d4T, noting, "…that the use of the medicine should be severely restricted in both adults and children... Prescribers are reminded of the severe side effects seen with Zerit [d4T] and should only use the medicine when other appropriate treatments are not available. Patients being treated with Zerit should be assessed frequently and switched to appropriate alternatives as soon as possible." [5]

Evidence of d4T's toxicity in an operational setting has been reported from studies in Lesotho [6] and South Africa. [7]

There is no prospect that d4T 20 mg is a better option than tenofovir and retains significant toxicity even at lower doses. Results from over 10,000 patients randomised to receive 40 (30) mg or 20 (15) mg in early access (1992-94), reported rates of 15% vs 21% in the lower vs higher dose arms. [8]

The cost of these side effects will significantly reduce price savings

MSF report higher inpatient care and essential drug costs were higher for people on d4T than those on tenofovir. In Lesotho, the tenofovir-containing regimen generated higher life years and QALYs than AZT or d4T-based treatment. [9] As the costs of tenofovir and especially efavirenz drop, the cost benefit to patients and to health systems will become clearer. Since the study was completed, the global best price of efavirenz – which partly drives tenofovir costs – has almost halved ($97 ppy in 2009 to $52 today).

d4T's long-term toxicity will not be studied

The proposed 20 mg d4T dose might be acceptable in a short-term 48- or even 96-week virologic endpoint study (although Bristol-Myers Squibb studied and rejected 20 mg BID). But, because mitrochondrial toxicity is both dose and time dependent, many of d4T's most serious side effects (such as peripheral neuropathy and lipoatrophy) would not necessarily emerge until after such a study was completed. This study does not include monitoring of surrogate markers for mitochondrial toxicity, so it cannot shed light on the incidence of this serious adverse event.

This trial will not therefore be able to answer the primary policy question which drives it - whether long-term 20 mg d4T BID is as good as tenofovir QD in first-line ART regimens for use in public health programmes in resource-limited settings.

Implications for HBV coinfection

A tenofovir-based regimen is recommended for HIV/hepatitis B (HBV) coinfection, because d4T has no activity against HBV and resistance to lamivudine is inevitable. While HIV/HBV co-infection is an exclusion criterion for this trial, it may encourage persistent use of a suboptimal regimen for HIV/HBV co-infected people. Giving a d4T/lamivudine-based regimen to HIV/HBV co-infected people will create lamivudine resistant HBV in this population (90% at four years). [10, 11]

Potential savings may be out-dated when the study ends

The rationale for this trial is to lower treatment costs but the price of alternatives, notably tenofovir, has come down dramatically in the last several years, and is expected to decrease further as demand increases. According to MSF's annual ARV pricing report, tenofovir is now cheaper than AZT, with the price of single-drug tenofovir having decreased by 52% from 2008 to 2011, and the price of the triple fixed-dose combination of tenofovir, lamivudine and efavirenz having decreased by 53% to US$173 per person per year over that same time period. [12]

The proposed study will not have 96-week results before 2014, and will need perhaps five-year field effectiveness trial to determine longer-term tolerability.

The anticipated cost savings associated with d4T could easily be overtaken by expected further price reductions for tenofovir. Currently a one-pill-once-a-day regimen containing efavirenz and tenofovir costs roughly half of what d4T-based combinations cost when they was first introduced a decade ago.

Potentially greater savings could be achieved if the tenofovir prodrugs in development with both Gilead and Chimerix are approved. A recent announcement by Gilead of an agreement with Tibotec to develop an FDC of darunavir, emtricitabine, GS 7340 and cobicistat with "less than one tenth of the amount of the 300 mg of tenofovir disoproxil fumarate contained in Viread and Truvada" suggests that this is feasible. [13] Low milligram dosing (and therefore low potential cost) is also used for the integrase inhibitor dolutegravir (50 mg once daily).

The letter was signed by activists from Médecins Sans Frontières , HIV i-Base , Treatment Action Group (USA), Treatment Action Campaign (South Africa), Health GAP (USA) and the European AIDS Treatment Group.

The letter can be read in full on the TAG website:

http://www.treatmentactiongroup.org/hiv/2011/lowdose-stavudine-trial

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C O M M E N T

In the short time since the letter was distributed two further publications has supported caution into further use of d4T. Vichet Phan and colleagues published data on rates of severe d4T-associated toxicity in a cohort of patients in Cambodia, with 7% of people having neuropathy within the first years and a cumulative incidence of lipoatrophy of 56% by 3 years and 72% by 6 years. [14]

Further concerns from people directly affected by continued use of d4T, the Malawi Network of People Living with HIV/AIDS (MANET+) held a press briefing concerned by the slow pace for phasing out current use of this drug in Malawi. Despite the funding crisis the Malawi government has a priority for this to be completed by June 2012. [15]

It is unclear why the Gates Foundation considers this study to be a priority and it seems an aberration in an otherwise carefully considered strategy for supporting research into the optimisation of ART for resource limited settings . This includes the ENCORE 1 study of low dose efavirenz, the reformulation of tenofovir to increase its bioavailability (working with CHAI) and the development of innovative potentially long acting formulations.

As Bad Science's Ben Goldacre wrote: "Why is the Gates Foundation supporting this trial of a rubbish AIDS drug?". [16]

References

1. Andrieux-Meyer I et al. Letter Opposing a Proposed Low-dose Stavudine Trial (14 December 2011). http://www.treatmentactiongroup.org/hiv/2011/lowdose-stavudine-trial
2. A randomised, double-blind study to demonstrate non-inferiority of stavudine (20 mg BID) compared with tenofovir (300 mg QD) co-administered with lamivudine and efavirenz in antiretroviral-naive patients over 96 weeks. If funded and approved, the trial is anticipated to start early 2012.
3. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 29 October 2004. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL10292004002.pdf
4. WHO Rapid Advice: Antiretroviral therapy for HIV infection in adults and adolescents. November 2009, page 10. http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf
5. EMA 17 February 2011. EMA/127094/2011. EMEA/H/C/000110/R/79. Questions and answers on the review of Zerit (stavudine): Outcome of a renewal procedure. http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/human/000110/WC500102227.pdf
6. Adjusted hazard ratio: 5.43, 95% confidence interval: 3.31 to 8.91. Bygrave H et al. 2011. Implementing a tenofovir-based firstline regimen in rural Lesotho: clinical outcomes and toxicities after two years. J Acquir Immune Defic Syndr. 2011 Mar 1;56(3):e75-8. http://www.ncbi.nlm.nih.gov/pubmed/21164354
7. Menezes et al. A longitudinal study of stavudine-associated toxicities in a large cohort of South African HIV infected subjects. BMC Infectious Diseases 2011, 11:244 doi:10.1186/1471-2334-11-244
8. Anderson R et al. Design and implementation of the stavudine parallel track programme. Comparison of safety and efficacy of two doses of stavudine in a simple trial in the US parallel track programme. J Inf Dis. 1995; 171:118-22.
9. Jouquet et al. Cost and cost-effectiveness of switching from d4T or AZT to a TDF-based first-line regimen in a resource limited setting in rural Lesotho. JAIDS Publish Ahead of Print. DOI: 10.1097/QAI.

10. Communication Dr Mark Sonderup, Division of Hepatology, University of Cape Town.
11. Benhamou Y et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virusinfected patients. Hepatology. 1999;30:1302-1306.
12. Untangling the Web of Antiretroviral Price Reductions, 14th Edition. July 2011. Médecins Sans Frontières Campaign for Access to Essential Medicines
13. Gilead press release. Gilead Sciences finalises agreement with Tibotec Pharmaceuticals to develop and commercialise a single-tablet regimen of Prezista(R) with Emtriva(R), GS 7340 and Cobicistat. (15 November 2011).
14. Phan V et al. Incidence of Treatment-Limiting Toxicity with Stavudine-Based Antiretroviral Therapy in Cambodia: A Retrospective Cohort Study. PLoS ONE 7(1): e30647. doi:10.1371/journal.pone.0030647
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0030647
15. Nkhoma P. Manet+ wants ARV d4T phased out. The Daily Times (Malawi). (30 January 2012)
http://www.bnltimes.com/index.php/daily-times/headlines/national/4079-manet-wants-arv-d4t-phased-out
16 Goldacre B. Why is the Gates Foundation supporting this trial of a rubbish AIDS drug?
http://bengoldacre.posterous.com/why-is-the-gates-foundation-supporting-this-t

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$\pm$ 0.07 (point estimate $\pm$SE) lower for each year older at initiation and their long term z-score -0.5$\pm$ 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.

OIs AND COMPLICATIONS

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

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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]

Reference

1. Kowalska JD et al. for EuroSIDA. Long-term exposure to combination antiretroviral therapy and risk of death from specific causes: no evidence for any previously unidentified increased risk due to antiretroviral therapy. AIDS 26:315–323. (28 January 2012). Free full text online.
   http://journals.lww.com/aidsonline/Fulltext/2012/01280/Long_term_exposure_to_combination_antiretroviral.7.aspx
2. Fisher M and Cooper V. 2012. HIV and ageing: premature ageing or premature conclusions? Curr Opin Infect Dis 25:1–3. Free full text online.
   http://journals.lww.com/co-infectiousdiseases/Fulltext/2012/02000/HIV_and_ageing___premature_ageing_or_premature.2.aspx

TUBERCULOSIS

Need for expanded access to two promising MDR TB drugs

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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.

Delamanid

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 bedquiline, 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.

References
1. Geffen N. 2009. TMC207 reduces time to sputum conversion in phase II trial on patients with drug-resistant TB. HTB 10(7) July/August 2009. http://i-base.info/htb/4403
2. Clayden P. 2011. Faster conversion rates with TMC-207 versus placebo plus OBT for the treatment of MDR-TB. HTB 12(1-2) January/February 2011. http://i-base.info/htb/14441
3. Presentation by Tibotec to Global TB Community Advisory Board at CPTR 2011.
4. Otsuka. A Placebo-controlled, phase 2 Trial to Evaluate OPC 67683 in patients with pulmonary sputum culture-positive, multidrug-resistant tuberculosis (TB). http://www.clinicaltrials.gov/ct2/show/NCT00685360 5.
5. Otsuka. Safety and efficacy trial of delamanid for 6 months in patients with multidrug resistant tuberculosis. http://www.clinicaltrials.gov/ct2/show/NCT01424670

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

Ref: Kredo T et al. The interaction between artemether-lumefantrine and nevirapine-based antiretroviral therapy in HIV-1 infected patients. Antimicrob Agents Chemother, 2011, 55(12): 5616-5323.

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).

http://www.hiv-druginteractions.org/LatestArticlesContent.aspx?ID=567

Ref: Müller AC, Kanfer I. Potential pharmacokinetic interactions between antiretrovirals and medicinal plants used as complementary and African traditional medicines. Biopharm Drug Dispos, 2011, 32(8): 458-470.

http://www.ncbi.nlm.nih.gov/pubmed/22024968

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

Contraceptive failure with etonogestrel implants and efavirenz: case reports

www.hiv-druginteractions.org

Two case reports of unintended pregnancies suggest that etonogestrel implants should be used with caution in patients on efavirenz.

The first case had been receiving efavirenz, zidovudine and lamivudine since November 2002 and had an etonogestrel implant inserted in January 2004. Pregnancy was detected in April 2006 and conception dated to December 2005. The second case had an etonogestrel implant inserted in July 2005 and started efavirenz, tenofovir and emtricitabine in April 2007: in October 2007 she became pregnant following a condom rupture. In both cases, implants were removed at pregnancy diagnosis and were found to have been properly inserted.

The most probable mechanism explaining the contraceptive failure is low etonogestrel concentrations due to induction of cytochrome P450 by efavirenz. As it is not currently possible to predict the decrease of etonogestrel implant efficacy when an enzyme inducing drug is coadministered, an alternative method of contraception should be recommended.

Source: hiv-druginteractions.org (06 December 2011).

http://www.hiv-druginteractions.org/LatestArticlesContent.aspx?ID=568

Ref: Leticee N et al. Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. Contraception, 2011, epub ahead of print.

http://www.ncbi.nlm.nih.gov/pubmed/22036046

GUIDELINES

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

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 l 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

TRANSMISSION & PREVENTION

NICE guidance on increasing the uptake of HIV testing

The two NICE guidance topics that published in March 2011 are:

- **Increasing the uptake of HIV testing among black African communities living in England**
- **Increasing the uptake of HIV testing among men who have sex with men**

The free access support tools from NICE includes:

- Online educational module developed in conjunction with BMJ Learning to help healthcare professionals in primary care and non-HIV specialist settings improve their knowledge of key clinical areas in relation to HIV testing
- Audit support for general practice, secondary care and specialist services to assist with the audit process, thereby helping to ensure that practice is in line with the NICE recommendations. This consists of audit criteria and data collection tool(s) and can be edited or adapted for local use
- Self assessment tools for services or local partnerships to establish how close their current practice is to that recommended in the guidance and to help with prioritising implementation activity
- Costing report which provides an overview of both the potential costs and savings from putting the NICE guidance into practice
- Costing template helps individual NHS organisations and local health economies to quickly assess any impact that the NICE guidance may have on local budgets
- Slide set for primary and secondary care featuring key recommendations for clinical practice: developed to support professionals in general practice and secondary care who are not specialists in HIV testing or treatment
- Clinical indicator diseases table (reproduced with kind permission from the British HIV Association) to accompany the above slide set
- Slide set for commissioning of specialist sexual health services developed for those involved in the commissioning or strategic planning of sexual health services, it provides an overview of all recommendations from both pieces of guidance.

The NICE tools and guidance are online via the following guidance pages:

http://guidance.nice.org.uk/PH33

http://guidance.nice.org.uk/PH34

OTHER NEWS

London Commissioning: new announcements

London SCG Commissioning Intentions Published

The London SCG Commissioning intentions have been published and are available at this link below.

http://www.londonspecialisedcommissioning.nhs.uk/?assetId=705&assetGroupId=704

London Adult HIV Needs Assessment

The London SCG has published the Executive Summary of the Adult HIV Needs Assessment, This shows that HIV is one of the fastest growing chronic conditions in London.

http://www.londonspecialisedcommissioning.nhs.uk/?assetId=707&assetGroupId=704

Ensuring access to HIV care and treatment in London

With over 30,000 HIV positive patients receiving care in London, developing a plan to secure continued access to the best available treatment is critical.

http://www.londonspecialisedcommissioning.nhs.uk/?assetId=709&assetGroupId=704

BOOK REVIEW

Testosterone: A man's guide: practical tips for boosting physical, mental and sexual vitality; by Nelson Vergel

Simon Collins, HIV i-Base

This is the second edition of a book by the US activist Nelson Vergel. It is a users guide to testosterone by an HIV positive man who has researched the subject over many years for his own care.

The non-technical sections include helpful tips about what not to do as well as the best approaches. This looks at how to assess potential testosterone deficiency, including what to measure (free vs total), when and how, and the impact of age on target ranges including fluctuation in levels throughout the day. The information is in the context of supplementary approaches being dependent on working with your doctor, not only to ensure that an appropriate dose and formulation are used (oral supplementation being the least useful), but that routine monitoring guides the safety of this approach.

Replacement therapy is discussed, usually recognising this as a lifelong treatment, as testosterone supplementation reduces the need and ability for the body to continue it own production. The risks from interrupting treatment and a period of testosterone depletion until the body adjusts include depression, weight loss, lack of motivation and reduced sex drive - often the symptoms that suggested treatment in the first place.

The guide also discusses side effects from testosterone and how to manage these, including the experimental use of Human Chorionic Gonadotropin (HCG) to maintain normal testicular function and reverse shrinkage. It discusses alternative treatment for low sex drive and erectile dysfunction including a review of data (or lack of it) for non-approved products. It also includes the importance of lifestyle modifications including diet and exercise, the importance of adherence and on finding a doctor that will monitor and prescribe treatment.

This is a users guide, written by an activist who has used many of the available approaches for over 16 years and he shares his experiences of different approaches. But the author professionally trained as a chemical engineer, and this informs his discussion on the chemistry behind a daunting range of formulations (including injections, topical creams, patches, implants, underarm products and sublingual and buccal preparations).

Although titled "a man's guide" the book includes information on testosterone use in women, including links for further reading, though for future editions this might be helpful if this was collated and compiled in a separate chapter.

Nelson is also co-author of Built to Survive, a similar guide to using anabolic steroids, nutrition and exercise to develop and maintain muscle mass for HIV positive men.

Nelson Vergel - Testosterone: a man's guide: practical tips for boosting physical, mental and sexual vitality; 2nd edition, 2011.

IBSN: 978-0-9837739-1-7. £12.00, paperback; £ 6.41 Kindle.

ON THE WEB

Conference abstracts

2011 HIV Persistence Workshop

6–9 December 2011, St Maarten.

The abstract book and the late breakers are available in PDF format. This site includes daily summaries of the workshop that will be followed in the next few weeks by more detailed reports.

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

Online reports

A Call for Comprehensive Responses to HIV in People Who Use Drugs

The Lancet article "Time to Act: A Call for Comprehensive Responses to HIV in People Who Use Drugs" originally published in July 2010 is now available in Chinese, Farsi, French, Japanese, Polish, Russian and Spanish from the Open Society Foundation.

The article reviews the available evidence to demonstrate how a comprehensive response can reduce HIV infection rates in people who use drugs, by implementing coherent public health and law enforcement strategies. It is argued that cost-effective interventions such as needle and syringe exchange programs, increased access to treatment and the decriminalisation of people who use drugs, to name but a few, would benefit individuals, families and communities.

The documents can be downloaded from:

http://www.soros.org/initiatives/drugpolicy/articles_publications/publications/time-to-act-20100907

Free full text online articles:

Achieving a cure for HIV infection: do we have reasons to be optimistic?

Le Douce V et al. J. Antimicrob. Chemother. (2012) January 2012.

http://jac.oxfordjournals.org/content/early/2012/01/31/jac.dkr599.full

Are there reasons to be optimistic that a cure for HIV infection may be achieved? From our point of view the answer is 'yes', but this will not be achieved in the short term.

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

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

The i-Base website is designed with portals for healthcare professionals, HIV-positive people and community advocates.

It is fast and easy to access, use and navigate.

http://www.i-Base.info

All i-Base publications are available online, including editions of the treatment guides. The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

The Q&A web pages enable people to ask questions about their own treatment:

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

RSS news feed is available for HIV Treatment Bulletin for web and PDA.

The advocacy resources include an online training manual with eight 2-hour modules that include questions and evaluation. Training modules start with basics, including CD4, viral load and other monitoring tests, combination therapy and side effects, and include overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment.

An average of 100,000 pages individual ISP accounts contact the website each month, with over 6000 hits a day.

Non-technical treatment guides

i-Base treatment guides

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

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

- Introduction to combination therapy (March 2012)
- HIV testing and risks of sexual transmission (February 2012)
- HIV and quality of life: side effects & complications (December 2010)
- Guide to changing treatment and drug resistance (February 2011)
- Guide to HIV, pregnancy & women's health (September 2011)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)

Publications and reports

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published every two months in print, PDF and online editions.

HTB South

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

HTB Turkey

HIV Tedavi Bülteni Türkiye (HTB Turkey) is a Turkish-language publication based on HTB and produced three times a years by an independent group of Turkish doctors, activists and health care workers.

ARV4IDUs

An electronic publication, Antiretroviral Treatment for Injecting Drug Users (ARV4IDUs) is produced in English and Russian language editions, to provide an overview of research related to IV-drug use and antiretroviral treatment.

Why we must provide HIV treatment information

Photography by Wolfgang Tillmans

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

Text is provided by activists from 25 countries and 50 full colour photographs by Wolfgang Tillmans.

Translations of i-Base publications

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

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

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

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

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

Languages include:

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

Advocacy resources

Online treatment training for advocates

http://i-base.info/ttfa

Entry-level curriculum relating to HIV and treatment. Eight modules include: immune system and CD4 count; virology, HIV and viral load; an introduction to antiretrovirals (ARVs); side effects of ARVs; opportunistic infections and coinfections: HIV and pregnancy; drug users and HIV; and clinical trial design and the role of advocates

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

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community advocates from across the UK that has been meeting since 2002. It now includes over 480 members from over 120 organisations. The CAB has a separate website, where reading material, reports and presentations from all meetings are posted. Membership is free.

http://www.ukcab.net

Phoneline and information services

Treatment information request service - 0808 800 6013

i-Base runs a specialised treatment information service.

We can provide information by phone, email and online based on the latest research.

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

Online Q&A service

An online question and answer service that now has over 1500 questions online. Questions can be answered privately, or with permission, can be answered online.

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

Other resources

Treatment 'Passports'

Booklets for HIV-positive people - whether newly diagnosed or positive for a long time - to record health and treatment history. Like other publications, they are available free as single copies, or in bulk.

Generic clinic forms

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

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

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

i-Base can add your hospital or Trust logo to these forms.

Order publications and subscribe by post, fax or online

All publications can be ordered online for individual or bulk copies. All publications are free. Unfortunately bulk orders are only available free in the UK.

http://i-base.info/order

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

htb(e)

HIV TREATMENT BULLETIN (e)

HTB(e) is the electronic version of HTB, which is published six times a year by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered by fax or post using the form on the back page or directly from the i-Base website:
http://www.i-Base.info
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Dr Stephen Taylor, Birmingham Heartlands Hospital.
Dr Gareth Tudor-Williams, Imperial College, London.
Dr Edmund Wilkins, Manchester General Hospital, Manchester.

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

Some articles are reproduced from other respected sources. Copyright for these articles remains with the original credited authors and sources. We thank those organisations for recognising the importance of providing widely distributed free access to information both to people living with HIV and to the healthcare professionals involved in their care. We thank them for permission to distribute their work and encourage HTB readers to visit the source websites for further access to their coverage of HIV treatment.

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http://www.i-Base.info

HIV i-Base is a registered charity no 1081905 and company reg no 3962064. HTB was formally known as DrFax.

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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If your employer operates a Give-As-You-Earn scheme please consider giving to i-Base under this scheme. Our Give-As-You-Earn registration number is **000455013**. Our Charity registration number is 1081905

Since many employers match their employees donations a donation through Give-As-You-Earn could double your contribution. For more information on Give-As-You-Earn visit www.giveasyouearn.org

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From April 2005 the Inland Revenue is operating a system whereby you can request that any refunds from them should be paid to a charity of your choice from the list on their website. If you feel like giving up that tax refund we are part of this scheme and you will find us on the Inland Revenue list with the code: **JAM40VG** (We rather like this code!) Any amount is extremely helpful.

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- **Guide To HIV Testing and Risks of Sexual Transmission** *(February 2012)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Guide To HIV, Pregnancy and Women's Health** *(September 2011)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Introduction to Combination Therapy** *(July 2010)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Guide to Changing Treatment and Drug Resistance** *(February 2011)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **HIV and your Quality of Life: Side Effects and other Complications** *(December 2010)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Guide To HIV and hepatitis C coinfection** *(March 2009)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Clincical Trials: a community guide to HIV research** *(March 2009)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____

Treatment guides in other languages are available as PDF files on the website

- **Adherence planners and side effect diary sheets - In pads of 50 sheets for adherence support**
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