

july–august 2012

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EDITORIAL

This issue of HTB mostly represents the wealth of data presented before and during the 19th IAS World AIDS Conference in Washington DC in July.

Our first reports from IAS 2012 focus on new antiretrovirals, regimens and strategies including the investigational integrase inhibitor dolutegravir and booster cobicistat; in vitro and animal data that might help to assuage concerns about potential toxicities with BMS-98600, which being a derivative of d4T has a hard reputation to shake off; and first observed association between atazanavir and gall stones.

There was some overlap between IAS 2012 and the excellent 4th International Workshop HIV Pediatrics preceding it so we have combined the reports from both meetings. These include the first data from infants and children receiving Cipla's sprinkle formulation of lopinavir/ritonavir from CHAPAS-2 (supported by the Monument Trust). We have been following this development for some time and it is encouraging to see a product under investigation specifically targeting this population in resource limited settings where infants and young children badly need new options that are fit for purpose.

Prevention studies included disappointing results from using maraviroc in macaques but interesting new data on mechanisms for the benefit from medical male circumcision.

We also provide an overview of cure research presented at the meeting - which had a high profile including an interesting satellite.

As well as these reports we have a round of some of the more useful publications released at IAS 2012, which were abundant (and of variable quality). MSF had a particularly bumper crop.

Also preceding the main conference was the 14th International Workshop on Co-morbidities and Adverse Drug Reactions (Lipodystrophy Workshop). From this we report on a study looking at proteinuria as a potential early marker of tenofovir-related renal toxicity and an ageing study showing a higher incidence of one or more co-morbidity plus a higher number of co-morbidities in HIV positive people compared to negative controls.

Finally, for a change of scenery, we include reports from Sitges in June, where 20th International HIV Drug Resistance Workshop was held. From this meeting we have - among others - a further report of in vitro data for BMS-98600, this time showing its resistance profile, and a depressing first case report of transmission with five-class drug resistance. Plus, TAG's Richard Jeffreys urges caution when interpreting new data on the Berlin patient presented here and provoking some misleading articles.

In the midst of all this activity, in July, the US Food and Drug Administration (FDA) approved Truvada (tenofovir/FTC) to reduce the risk of HIV infection in uninfected people who are at high risk of acquiring HIV. The first antiretroviral approval for PrEP.

So, if you have a post-Olympic gap to fill there is plenty of summer reading to be had!

HTB SUPPLEMENTS

HIV and your quality of life: a guide to side effects and other complications (July 2012)

This updated guide to side effects has been expanded to include information on health issues related to HIV and ageing.

This edition includes new sections on the importance of staying active and how to eat well: both diet and exercise become increasingly important options for living well with HIV.

Available in print, online and in PDF format. Please order print copies online, free to all UK clinics, organisations and individuals.

<http://i-base.info/guides/7463>

i-Base/TAG 2012 pipeline report

Not a printed supplement this time (although some of you might have picked one up at the conference) but the annual i-Base/TAG pipeline report is now published online.

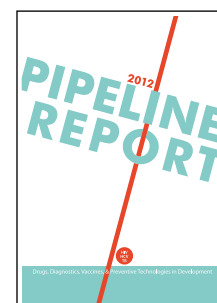
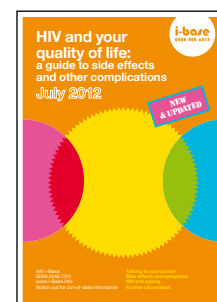
The report reveals the deepening gulf between new scientific advances that make it possible to prevent, treat, and in some cases cure people living with HIV, hepatitis C virus (HCV), and tuberculosis (TB), and access to these where they are most needed.

There are many promising new candidates in the pipeline, as Simon Collins's chapter on adult antiretrovirals reveals, with at least 15 new drugs and combinations in phase 2 and 3 studies.

And for the paediatric HIV pipeline, Polly Clayden demonstrates that some companies have also made significant progress in more rapidly developing new antiretroviral options for children living with HIV.

Richard Jeffreys covers this year's groundbreaking FDA review of Truvada for PrEP, HIV cure research, and the ongoing challenge to discover and develop safe and effective vaccines to prevent HIV transmission.

For the hepatitis C virus (HCV) Tracy Swan and Karyn Kaplan provide a sweeping overview of the exciting developments in HCV combination therapy and cure, with over 25 direct-acting antivirals (DAAs) in development for HCV.



Tuberculosis (TB) research is also livening up, particularly in TB drugs and regimens, although hardly a revolution (unlike HCV), but Erica Lessem shows significant progress in new TB drug and regimen development.

Read the report online and download PDF format.

<http://i-base.info/htb/17118>

We have also launched a new website in partnership with TAG with search features and archives of previous reports.

This will be updated as new developments occur, in addition to the annual report. We will also be adding new materials - such as slide sets - and hope that it will be a useful new resource.

www.pipelinereport.org

CONFERENCE REPORTS

19th IAS World AIDS Conference

22–25 July 2012, Washington

Introduction

Over the last decade, the International AIDS Society (IAS) World AIDS Conference has increasingly focused on social rather than scientific aspects of HIV and this trend continued this year. About 85% of over 3000 studies and presentations were on human rights, funding, access, policy, prevention, access to care and issues of stigma. The majority of clinical studies were posters (a summary presented on a 2 x 1 metre display) and this year, only 25 posters each day focused on early or basic science (Track A) and less than 75 on clinical studies (Track B). From over 80 hours of podcasts only five sessions were focused on treatment.

So although the important clinical studies are reported below, the web casts on the social, political and human rights aspects provide the context for the main meeting. The panelists and speakers in many of these sessions sometimes provide more insight into some settings than a test tube or statistical calculation.

More than 20,000 delegates attend, but within a few hours of the closing sessions the halls empty and the venue prepares for computer games (where IAS stands for Increased Attack Speed), or life empowerment, booked for the following week. And it becomes easier to distill the point of the activity and expense.

With this more than other medical conferences, certain issues usually come to represent the meeting rather than headline results based on new scientific advances. Remembering the impossibly slow progress of the “3x5” campaign (3 million people on treatment by 2005), this conference, with its shift to focus on treatment access has sailed past this once-daunting goal.

So this year the conference marked the time when more than eight million people in low and middle-income countries are able to access and remain on treatment. And although the media focus was “Turning the Tide Together”, achieving 8 million people on treatment is probably a more tangible focus.

Programme strengths this year included:

A platform for speeches

On policy and access, and for HIV positive people and activists leading many of the community responses to give their diverse perspectives on a world stage.

Asserting the focus on a cure

Many sessions included early research connected to a cure, including a pre-meeting workshop.

Clinical data

Highlights included new drugs for HIV and TB, children’s health and other studies.

HIV prevention

With an emphasis this year focusing on policy and implementation rather than new clinical data. This especially focused on Treatment as Prevention (TasP), PrEP, circumcision, needle-exchange, and infant and maternal access to treatment.

HIV and long-term health

The increasing focus on inflammation as a concern, overlapping with ageing and use of earlier treatment.

To launch publications and reports

Many publications contain more detail and planning that could fit into a single symposium or poster, and most are available free online.

Other community events

The conference included a “Global Village” for many community events. This year, more than 50,000 quilts hung in the conference halls and laid out along part of the National Mall Park near the Washington Memorial and 50 other locations in Washington.

Reports in this issue of HTB include:

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- In vitro and animal data support safety profile of BMS 986001: d4T-like NRTI currently in clinical trials
- Switching to rilpivirine/tenofovir/FTC fixed dose combination from boosted-PI regimen: SPIRIT study draws the line at 24 weeks
- Maraviroc plus atazanavir/ritonavir in a nuke-sparing regimen in treatment-naive patients
- Five-year results with raltegravir in naïve and experienced patients
- First report: atazanavir-related gallstones (cholelithiasis)
- Paediatrics studies at 19th International AIDS Conference and the 4th International Workshop on HIV Pediatrics
- Novel lopinavir/ritonavir sprinkle formulation for children in resource-limited settings
- Update on new antiretrovirals for children and adolescents
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- High prevalence of peripheral neuropathy in children taking d4T in rural South Africa
- High levels of maraviroc in rectal tissue fail to protect macaques from SIV transmission following rectal exposure
- Mechanisms for circumcision to reduce HIV transmission in different penile tissue: target cell differences rather than keratinisation
- Launch of publications during IAS

AIDS 2012: WEBCASTS

IAS: social and political talks online as web casts

Simon Collins, HIV i-Base

This conference has one of the highest profiles for public speeches on policy and many sessions are online and available as podcasts.

If you can be moved by carefully chosen words that elevate human rights with the dignity they deserve, focused on strategies for change, then take time to listen online or by podcast.

When available, IAS webcast links are to the individual talk, rather than to the whole session (this occurs for Kaiser Foundation webcasts). More than 80 sessions are available. Most focus on social issues, policy and human rights and vary from 1-2 hours for sessions and vary from 5 to 30 minutes for individual speeches.

Links to web casts of a few highlights are included below.

Opening programme

<http://pag.aids2012.org/session.aspx?s=53>

The auditorium was filled for this diverse and moving programme.

This included **Elly Katabira** (departing IAS president) and **Diane Havlir**, the co-chair for the conference, the **Gay Men’s Choir** (Washington) and 24 year old **Annah Sango** from Zimbabwe talking about her hopes as an HIV positive woman.

Also, **Jim Yong Kim**, current president of the World Bank (and the first to address the AIDS conference) and former director of HIV/AIDS department at the WHO, talks about why an end to AIDS should be more a reality now than “3x5” was in 2002, and how the World Bank has a commitment to ending AIDS and poverty.

“As we look back on the history of this epidemic, it is hard to say any one moment when the tide began to turn because the truth is that we have been turning back the tide, step by painful step, for 30 years. And at nearly every turn it is activists and their communities that lead the

way. It was activists and their communities that devised safer sex, condom use, needle exchange and virtually all the behavioural prevention that we use today.”

“It was activists that transformed drug development and regulatory policies and involved patients in clinical research, cutting drug approval times in half in the global north. It was activists in Durban, who in 2000 began to push for access to antiretrovirals in the developing world, and who kept pushing and are pushing still today for them to be affordable and available to everyone who needs them, everywhere.”

“And it was activists whose deep understanding of the communities most affected by AIDS that has spurred a movement to promote the health and dignity of gay men, sex workers, drug users that has now reached every corner of the world. It was TASO in Uganda, ACT-UP in the US, TAC in South Africa, Grupo de la Vida in Brazil, the Layers Collective in India, the Thai Drug Users Network, and countless organisations like them, that have woven together one of the most extraordinary movements that the world has ever seen.”

Michel Sidibe (UNAIDS)

“Held for the first time in 22 years after the US lifted the HIV travel ban [...] If we do not scale up treatment as prevention, if we do not reach 15 million people on treatment by 2015, if we do not eliminate new infections in children, if we do not close the funding gap... history will never forgive us [...] The funding gap of \$7 billion a year is killing people. [...] The end of AIDS is not free, it is priceless.”

Françoise Barré-Sinoussi (IAS)

<http://pag.aids2012.org/flash.aspx?pid=368>

Virologist, advocate and IAS president for the next year, who speaking on her 2008 Nobel laureate for medicine for her role in discovering HIV, said “it does not belong to me but to all of us”.

And outlining key issues for the next year:

“As a scientist, in 2012 it is unacceptable that more than 300,000 babies are born HIV-infected each year when we have had, since the 1990s, the tools to prevent mother to child transmission; that risk reduction strategies including needle exchange programmes are not implemented everywhere when we know this is one of the most effective scientific interventions to prevent HIV infection in IV drug users; and that intellectual property rights undermine access to high quality medicines and diagnostic tools in resource limited settings”.

Bill Clinton

Plain-speaking assertion that continued treatment roll-out is both achievable and affordable from one of the key movers behind price reductions for first and second-line ART.

<http://pag.aids2012.org/flash.aspx?pid=365>

Phill Wilson

HIV positive US activist, highlighting the complexity of HIV healthcare in the US where young gay men especially if they are black continue to have high rates of new infections and still have their lives cut short: 60% of black MSM are likely to be HIV positive by age 40.

<http://pag.aids2012.org/flash.aspx?pid=1558>

AIDS activism today: reigniting the spark

<http://globalhealth.kff.org/en/AIDS2012/July-26/AIDS-Activism-Today.aspx>

This webcast included activists, many of who are HIV positive talking about human rights issues and activism in very different circumstances: **Alexei Kurmanaevskii** talking about drug users and the fight for access to treatment in Russia. **Khavtini Slamah** in a web link from Malaysia because the US denied visa access to sex workers talking about the sex worker activist response. **Gina Brown** talking about AIDS activism in the US and this links with the civil rights and women’s movement.

Anthony Fauci

Overview of the scientific advances and implemented global programmes for treatment and prevention that give hope for eliminating HIV. (17.5 minutes into session)

<http://pag.aids2012.org/flash.aspx?pid=1559>

Hilary Clinton

[Talking over a protest against US trans-pacific trade deals that limit access to generic drugs]: “What would an AIDS conference be without a little protesting? Part of the reason we have come as far as we have is because so many people all over the world have not been satisfied that we have done enough, and I am here to set a goal for a generation that is free of AIDS.”

An essential talk to understand the changing US political approach to HIV, notably different to an “emergency” response (the “E” in PEPFAR). “If we want to save more lives we have to go where the virus is [...] And that means science should guide our efforts”. Political and personal. (78 minutes into the Turning the Tide session).

<http://globalhealth.kff.org/AIDS2012/July-23/ending-the-epidemic.aspx>

Rolake Odetoynbo

"Women with HIV have come a long way, from being zero – lower than trash to having seats at the table – we had to earn our place [...] We have fought for this but also salute those people who have helped open doors... We did not ask to be the face of HIV, but 60% of HIV positive people in Africa are women. Women are 80% of care providers – doctors, nurses and counsellors - grandmothers and mothers and sisters and people leaving school to care for our dying relatives."

In a session of on women in leadership that included a video message of support from Aung San Suu Kyi and an address by Laura Bush, Rolake, 50 minutes in, is the one not to miss.

<http://globalhealth.kff.org/AIDS2012/July-26/leadership.aspx>

Naomi Akers

Five minute personal contribution on why sex work is work, the differences between legal and illegal settings and lack of rights.

<http://pag.aids2012.org/flash.aspx?pid=10392>

Anna Zakowicz and Ian McKnight

Activists from Poland and Jamaica giving their perspectives in the closing session. In the call for universal treatment they challenged pharmaceutical companies: "Why are you not in the Medicine Patent Pool? Why are you restricting access to generic medications? Why are you wining and dining doctors at this conference when people are dying of AIDS on the streets on the streets of Harare, Soweto and Islamabad". And to the US, "Why are you, on the one hand providing treatment through PEPFAR while only the other hand you are denying treating by supporting free trade agreements that block access to low cost generics".

<http://pag.aids2012.org/flash.aspx?pid=371>

Sharon Lewin

<http://globalhealth.kff.org/AIDS2012/July-27/Closing-Session.aspx>

Also in the closing session, Sharon Lewin with a promise that all delegates will be welcomed to Melbourne in 2014, including former and current sex workers and injecting drug users. US entry restrictions had prevented these delegates from countries outside the US from openly attending the conference - and this was highlighted in many presentations.

AIDS 2012: ANTIRETROVIRALS

New booster - cobicistat as an alternative to ritonavir

Simon Collins, HIV i-Base

The pharmacokinetic booster cobicistat is one component of the recently FDA-approved, single-pill, integrase inhibitor-based combination Quad.

Cobicistat has similar pharmacokinetic boosting properties to ritonavir by inhibiting the cytochrome P450 3A4 liver enzyme, but without direct antiretroviral activity. In Washington, results were presented from a phase 3 registrational study that compared cobicistat to ritonavir to boost atazanavir in 692 treatment-naïve patients, in combination with tenofovir/FTC. Exclusion criteria included preexisting renal impairment defined as eGFR <70 mL/min.

Groups were closely matched with approximate baseline characteristics that included 83% male, 60% white ethnicity and median age 36 years. Median CD4 and viral load were approximately 340 cells/mm³ and 60,000 copies/mL.

For the primary endpoint of viral efficacy (<50 copies/mL at 48 weeks), similar responses were reported for the two groups, at 85% in the cobicistat versus 87% ritonavir arms (difference: -2.2%; 95% CI: -7.4 to 3.0) and 86% in each arm for patients with a baseline viral load >100,000 copies/mL.

Similar outcomes were seen in safety analyses, with 7% of patients in each arm discontinuing due to grade 3/4 side effects.

Median increases in total bilirubin at week 48 in the cobicistat vs ritonavir group were 1.9 and 1.7 mg/dL, with 4% vs 3% having bilirubin-associated side effects. Median increases in serum creatinine were 0.13 and 0.09 mg/dL respectively. Median changes in total cholesterol were +4 and +10 mg/dL and increases in triglycerides were +16 and +24 mg/dL.

Mean steady state plasma exposures of atazanavir were comparable (C_{tau} = 796.1 vs 853.4 ng/mL).

An earlier study this year reported that the boosting impact of cobicistat does not match ritonavir with all protease inhibitors and may not be appropriate to use with tipranavir. Also, cobicistat increases serum creatinine, which in turn affects the calculation of eGFR, complicating the standard monitoring for tenofovir-related renal toxicity. Currently an increase of 0.4 mg/dL or greater is proposed as a conservative cut-off to address concerns about potential tenofovir renal tubular toxicity.

Cobicistat does not appear to improve the gastrointestinal or lipid side effects of ritonavir, it has already lead to new coformulations that have studies underway. These include four-in-one combinations of a new Quad with darunavir/cobicistat/FTC plus the investigational tenofovir prodrug GS-7340; the first single-pill protease inhibitor formulation of darunavir/cobicistat/GS-7340/FTC; and two combined PI/booster pills of atazanavir/cobicistat and darunavir/cobicistat.

Cobicistat was submitted to the FDA on 28 June 2012. [2]

Reference

1. Gallant J et al. Cobicistat versus ritonavir as pharmacoenhancers in combination with atazanavir plus tenofovir disoproxil fumarate/emtricitabine: phase 3 randomized, double blind, active-controlled trial, week 48 results. 19th International AIDS Conference. 22-27 July 2012, Washington. Oral abstract TUAB0103.
<http://pag.aids2012.org/Abstracts.aspx?SID=202&AID=13085>
<http://pag.aids2012.org/flash.aspx?pid=1204>
2. Gilead press release. Gilead submits new drug application to the U.S. FDA for boosting agent cobicistat. (28 June 2012).
http://www.gilead.com/pr_1710422

Dolutegravir vs raltegravir in treatment-naive patients: 48 week results from the SPRING 2 study

Simon Collins, HIV i-Base

Francois Raffi, from University of Nantes, France, presented the SPRING-2 study as an oral late breaker.

This was a randomised, double-blind, double-placebo controlled, non-inferiority study in treatment-naive patients. Participants (from Canada, US, Australia and Europe) were randomised (1:1; n=411 in each arm) to receive either 50 mg dolutegravir once-daily or 400 mg raltegravir twice-daily (plus matching placebo) with investigator selected tenofovir/FTC (60%) or abacavir/3TC (40%), stratified by baseline viral load (above and below 100,000 copies/mL) and by NRTI choice. The primary endpoint was viral suppression to <50 copies/mL with a lower margin confidence interval set at -10% to determine non-inferiority.

This was a largely white, male study population in patients with early-stage HIV. Approximate baseline characteristics for the study included median age of 36 years, 85% male, 85% white and 10% African American. Median viral load and CD4 count were approximately 35,000 copies/mL and 360 cells/mm³ respectively. No figures for the range or IQR were provided for the median values. However, 28% of patients had baseline viral load >100,000 copies/mL and 12% had a CD4 count <200 cells/mm³. Approximately 2% and 10% were coinfecting with hepatitis B and C respectively.

Viral efficacy rates were 88% for dolutegravir and 85% for raltegravir, which, after adjusting for baseline viral load and NRTI, met the criteria for non-inferiority (difference 2.5%; 95% CI: -2.2% to 7.1%). Dolutegravir had a similarly rapid, or perhaps slightly faster, response compared to the already racy drop seen with raltegravir, with 70% of patients undetectable by week 4 and >80% by week 8.

Discontinuations were similar between the dolutegravir and raltegravir arms (11% vs 14%) and occurred for similar reasons (4% vs 6% for lack of efficacy, 3% each for protocol violations, 2% each for side effects, and <1% vs 2% for each of loss to follow up and withdrawal of consent).

There were 7% of patients in each arm without 48-week data, with these discontinuations driven predominantly by reasons other than side effects.

Median CD4 counts increases were similarly close at weeks 8, 24 and 48: +88, +182 and +230 cells/mm³ in each arm.

Stratification by baseline viral load and nucleoside/tide use also met non-inferiority endpoints. Response rates were 90% vs 89% with <100,000 copies/mL (difference 0.4; 95%CI -4.5, 5.3) and 82% vs 75% (difference: 7.5; 95%CI -3.1, 18.0) with >100,000 copies/mL; and 86% vs 87% using abacavir/3TC (difference -0.8; 95%CI -8.2, 6.6) and 89% vs 85% using tenofovir/FTC (difference 4.6; 95%CI -1.3, 10.6) – all dolutegravir vs raltegravir, respectively.

There were slightly fewer patients with virological failure, defined as confirmed viral load >50 copies/mL at week 24 or after, in the dolutegravir arm (5% vs 7%; n=20 vs 28) with most (19/20) being between 50 and 400 copies/mL. Two patients in the raltegravir arm rebounded to 10-50,000 copies/mL and one to >100,000 copies/mL. One of these patients developed integrase inhibitor and NRTI mutations, with NRTI resistance only in three others. No mutations were detected in the dolutegravir arm.

Tolerability was good in both arms with low numbers of patients with grade 3 (n=2 vs 5) and grade 4 (n=2 vs 0) side effects. Serious adverse events occurred in 7% vs 8% (n=29 vs 31) but were only judged to be drug-related in 3 vs 5 patients. These included arrhythmia, hypersensitivity and hepatitis (dolutegravir) and convulsion (2), hypersensitivity/hepatitis, diarrhoea (raltegravir). Only 2% of patients in each arm discontinued due to side effects.

Grade 3/4 laboratory abnormalities were infrequent and included increases in creatinine phosphokinase (5 vs 3%), AST (3 vs 2%) ALT (2 vs 2%) and lipase (2 vs 3%), all dolutegravir vs raltegravir. Slightly higher increases in mean creatinine (+12/3 vs +4.7 mmol/L; p=NS) and changes in creatinine clearance (-15.5 vs -5.4 mL/min; p=NS) occurred in the dolutegravir arm but dolutegravir does not affect eGFR and there were no discontinuations related to renal events in either arm.

C O M M E N T

These results show similar levels of efficacy for both integrase inhibitors in treatment-naive easier to treat patients, with good tolerability.

Of note, both drugs also have paediatric formulations currently in development and/or clinical studies.

Reference:

Raffi F et al. Once-daily dolutegravir (DTG; S/GSK1349572) is non-inferior to raltegravir (RAL) in antiretroviral-naïve adults: 48 week results from SPRING-2 (ING113086). 19th International AIDS Conference. 22-27 July 2012, Washington. Late breaker oral presentation THLB04.

<http://pag.aids2012.org/abstracts.aspx?aid=20990>

<http://pag.aids2012.org/flash.aspx?pid=3888>

Elvitegravir vs raltegravir: 96 week phase III results in treatment experienced patients

Simon Collins, HIV i-Base

Richard Elion from Whitman-Walker Health in Washington presented updated 96 week results from the phase 3 head-to-head study of elvitegravir vs raltegravir. [1]

The 48 week results, first presented at the IAS conference in Rome last year showed elvitegravir to be non-inferior to raltegravir based on viral suppression to <50 copies/mL. [2]

This phase 3 study randomised 712 treatment-experienced patients to either the investigational integrase inhibitor elvitegravir (150 mg once-daily) or raltegravir (400 mg twice-daily), each with matching placebo, plus a background regimen of a boosted protease inhibitor (PI) plus a third drug.

Baseline characteristics included mean age 45 years; 18% women; mean CD4 count 260 cells/mm³ (45% with CD4 <200), median viral load 20,000 copies/mL (with 26% >100,000 copies/mL) and 5% and 15% of patients were coinfecting with HBV or HCV respectively. Approximately 63% patients had primary resistance to drugs in two or more classes (PI 33%, NRTI 72%, and NNRTI 61%), balanced between arms. Choice of background PI was largely darunavir (58%), lopinavir/r (19%) or atazanavir (16%). The third drug was an NRTI in 80% of patients (tenofovir 59%, tenofovir/FTC 27%, abacavir 4%, 3TC 3%, other 7%) with 13% using etravirine and 6% using maraviroc.

The primary endpoint of viral load <50 copies/mL through week 48 (time to loss of virologic response [TLOVR] analysis) was achieved by 59% of elvitegravir vs 85% raltegravir patients respectively.

Virological response out to 96 weeks dropped similarly in each arm (to 48% vs 45%), maintaining non-inferiority for the comparison (difference 2.6; 95%CI -4.6, +9.9). Approximately 40% of patients in each arm discontinued before week 96. Reasons were balanced between arms (non-compliance: 39 vs 34; loss to follow-up: 29 vs 31, lack of efficacy: 17 vs 21, etc) except for withdrawal of consent (30 vs 17), all elvitegravir vs raltegravir, respectively. The respective percentages of patients with virological failure increased to 26% vs 29% and 26% of patient in each arm had discontinued for other reasons (including side effects). CD4 increases were similar at +205 vs +195 cells/mm³ (all elvitegravir vs raltegravir, respectively).

Genotypic resistance test results were available for approximately 25% of patients with virological failure in each arm, with a quarter of these in each arm (23/87 vs 26/93) having integrase inhibitor-associated mutations. Although some mutations were shared, elvitegravir was associated with T66I/A (n=8), E92Q/G (n=7), N155H (n=5), T97A (n=4), S147G (n=4) and Q148R (n=4); and raltegravir with N155H (n=16), Q148H (n=7) and T97A (n=4). Resistant mutations associated with NRTIs (3%), PIs (1%) and NNRTIs (2-3%) were similar in each arm. A more detailed analysis of the resistance results was presented as a separate poster. [3]

Grade 2-4 side effects were similar (68% in each arm) with slightly higher diarrhoea with elvitegravir (13% vs 7%). Limited details were provided for the 20% rate of serious side effects in each group but these only led to discontinuation in 4% vs 3% of patients. Grade 3/4 laboratory abnormalities were also similar, except for slightly higher ALT/AST/GGT in the raltegravir arm (2-3% vs 5-7%).

Elvitegravir has already been submitted to both the FDA and EMA for a decision on regulatory approval as a single agent.

References

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In vitro and animal data support safety profile BMS 986001: d4T-like NRTI currently in clinical trials

Simon Collins, HIV i-Base

Two posters were presented on a new d4T-like nucleoside in development with BMS.

This molecule is structurally similar to d4T but, according to in vitro data, it is 75-fold more virologically potent and more than 200-fold less active as an inhibitor of mitochondrial polymerase-gamma, responsible for toxicity associated with d4T.

While d4T (stavudine) has long been dropped as an option in Western countries and even in WHO guidelines, it continues to be widely used in resource-limited settings where it continues to produce irreversible peripheral neuropathy and facial lipoatrophy.

Both side effects, together with more rare but potentially fatal complications that include lactic acidosis, are mediated by the impact of the drug on mitochondrial function. So the prospect of a new d4T-like compound rolling into clinical trials must be dependent on pre-clinical data that has cleared this toxicity hurdle.

The first of two posters reported in vitro results from exposing renal, muscle and fat cells to therapeutic dose concentrations of BMS 986001 and four other NRTIs: tenofovir, AZT, d4T and abacavir.

Primary cultures of human renal proximal tubule epithelium, muscle, preadipocytes and differentiated adipocytes (subcutaneous) were exposed to each of the NRTIs at their reported C_{max} concentration and at 200 µM for 5, 10, 14 and 19 days.

Six in vitro cytotoxicity parameters were measured: percent dead cells, cell protein and ATP content, lactate concentration in the media, and mtDNA (ATP8) content by qualitative PCR.

BMS 986001 was not cytotoxic in any of the four cell cultures tested. Tenofovir showed toxicity in muscle cells and preadipocytes with regard to mtDNA content which decreased in a concentration- and time-dependent manner to approximately 40% control values. In contrast, AZT and d4T were cytotoxic in all four cell culture types and for all measured parameters. Abacavir was only significantly cytotoxic at the 200 µM concentration.

A second poster reported finding no BMS-986001-related changes in renal function (serum and/or urine urea, creatinine, total protein and excretion, albumin, phosphorus, calcium, and glucose) or biomarkers of renal toxicity (serum cystatin C and renal b2-microglobulin, clusterin, and NGAL), or in bone formation (serum osteocalcin) or bone resorption (serum free deoxy pyridinoline and C-terminal cross-linking telopeptide of type I collagen [C-Tx]; and urine N-Tx) following oral six month dosing, at any dose tested compared to control group in rat and cynomolgus monkeys. [2]

C O M M E N T

These in vitro data contribute to supporting the safety of the ongoing clinical trials programme for this new compound.

The major pre-clinical toxicity with BMS-986001 (up to 6-month duration) at high exposures has been dyserythropoiesis in the bone marrow with lower myeloid to erythroid ratios and decreased red blood cells, and thrombocytopenia.

There remains a need for NRTIs with improved tolerability both in the developed and developing world. If this compound is being primarily developed for the former, it should have a parallel programme for the later, including early discussions with generic manufacturers to help ensure its access (if successful and approved) where d4T continues to be used.

Reference

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Switching to rilpivirine/tenofovir/FTC fixed dose combination from boosted-PI regimen: SPIRIT study draws the line at 24 weeks

Simon Collins, HIV i-Base

Frank Palella from Northwestern University, Chicago, presented results from an international study of 476 patients on stable boosted-PI combinations who were randomised 2:1 to switch to open label rilpivirine/tenofovir/FTC (n=317) or continue on their current treatment (n=159).

Although patients could be on first or second line treatment, they had to be NNRTI-naive, although, inexplicably, detection of the primary NNRTI mutation K103N was allowed. The primary endpoint was viral suppression (<50 copies/mL) at week 24 with non-inferiority defined by a lower margin for the confidence interval of -12%, and follow up for the rilpivirine arm until week 48. Lipid changes were also evaluated.

Baseline characteristics were balanced between arms and included approximate median age 42 (IQR 35-49), 86%-91% male, 75% white, 19% black. Median time since first ART was just under 3 years (IQR 1.7-4.8) and mean CD4 count was around 600 cells/mm³ (SD +/- 237). Approximately 80% of people were taking tenofovir/FTC at baseline with PI use predominantly atazanavir/r (37%), lopinavir/r (33%) and darunavir/r (20%).

At week 24, virologic suppression was similar with 94% vs 90% in the NNRTI vs PI arms (difference 3.8; 95%CI -1.6 to +9.1) remaining suppressed <50 copies/mL. Approximately 5% of patients in each arm had missing data. CD4 increases were also similar (+20 vs +32 cells/mm³ respectively; p=0.28).

Approximately 2% vs 5% of patients were defined as non-suppressors in the NNRTI vs PI arms. This represented three people in the NNRTI arm: one who was <400 copies/mL, one at 410 copies/mL with the M184V mutation and one who rebounded to 11,000 copies/mL and who failed with M184V, V90I, L100I and K103N. This last patient was reported as a protocol violation due to previous use of efavirenz and not meeting the criteria of viral suppression for six months prior to study entry.

The majority of patients with detectable viral load in the PI/r arm (7/8) had viral load between 50 and 400 copies/mL and were likely to be blip results, but one had rebounded to 13,000 with the M184V mutation. Of the patients without 24 week data, three patients in the NNRTI arm switched due to CNS-like side effects (sweats, fatigue, depression, anxiety and insomnia) or renal impairment; and approximately 3% in each arm discontinued for other reasons, but had viral load of <50 copies/mL at the time.

In one of those parallel universe moments (did I really hear this?), it was not very helpful for the presenter to refer to an “intent-to-treat, missing = excluded” analysis as being “a more standard analytic approach” when for at least ten years a “missing = failure” analysis has been emphasised - primarily because near 100% efficacy results are easy to achieve if the data on people for whom the treatment was not effective are excluded. The claim of a significant difference between the two arms when this analysis reported a 99.7% response for the NNRTI arm should fool no one. However, the 17 patients with historical evidence of K103N who were switched to the rilpivirine FDC had maintained viral suppression to week 24.

Grade 3/4 laboratory abnormalities were reported in 6% vs 11% of the NNRTI vs PI groups, mainly creatinine kinase (likely related to rilpivirine) or atazanavir-related increases in bilirubin.

Changes in baseline lipids (mg/dL) all were significantly reduced in the NNRTI vs PI arms: total cholesterol (-25 vs 1), LDL (-16 vs 0), triglycerides (-53 vs +3), HDL (-4 vs -1); all $p < 0.01$. Changes in the TC:HDL ratio (-0/27 vs + 0.08) also favoured the NNRTI, which also resulted in a statistically significant difference in Framingham risk score.

C O M M E N T

Although switch data are interesting, week 24 data is a very early time point and it is therefore disappointing that longer durability data will not come from this study: at week 24 all patients are being switched to the rilpivirine FDC, thereby eliminating a control group for the week 48 analysis.

This makes the detail for non-suppressors and missing data patients important as they hint at possible poorer tolerability, and perhaps even virological differences, that do not favour the rilpivirine arm.

Although seen as an alternative to Atripla for people who have side effects to efavirenz, the CNS events are only halved rather than eliminated, and there are important differences between the FDCs that are often not communicated to patients: the rilpivirine-based FDC needs to be taken with a 550 calorie meal; efficacy in naive patients is reduced when baseline viral load is greater than 100,000 copies/mL; and the shorter half life of rilpivirine compared to efavirenz doesn't support a wide flexibility in dosing time.

The fixed dose combination (FDC) of rilpivirine/tenofovir/FTC was approved last year and is marketed as Complera in the US and Eviplera in Europe.

References

Palella F et al. SPIRIT study: switching to emtricitabine/rilpivirine/tenofovir (FTC/RPV/TDF) single-tablet regimen (STR) from a ritonavir-boosted protease inhibitor and two nucleoside reverse transcriptase inhibitors (NRTIs) maintains HIV suppression and improves serum lipids in HIV-positive subjects. 19th International AIDS Conference. 22-27 July 2012, Washington. Oral Abstract TUAB0104.

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Maraviroc plus atazanavir/ritonavir in a nuke-sparing regimen in treatment-naive patients

Simon Collins, HIV i-Base

Results at 96 weeks were presented from a randomised open-label, phase 2b pilot study that compared dual therapy with atazanavir/ritonavir plus either maraviroc (n=60) or tenofovir/FTC (n=61) as a standard of care control arm, in treatment-naive patients.

Although maraviroc does not have a license indication for treatment-naive patients, the pharmacological benefits of this approach include using a 150 mg once-daily dose for maraviroc, halving the standard dose, and therefore halving the cost.

Approximate baseline characteristics for the study included mean age 37 years (range 18–68), 90% male, 75% white and 20% black. Median CD4 count and viral load were approximately 350 cells/mm³ (range 110 – 744) and 40,000 copies/mL (range 2,000 – 795,000), with 27% vs 36% having baseline viral load >100,000 copies/mL, in the maraviroc vs tenofovir/FTC arms respectively.

Viral efficacy response rates at week 96 suggested that the dual combination was not as good, with 67.8% (40/59) versus 82.0% (50/61) patients having viral load suppressed to <50 copies/mL. Using the <400 cut-off, results were 78% vs 84%. Viral load in the eight patients in the maraviroc arm with viral load >50 at week 96, ranged from 54 to 7600, with 5/8 <200 copies/mL. The single detectable patient in the tenofovir/FTC arm blipped at 77 copies/mL.

No resistance (genotypic or phenotypic) or change in tropism was detected in the patients with viral load >500 copies/mL (maraviroc = 4; tenofovir/FTC = 1).

Median CD4 increases from baseline were 269 and 305 cells/mm³ in the maraviroc vs tenofovir/FTC arms. Greater reductions in creatinine clearance (-5.5 versus -18 mL/min) occurred with tenofovir/FTC compared to maraviroc. Although serum bone formation markers were lower in the maraviroc arm at both weeks 48 and 96, baseline values for either group were not available. While the study numbers were small, other side effects seemed broadly similar, with 21% vs 18% for serious side effects, 53% vs 33% for grade 3/4 events, 3% vs 0 discontinuing due to side effects, and 70% vs 56% for grade 3/4 hyperbilirubinaemia, all maraviroc vs tenofovir/FTC respectively.

C O M M E N T

Although the researchers emphasised that the study was not powered for between-group differences, the results generated sufficient caution for the subsequent phase 3 study of this nuke-sparing approach, now ongoing, to pair maraviroc with darunavir/ritonavir rather than atazanavir/r.

Reference

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Five-year results from raltegravir registrational studies

Simon Collins, HIV i-Base

Two posters at IAS included five-year results from the phase 3 registrational studies of raltegravir.

A late breaker poster detailed the final five year results of the phase 3 placebo-controlled registrational study comparing raltegravir to efavirenz, that reported non-inferiority at primary and secondary endpoints of 48 and 96 weeks and superiority at week 192, largely driven by high side-effect related discontinuations in the efavirenz arm. [1]

The STARTMRK study randomised 566 treatment-naïve patients to either raltegravir to efavirenz, both plus tenofovir/FTC. Virological efficacy was measured as percentage of patients with viral load <50 copies/mL counting non-completers as failures. After initial non-inferiority, subsequent tests for superiority adjusted for previous analyses, although no formal hypotheses were formulated for week 240.

At five years, raltegravir continued to show superiority with 71% vs 61% suppressed to <50 copies/mL (difference +9.5; 95%CI +1.7 to +17.3), $p < 0.001$). Numerically greater CD4 increases were also reported in the raltegravir arm: +374 vs +312 cells/mm³ (difference +62; 95%CI: 22, 192).

Discontinuations were reported in 25% of patients in the raltegravir (71/281) compared to 35% (98/282) in the efavirenz arm.

Virological failure occurred in 19.6% vs 20.9% of the raltegravir vs efavirenz arms, with non-response higher with efavirenz (3.6% vs 8.5%) but viral rebound higher with raltegravir (16.0% vs 12.4%).

Discontinuations due to clinical adverse events occurred in 5% (n=14) vs 9% (n=28), respectively. Drug-related side effects occurred less frequently with raltegravir: 52% (n=146) vs 80% (n=226), $p < 0.001$. Time to discontinuation was significantly earlier in the efavirenz group (observed = failure; log rank p-value = 0.023). However, fewer patients in the raltegravir group were using lipid-lowering drugs (9% vs 15%) and fewer patients initiated new lipid treatment (n=13 vs n=34).

Although the raltegravir arm reported significant benefits in fasting lipids (lower TC, LDL, non-LDL, all $p < 0.001$ and TG, $p = 0.004$) the higher increase in HDL with efavirenz meant that there was no significant difference in TC:HDL (-0.22 vs -0.08; difference -0.11; 95%CI -0.36 to +0.14, $p = 0.375$).

Superiority with raltegravir is driven by fewer CNS side effects (dizziness/headache/drowsiness: 18% vs 50% and abnormal dreams/nightmare: 18% vs 31%) though discontinuations due to serious side effects (3.9% vs 3.5%) and numbers of deaths (1.8%, n=5 in each arm) were similar. Fatigue, GI-related side effects and rash also occurred more frequently with efavirenz.

A second poster presented five-year results from the BENCHMRK study that randomised 703 triple-class resistant, treatment experienced patients (2:1) to raltegravir or placebo, both with optimised background regimens. All patients had the option to switch to open-label raltegravir after three years. For the safety analyses different exposure rates were adjusted with results presented as event rates/100 patient years. Virological analyses at five years were also analysed based on responses at week 48. [2]

Patients randomised to raltegravir continued to have better virological response rates throughout five-years and this was not balanced by later access to raltegravir: 42% vs 16% for <50 copies/mL and 45% vs 17% using <400 copies/mL (non-completer=failure).

Exposure-adjusted rates of clinical adverse events were 20 vs 37 per 100 patient years of follow-up in the raltegravir vs placebo arm respectively.

C O M M E N T

As a note to patient commitment, blinding was maintained for five years in STARTMRK and participants continued on a 6 pills a day, twice-daily combination, despite easier combinations if switched to open-label drugs. Tenofovir/FTC was taken in the morning with food,

raltegravir (or matching placebo) was taken every 12 hours without regard to food, and efavirenz (or matching placebo) was taken at night without food.

Perhaps new drugs need longer or larger studies to be sufficiently powered to differentiate differences to similar comparator arms, especially when a composite efficacy and tolerability endpoint is likely to show differences compared to efavirenz.

Reference

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AIDS 2012: SIDE EFFECTS

First report: atazanavir-related gallstones (cholelithiasis)

Simon Collins, HIV i-Base

A poster presentation included the first reports of atazanavir-related gallstones. [1]

Following two cases of gallstones in patients on atazanavir reported to the pharmacovigilance departments of two hospitals in western France, Poinsignon and colleagues performed a case review for all patients attending these clinics between 2008 and 2011. The review was limited to cases where spectrophotometry analysis of the stones showed significant levels of atazanavir.

They identified 11 patients (10 men, 1 woman) who had undergone cholecystectomy. Mean age was 49 years (range 32-82) and mean BMI of 23 kg/m² and all were virally suppressed on atazanavir-based combinations (mean atazanavir duration of 50 months). The mean CD4 cell count was 683 (± 310) cells/mm³.

Co-morbidities included HCV-coinfection (n=6, of whom 1 had cirrhosis, 1 hepatocellular carcinoma, and 1 HBV and HDV co-infections), past intravenous drug use (n=3), haemophilia A (n=2), and chronic alcohol abuse (n=2). Final diagnoses included acute pancreatitis (n=3), acute cholecystitis (n=3), and angiocholitis (n=1). Ten patients underwent laparoscopic cholecystectomy, and one had endoscopic sphincterotomy (two patients had both).

Atazanavir was found in biliary stones from eight patients, composing 10% to 100% of the total weight (mean 72%), but included 4 patients with 100% composition. Three other patients did not contain atazanavir but included bilirubinate calcium, carbapatite and cholesterol. Atazanavir was boosted in 6/8 (using doses of 150 mg to 400 mg) and unboosted in 2/8. Atazanavir plasma levels for all patients were within the therapeutic range.

Biochemical and infrared spectrometry analysis of the stones led the researchers to determine this was related to direct atazanavir precipitation in 8/11 cases and to biliary elimination through the UGT1A1 metabolic pathway in 3/11 cases.

All patients switched atazanavir to raltegravir, an NNRTI or an alternative PI. All patients survived and none relapsed, with a mean follow-up of three years.

The authors noted that these cases were mostly in men coinfecting with HCV with mean atazanavir exposure of four years and that based on these cases they estimated an incidence in their region of 2-2.5 cases per 1000 patients years (of atazanavir).

They also concluded, "atazanavir-treated patients with abdominal pain necessitate liver function and lipase tests as well as hepatobiliary ultrasound examination to evaluate medico-surgical care" and that possible calculus analysis must be undertaken and the case reported to drug safety surveillance systems.

Reference

- Poinsignon Y et al. Complicated atazanavir-associated cholelithiasis: a report of eight documented cases among 11 cases. 19th International AIDS Conference. 22-27 July 2012, Washington. Poster abstract MOPE099. <http://pag.aids2012.org/Abstracts.aspx?AID=6375>

AIDS 2012: PAEDIATRIC CARE

Paediatrics studies at 19th International AIDS Conference and the 4th International Workshop on HIV Pediatrics

Polly Clayden HIV i-Base

After a long time languishing in the margins, paediatric HIV has gained a little more attention over the past few years, including a dedicated annual meeting organised by Virology Education, scheduled to precede the IAS one, and now at number four.

Although investigators have the opportunity to submit abstracts to both conferences - so there is some duplication - the workshop provides a very focused update on an area of research that is often harder to find at the big meeting, where basic and clinical science gets eclipsed by rhetoric (particularly where babies and children are concerned).

Presentations and abstracts from this meeting can be found at:

http://www.virology-education.com/index.cfm/t/Workshop_Material/vid/E567E653-9DEA-55A2-5505C3C88C07A3A0

In addition, the Drugs for Neglected Diseases initiative (DNDi), alongside the International AIDS Society-Industry Liaison Forum (IAS-ILF) organised a symposium entitled *Catching Children Before They Fall: Addressing Urgent Needs in Developing Drugs for Young Children Living with HIV*. This satellite looked at the development of drugs and formulations for infants and young children in resource-limited settings, reflecting DNDi's recent non-profit R&D work to do exactly that (see below).

<http://dndi.org/events/1214-aids2012.html?start=3>

Novel lopinavir/ritonavir sprinkle formulation for children in resource-limited settings

Polly Clayden, HIV i-Base

Suitable formulations for infants and young children in resource-limited settings are still urgently needed.

The Indian generic manufacturer, Cipla, has been developing a coformulated twice-daily sprinkle formulation of lopinavir/ritonavir (LPV/r), using melt extrusion technology, and stored in delivery capsules with 40/10 mg per capsule.

Bioequivalence data for the sprinkles versus the innovator syrup in healthy adults were presented earlier this year at CROI and showed, for LPV, the pharmacokinetic (PK) parameters AUC_{0-t} and AUC_{0-IFN} fell within the conventional bioequivalence range of 80 -125%, while for C_{max} it was just outside. For ritonavir (RTV), AUC_{0-t} and C_{max} fell just outside the range but AUC_{0-IFN} was within it. The differences were modest, and based on this pilot PK study, the sprinkle formulation is now being studied in HIV-infected children in the **Children with HIV in Africa - Pharmacokinetics and Adherence of Simple Antiretroviral Regimens (CHAPAS-2)** trial conducted in Uganda. [1]

In a late breaker oral presentation at the 4th International Workshop on HIV Pediatrics, **Rosette Keishanyu from the CHAPAS-2 group** presented preliminary findings from the trial. [2]

The objectives were to determine and compare the PK of LPV/r in the sprinkle formulation versus 1) twice daily, coformulated, 100/25 mg paediatric tablet (Cipla) in children 4 to 13 years of age and <25 kg and 2) twice daily, coformulated, 80/20 mg per mL oral solution (Abbott) in infants 3 months to <1 year of age.

In addition the study collected acceptability data comparing the formulation preferences of sprinkles versus tablets among older children and carers and sprinkles versus oral solution among infants' carers.

Cohort 1 enrolled 29 children with a median age of 6.2 years at baseline 55% were girls. Cohort 2 enrolled 14 infants with a median age of 6 months and 57% were girls.

CHAPAS-2 was a randomised cross-over study. Four weeks after randomisation, intensive PK plasma sampling was performed 0,1,2,4,6,8,12 hours after observed intake of a regimen of LPV/r plus two nucleosides (given with food). The children were dosed in accordance with WHO 2010 weight band table dosing. They were then switched to the alternate formulation and PK sampling was repeated at week 8. LPV concentrations were determined using high-performance liquid chromatography. See tables 1 and 2 for PK results presented as geometric means (GM) and geometric mean ratios (GMR).

Subtherapeutic trough levels (<1.0 mg/L) were reported in 4(16%)/1(4%) sprinkles/tablets, (p=0.35), and 0(0%)/3(27%) sprinkles/oral formulation, (p=0.21).

There was high variability with all formulations.

Table 1: Tablets versus sprinkles 4 to 13 years

PK parameter	Tablets GM (95% CI)	Sprinkles GM (95% CI)	Sprinkles:tablets GM (90% CI)	Historical data in children*
AUC0-12h (h*mg/L)	115.6 (103.3-129.8)	83.1 (66.7-103.5)	0.72 (0.60-0.86)	72.6 (41.5-103.7)
Cmax (mg/L)	13.9 (12.9-15.1)	10.3 (8.6-12.2)	0.74 (0.64-0.85)	8.2 (5.3-11.1)
C12h (mg/L)	4.4 (3.3-5.9)	2.6 (1.7-4.1)	0.59 (0.43-0.81)	3.4 (1.3-5.5)

*>2 years receiving steady state LPV/r 230mg/m² twice daily oral solution.

Table 2: Oral solution versus sprinkles

PK parameter	Oral solution GM (95% CI)	Sprinkles GM (95% CI)	Sprinkles:oral solution GM(90% CI)	Historical data in children*
AUC0-12h (h*mg/L)	62.5 (35.6-109.7)	70.9 (41.8-120.2)	1.13 (0.62-2.06)	72.6 (41.5-103.7)
Cmax (mg/L)	9.3 (6.2-13.9)	9.1 (6.1-13.7)	0.98 (0.65-1.49)	8.2 (5.3-11.1)
C12h (mg/L)	2.1 (0.9-5.1)	3.4 (2.1-5.7)	1.62 (0.67-3.96)	3.4 (1.3-5.5)

The investigators collected acceptability data from questionnaires administered at weeks 0, 4, 8 and 12. The children and/or carers choose which formulation to continue with at week 8.

In cohort 1, older children already established on tablets preferred tablets, particularly as they had a better taste and 22/29 (76%) chose to continue with tablets. Porridge and honey were commonly given with the sprinkles. Several caregivers mentioned the number of capsules they had to open to deliver the dose for the older children.

In cohort 2, the sprinkles were easier to swallow than the oral solution. The majority of the infants (83%) were breastfed. The caregivers also found transport and storage much easier with this formulation and for this age group 10/14 (71%) chose to continue with the sprinkles.

At baseline 41% of caregivers in cohort 1 and 50% of caregivers in cohort 2 thought they would prefer sprinkles.

Virological response data was not shown in this presentation and is awaited.

A cross-over study in cohort 3 (1 to 4 year olds) comparing oral solution to sprinkles is ongoing.

C O M M E N T

Cipla have been working on the “Lopimune” sprinkle formulation of LPV/r for a while now [1, 3], so it is good to see this promising data in children from CHAPAS-2. Collecting acceptability data together with PK is critical in infants, children and their carers and these findings once again underline the importance of getting the formulation right from this point of view (including the taste).

At the DNDi/IAS-ILF satellite, DNDi announced a new collaboration with Cipla to develop an optimised first-line regimen of a fixed-dose combination of Lopimune Sprinkles, with one of two nucleoside backbones (either ABC/3TC or AZT/3TC). This will be a 4-in-1 combination sachet product, in which the four antiretrovirals will be formulated in taste-masked sprinkles. The partnership will also develop an adapted 4-in-1 sachet with LPV/r dosed at 1:1 for superboosting when ART is given with TB treatment.

The programme also includes additional support for Chapas-2 cohort 3 (1-4 years old), a superboosting study, plus PK and efficacy studies using currently available ARV formulations (sprinkles of LPV/r and dispersible tablets of NRTIs).

The aim is to gain approval by 2015, to make the product affordable in the public sector in poor countries and to assist with registration and implementation.

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Update on new antiretrovirals for children and adolescents

Polly Clayden, HIV i-Base

There have been several recent FDA approvals for children in various age groups [1, 2, 3] and supporting data used to obtain these were shown in Washington at either the 19th International AIDS Conference (IAC) or the 4th International Workshop on HIV Pediatrics.

Additionally data from the adolescent cohort of the investigational antiretroviral dolutegravir were presented.

Dolutegravir

Dolutegravir is a promising new integrase inhibitor currently in phase 3 of development; results from SPRING-2, also at 19th IAC, showed it to be non-inferior to raltegravir at 48-weeks. [4]

Rohan Hazra presented the first paediatric data for DTG on behalf of the IMPAACT P1093 Study Team. [5]

IMPAACT P1093, is an ongoing, phase 1/2 multicentre, open-label pharmacokinetics (PK), safety dose finding, non comparative study of DTG plus optimised background regimen (OBR) in treatment experienced adolescents, children and infants ≥ 6 weeks of age, conducted in de-escalated age bands.

The paediatric doses selected will be those providing comparable PK exposure to the adult dose of 50mg, with AUC₀₋₂₄ as the primary endpoint and C₂₄ as the secondary endpoint. Protocol defined targets are: AUC 0-24, range of 37-67 ug*h/mL and C₂₄, range 0.77 – 2.26 ug/mL. The study is looking at short and long-term tolerability and evaluates steady state PK of DTG given with OBR.

The first cohort enrolled 10 adolescents ≥ 12 to <18 years of a median age of 13.5 years. The majority (70%) were girls and overall the cohort had median time on ART of 12.8 years. Their median baseline CD4 percentage and viral load were 21.5% (IQR 18.4-26) and 4.40 log copies/mL (IQR 4.17-4.84), respectively.

DTG was given at approximately 1 mg/kg once daily. The majority (90%) of the cohort weighed 40 kg or more and received the 50 mg adult tablet. Two reduced strength tablets of 25 mg and 10 mg have been developed to facilitate weight band dosing in older children. The remaining participant received 35 mg once daily (one 25 mg and one 10 mg tablet).

Intensive 24 hour PK evaluation was performed, following observed dose (days 5-10), after DTG was either added to a stable, failing regimen or started as monotherapy among those not currently taking ART. Background treatment was optimised immediately after completing the intensive PK.

Dr Hazra reported, in this cohort, target DTG exposure for both AUC₀₋₂₄ and C₂₄ was achieved. He noted there was moderate variability. The geometric mean (CV%) AUC₀₋₂₄ and C₂₄ were 46.0 (43%) ug*h/mL and 0.90 (58%) ug/mL, respectively.

At four weeks 70% (95% CI 34.7 – 93.3) of the cohort achieved viral load < 40 copies/mL and 90% (95% CI 55.5 – 99.8) <400 copies/mL; all the participants achieved at least 1 log₁₀ drop or <400 copies/mL. The median change from baseline was 2.8 log copies/mL (95% CI 3.1 - 2.6). DTG was generally well tolerated, with one Grade 3 and no Grade 4 AEs, no treatment discontinuations due to AEs and no trends in laboratory abnormalities.

Dr Hazra concluded that these results support the dose selection in this cohort and the enrollment of a further 12 participants. Enrollment for the next cohort in children age 6 to <12 years has now begun and the development of a granule formulation for the younger children and infants is underway. [3]

Raltegravir

In December 2011, the FDA approved a 100 mg scored chewable tablet and a 25 mg chewable tablet of raltegravir, and dosing recommendations for children 2 to 18 years of age and weighing at least 10 kg. [3]

IMPAACT P1066 is an ongoing phase 1/2 open label, multicentre trial to evaluate PK, safety, tolerability, and efficacy of multiple RAL formulations in treatment experienced adolescents, children and infants (those <2 years may have only failed PMTCT).

Sharon Nachman from the P1066 group presented 24 and 48 week results from 96 participants age 2 to 18 years receiving 400 mg twice daily of RAL adult film-coated tablet (6-18 years) and weight-based dosing (approximately 6mg/kg twice daily) of RAL orange banana flavour chewable tablet (2 to <12 years). [4] Dose selection was based on intensive PK data and RAL was given with an OBR. Children <2 years are given oral granules for suspension and this evaluation is ongoing. [5]

Adolescents and children were stratified sequentially in 3 age cohorts (I, 12 to 18 years; II, 6 to <12 years; III, 2 to <6 years); the oldest group - cohort I - enrolled first. Safety was assessed through week 48. The primary virologic endpoint was viral load <400 copies/mL or ≥ 1 log reduction. Secondary endpoints were viral load <50 copies/mL, and change in CD4 percentage.

At baseline, participants were a median of 13 years with a median CD4 count of 481 cells/mm³ (1087 cells/mm³ in cohort III, n=20) and a mean viral load of 4.3 log copies/mL. Approximately half were girls and most were NNRTI or PI experienced, 78% and 83% respectively.

At 48 weeks, overall 78.9% of participants achieved viral load <400 copies/mL and 56.7% <50 copies/mL, with mean CD4 increase from baseline 155.7 (4.6%) cells/mm³.

Dr Nachman reported, 15 participants had Grade 3 and above clinical AEs, including one with drug related psychomotor hyperactivity, abnormal behavior and insomnia; 16 participants had Grade 3 and above laboratory AEs including one with drug related AST and ALT; 14 participants had serious clinical AEs including one with drug related rash and two participants with serious laboratory AEs including one with drug related increased transaminase. There were no discontinuations due to AEs and no deaths.

She noted that these data were used to obtain US approval in the 2 to <10 years age group. Table 1 shows recommended doses for the chewable tablets based on approximately 6mg/kg twice daily. The 100 mg tablet is scored and so can be divided in half.

Table 1: Recommended doses for raltegravir chewable tablets

Weight kg	Dose mg twice daily	Tablets (number / size mg)
10 to <14	75	3 x 25
14 to <20	100	1 x 100
20 to <28	150	1.5 x 100
28 to <40	200	2 x 100
>40	300	3 x 100

Etravirine

The FDA also recently approved etravirine (ETR) scored 25 mg tablets and dosing recommendations for treatment experienced children and adolescents 6 to 18 years, weighing at least 16 kg, in March 2012.

Gareth Tudor-Williams presented data from the PIANO study used to obtain this approval.

PIANO (TMC125-C213) is a 48-week, phase 2, open-label trial of the safety, efficacy and PK of ETR 5.2mg/kg (maximum dose 200mg) twice daily in treatment-experienced children and adolescents 6 to 18 years of age, given with OBR.

Overall 101 participants enrolled in the study, of which, 41 were children (6 to 12 years) and 60 adolescents (12 to 18 years); 63% were girls. Their median age at baseline was 12 years; their viral load 3.9 log₁₀ copies/mL and CD4 count 385 cells/mm³. The majority (75%) was NNRTI experienced. Of those enrolled 75% completed the trial.

Most discontinuations were associated with AEs or non-adherence, both 8%.

Regardless of severity or cause 27% of participants had an upper respiratory tract infection and 23% rash. Rash was at least possibly related to ETR and grade 2 or more AEs in 13% of participants. Four percent discontinued due to rash.

Serious AEs were observed in 5% of participants while 14% experienced a grade 3/4 AE. Grade 3 or 4 treatment-emergent laboratory abnormalities were observed in 10%.

At 48 weeks, by intent to treat (non-completer equals failure) analysis, overall 67% and 56% achieved viral load of <400 copies/mL and <50 copies/mL respectively. Although the study was not powered to make statistical comparisons between children and adolescents, the younger age group appeared to have better responses: these proportions were 76% vs 68% and 62% vs 48% in children and adolescents respectively. The median time to <50 copies/mL was 16 weeks for children and 24 weeks for adolescents.

The mean change in CD4 count from baseline was 156 cells/mm³ overall, 178 cells/mm³ in children and 141 cells/mm³ in adolescents.

Adherence was measured by pill count and self reported questionnaire; self reported adherence was higher than that estimated by pill count. At 48 weeks, 65% of participants were adherent according to the results of the questionnaire. When evaluated by pill count, 39% (46% of children, 35% of adolescents) were >95% adherent; 70% were >80% adherent.

Overall 41% of participants were classed as virologic failures, this proportion was 50% of adolescents and 27% of children. Of these 29% were non-responders and 12% rebounders.

Of 30 with endpoint genotype data, 18 had NNRTI resistance-associated mutations. The most mutations were: Y181C (n=8), E138A (n=3), L100I (n=3) and/or V90I (n=3).

Dr Tudor Williams noted that the better responses observed in children than adolescents, were most likely due to less advanced disease, better adherence and less previous NNRTI use prior to treatment with ETR.

Fosamprenavir

An oral suspension of fosamprenavir/ritonavir (FPV/r) was also approved in the US earlier this year in April for use in children 4 weeks to less than 6 years of age.

Jorg Sievers presented data from the APV20002 study that looked at PK, safety and antiviral activity of FPV/r twice daily in PI-naive and PI-experienced children 4 weeks to <2 years of age. This evaluation was across two age cohorts: cohort 1, 6 months to <2 years and cohort 2, 4 weeks to <6 months of age.

APV20002 was a phase 2, open label, multicentre study in which Intensive pharmacokinetic sampling was performed at 2 or 8 weeks and pre-dose samples were collected every 4-12 weeks. Safety and viral load were monitored every 4-12 weeks.

The older cohort was dosed at 45/7 mg/kg FPV/r twice daily and the younger 45/10 mg/kg twice daily.

Overall 54 children were included in the intent-to-treat-exposed analysis (28 in cohort 1 and 26 in cohort 2). At baseline the children were a median age of 6 months (range 2 – 24), with a median viral load of 5.6 log₁₀ copies/mL (range 5 – 6.15) and CD4 percentage of 26% (range 18 – 34).

At 48 weeks, the median exposure to FPV/r was 640 days (range 8-1093), with 78% exposed >48 weeks and 50% >96 weeks.

When the investigators compared plasma amprenavir (APV) AUC_{0-t} to historical adult data, the geometric mean ratios were 0.744 (90% CI 0.542 – 0.957) and 0.720 (90% CI 0.568 – 0.975) in cohort 1 and 2 respectively. For the C_t these values were, 1.00 (90% CI 0.833 – 1.21) and 0.397 90.298 – 0.528).

Despite lower C_t in the younger cohort, antiviral response was similar across the age groups: 64% percent of children in cohort 1 and 58% in cohort 2 achieved viral load < 50 copies/mL at 48 weeks. The median increase in CD4 percentage was 5% in both cohorts.

The most common AEs were diarrhoea (54%), gastroenteritis (36%) and upper respiratory tract infection (36%). Drug-related grade 2-4 AEs occurred in 20% of children, most frequently increased blood cholesterol (10%) and gastroenteritis (3%). Twenty-two children experienced serious AEs, three were considered to be drug-related. Three children died following serious AEs including one two month old boy with traditional (herbal) medicine poisoning.

C O M M E N T

Although somewhat opaque in their approach, the EMA are expected to follow suit with these approvals in the not too distant future. More details on these drugs and others under investigation for children can be read in our paediatric antiretroviral pipeline report:

<http://i-base.info/htb/16891>

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Tenofovir prophylaxis for neonates

Polly Clayden, HIV i-Base

HPTN 057 is a prospective phase I trial of the PK and safety of tenofovir disoproxil fumarate (TDF) in HIV-positive pregnant women in labour and their neonates.

The trial was designed when the question of alternative strategies to intrapartum/neonatal single dose nevirapine was still considered relevant. [1]

The study had four cohorts, maternal infant pairs received local PMTCT standard of care plus TDF as described in Table 1.

Table 1: HPTN 057 maternal/infant cohorts

Cohort	n	Maternal TDF (single dose in labour)	Infant TDF
1	30	600 mg	None
2	20	None	4 mg/kg within 12 hours of birth, day 3 and day 5
3	30	900 mg	6 mg/kg within 12 hours of birth, day 3 and day 5
4	30	600 mg	6 mg/kg daily for 7 days

Data presented previously showed infants from cohorts 3 achieved cord blood tenofovir (TFV) concentrations above the target concentration of 50 ng/mL infants (the mean trough concentration in adults receiving treatment with TDF), but failed to keep infant concentrations above this target during the first week of life due to more rapid than expected TFV elimination. [2]

In an oral presentation at IAC 2012, Karin Nielsen-Saines showed data from cohort 4 in which women received 600 mg TDF at the onset of labour (or 4 hours before Caesarean section) and neonates received 6 mg/kg TDF suspension once daily for 7 days. [3]

In this study, 33 mother infant pairs were enrolled in Malawi (n=16) and Brazil (n=17). Twenty one infants were born by vaginal delivery and 12 by Caesarean section; the median time between maternal dose and delivery was 4.5 hours (range 0.6–11.4).

The investigators took samples from mothers at delivery, from cord blood and from infants before and 2, 10 and 24 hours after the 1st, 4th and 7th TDF doses.

TFV concentrations were determined by HPLC/MS/MS with a lower limit of quantitation of 5 ng/mL. Cord blood and maternal delivery concentrations are presented as geometric mean (%CV) in Table 2 and infant TFV PK in Table 3.

Table 2: Cord blood and maternal delivery TFV concentrations

Cord blood	61 (69.3%) ng/mL
Cord blood TFV >50 ng/mL	24/31 (77%).
Maternal delivery concentrations	108 (76.1%) ng/mL
Cord blood/maternal delivery ratio	0.55 (64.0%)

Table 3. Infant TFV PK parameters

Dose	Pre-dose (ng/mL)	% with pre-dose >50 ng/mL	Tmax (hr)	Cmax (ng/mL)	AUC (ng*hr/mL)	T1/2 (hr)
1	29 (67%)	45	6.9 (54.8%)	288 (49.9%)	3939.4 (31.6%)	13.2 (80.1%)
4	146 (84.5%)	100	2.3 99.2%	336 (40.5%)	4714.1 (37.4%)	14.5 (45%)
7	79 (77.2%)	84	3.4 (84.6%)	221 (66.1%)	3061 (49.0%)	14.6 (96.1%)

Amniotic fluid was obtained from a small subset of three women who had elective Caesarean sections. Paired amniotic fluid/serum samples (n=24) showed TDF achieved effective amniotic fluid concentrations with the highest levels 3 to 6 hours post dose.

The study team concluded that this regimen provides TFV exposure similar to adults receiving 300 mg daily doses and is appropriate for use in neonates in studies of TDF used for HIV prophylaxis or treatment.

One infant of 33 (3%) was infected in cohort 4 and 5/122 (4.1%) were infected in HPTN 057.

C O M M E N T

This presentation was interesting but perhaps the placement in the session that looked at PK in antiretrovirals for treatment a little misleading as this study used TDF as prophylaxis in the first week of life. To use it for treatment it would be very important to look at bone growth in infants given the large amount bone development at that age. There would need to be safety studies before a move toward routine use for treatment in infants.

The FDA recently approved TDF for the 2 to 12 age group and the EMA is looking at this. WHO has recently published the findings from a systematic review looking at the use of TDF in children and adolescents. [4]

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Efavirenz levels variable in children in the CHAPAS-3 study

Polly Clayden, HIV i-Base

WHO updated the guidelines for paediatric weight band dosing of efavirenz (EFV) in 2010. The generic manufacturer Cipla has developed scored 600 mg EFV tablets to facilitate appropriate weight band dosing.

These tablets are scored once on one side and twice on the other to provide 300 mg, 200 mg and 400 mg divided doses.

Children with HIV in Africa – Pharmacokinetics and Adherence/Acceptability of Simple Antiretroviral Regimens (CHAPAS-3) is an open-label

three centre randomised phase 2/3 trial evaluating new solid, dispersible scored antiretroviral fixed dose combination (FDC) and single agents in African children. [1]

A poster presentation at IAS authored by Quirine Fillekes and the CHAPAS-3 study investigators showed results from an evaluation of the new EFV weight band doses and scored generic tablets, to see if these result in optimal exposure in HIV-positive Zambian and Ugandan children. [2]

Children, weighing 10- to <20kg and receiving the generic double-scored EFV tablets in a regimen with new generic combination tablets of 3TC/abacavir(ABC) or 3TC/AZT were enrolled in a pharmacokinetic (PK) sub-study.

In accordance with the new guidelines, the once-daily EFV doses were 200 mg and 300 mg for those weighing 10 to <14 kg and 14 to <20 kg, respectively. Intensive 24 hour PK sampling was performed 6 weeks after ART initiation. Samples were obtained at 0, 1, 2, 4, 6, 8, 12 and 24 hours. AUC0-24, Cmax and C24h levels were analysed.

The substudy enrolled 31 Ugandan/Zambian children of which, 29 efavirenz profiles were evaluable: 11 in the 10 to <14 kg and 18 in the 14 to <20 kg weight bands. Just under half (43%) were girls and the children were a median of 4.6 (IQR 3.9-5.0) years of age.

The investigators reported, the geometric mean (95%CI) AUC0-24 was 46.5(29.4-73.6) and 49.7(30.9-79.9)h*mg/L for weight-band 10 to <14 and 14 to <20kg respectively, compared to 58 h.mg/L in adults.

They observed a large variability in the EFV PK parameters with CV% 133%, 104% and 156% for AUC0-24h, Cmax and C24h, respectively. However, they did not find significant variation between the two weight bands, p= >0.6.

EFV parameters were approximately 15% lower than those previously reported in adults receiving 600 mg once daily. But they were similar to those previously reported in children dosed according to the 2006 WHO guidelines: 200 mg for 10 to <14 kg and 250 mg for 14 to <20 kg once daily. See Table 1.

Table 1: PK parameters of EFV including historical comparisons

EFV	10 to <14 kg	14 to < 20 kg	Literature data children	Literature data adults
C24h (mg/L)	1.29 (0.75 – 2.20)	1.37 (0.77 – 2.43)	1.36 (1.00 – 1.85)	1.77 (1.01)
Cmax (mg/L)	2.94 (2.07 - 4.19)	3.42 (2.32 - 5.04)	3.5 (2.86 – 4.29)	4.07 (1.16)
AUC0-24h (mg/L.h)	46.5 (29.4 – 73.8)	49.73 (31.0 – 79.9)	54.0 (42.6 – 68.4)	58.08 (23.04)

Geometric mean (95% CI) and arithmetic mean (SD) for adult data

The investigators also observed a high number of sub-therapeutic (<1.0 mg/L) and supra-therapeutic (>4.0 mg/L) levels – these did not differ between weight bands, p=0.87. See Table 2.

Table 2: EFV concentrations after observed intake

Time after intake (hours)	Weight band (kg)	< 1.0 mg/L	> 4.0 mg/L
8 and/or 12	10 to <14	9%	27%
	14 to < 20	22%	28%
24 hours	10 to <14	55%	18%
	14 to < 20	67%	22%

The investigators wrote: “This study demonstrates the challenges of fixed dosing when the therapeutic range is narrow.”

Evaluation of EFV PK in higher weight bands (20 to <30 kg) is ongoing as is evaluation of toxicity, efficacy and acceptability of the new EFV tablet.

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Early initiation of ART is associated with growth recovery in children in NEVEREST-2

Polly Clayden, HIV i-Base

The effect of initiating ART early – before 6 months of age – on children’s growth has not been well characterised.

The NEVEREST-2 trial, conducted in Johannesburg, was designed to assess the reuse of nevirapine (NVP) in children who were previously NVP-exposed and had initiated ritonavir-boosted lopinavir (LPV/r) based ART before 24 months of age. After achieving virologic suppression, children (n=195) were randomised to either continue receiving LPV/r or switch to nevirapine (NVP).

A poster at the 4th International Workshop on HIV Pediatrics, authored by Stephanie Shiao and colleagues from NEVEREST-2, showed an evaluation of the effect of age at ART initiation on growth outcomes (including weight, height, body mass index [BMI] and head circumference) in children virologically suppressed and followed for 48 months in this trial.

In order to perform the growth analysis, the investigators divided the children into three groups according to when they initiated ART, <6 months (n=54, 27.7%), 6-12 months (n=69, 35.4%), and 12-24 (n=72, 36.9%) months of age.

Before starting ART, the children were a mean age of 10.7 (\pm 5.9 months) and their age- and sex-adjusted weight-for-age (WAZ), height-for-age (HAZ), BMI-for-age (BAZ), and head circumference-for-age Z-scores (HCAZ) - by WHO growth standards - did not differ between the groups. There was no difference in the proportions of children with low birth weight (<2500 grams; approximately 15% overall) or high pre-treatment viral load (just over half had \geq 750,000 copies/mL) between groups. The proportions of children that were underweight, stunted, or wasted did not differ either – overall more children were stunted (76%) than underweight (51%) or wasted (21%).

The children's weight height and head circumference were measured at regular 3 monthly study visits over 48 months after initiating ART.

The investigators used locally-weighted scatter plot smoothing to generate curves of WAZ, HAZ, BAZ, and HCAZ over time from ART initiation stratified by age when ART was started. They used generalised estimating equations to describe predictors of growth outcomes.

The investigators found overall, after ART initiation, WAZ increased in the first 12 months, dipped from 12 to 36 months and then was stable. HAZ increased steadily across the age groups for 48 months but remained below normal. BAZ increased in the first 12 months as WAZ increased and then declined through 48 months as HAZ increased. HCAZ steadily rose through 48 months in all age groups from a subnormal z-score to above 0.

Children <6 months when they started ART had a larger increase at first in both WAZ, 1.98 vs. 1.44, $p=0.084$, and HCAZ, 1.24 vs. 0.45, $p=0.004$, up to 12 months than children 12-24 months when they started ART. The youngest age group at initiation also had a larger increase in HAZ, 1.56 vs. 0.76, $p=0.004$, between 12 and 24 months on treatment than children 12-24 months at start of ART.

Between 24 and 36 months receiving ART, children who started ART <6 months had a significantly higher HAZ than children who started at 12-24 months ($p=0.009$). But, by 48 months on treatment there were no significant differences in the mean WAZ, HAZ, BAZ, or HCAZ between children <6, 6-12, or 12-24 months when they started ART.

The investigators also noted that girls had a significantly higher HAZ than boys, $b=0.311$, $p=0.049$ for all 48 months of follow up. They observed no differences in growth outcomes relative to time on ART between children with pre-treatment viral load above and below 750,000 copies/mL or between treatment randomisation groups. There was a greater change in WAZ in the group that switched to NVP relative to the time of randomisation.

Children with low birth weight had lower z-scores for all parameters over 48 months compared to those with higher birth weight. The WAZ for children who were underweight pre-treatment remained lower than that for those who were not underweight at this time point, as did the HAZ in the stunted children pre-treatment compared to those who were not.

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High prevalence of peripheral neuropathy in children taking d4T in rural South Africa

Polly Clayden, HIV i-Base

Peripheral neuropathy is a well-known side effect of older nucleosides, particularly d4T, which is still used widely in poor settings.

Although it clearly occurs, this phenomenon is less well characterised in children and it is difficult to assess, particularly with limited resources.

In an oral presentation at IAC 2012, Remco Peters from the Anova Health Institute, Khutso Kurhula Project, Tzaneen, South Africa, showed findings from an evaluation of neuropathy in children in the rural Mopani district. This district is a health priority area in South Africa and the institute runs a nurse managed ART programme in 100 public health care facilities with the support of PEPFAR.

The group used two clinical tools to screen for neuropathy – the neuropathy symptom score (NSS) and neuropathy disability screen (NDS). These tools are feasible for resource limited settings and the NDS only uses a reflex hammer, cotton buds, tooth pick and cold water (to access ankle reflex and perception of vibration, pin-prick and temperature).

It was a cross sectional study of 182 children of median age of 9 years (range 5-15 years) and receiving ART for a median of 2 years (range 2 months to 6.4 years). The majority (86%) received d4T-containing regimens.

Forty-nine (27%) children reported neuropathy symptoms and NDS was positive for 25 children (14%); 43 (25%) children fulfilled the study criteria for peripheral neuropathy.

Co-trimoxazole use was negatively associated with neuropathy OR 0.42, (95% CI 0.20 - 0.88, $p=0.019$) and there were trends for peripheral neuropathy to be associated with older age and longer time on ART but this analysis is still ongoing.

Dr Peters included quotes from the children: "My feet are burning, I must take off my shoes in class otherwise I can't concentrate" from one and, "I can't sleep at night because of the tingling of my feet; I'm tired during the day" from another.

He concluded that neuropathy is common and frequently undiagnosed in this region and that NSS and NDS are useful diagnostic tools in such settings. Most importantly he added: "Talk to the child!"

C O M M E N T

d4T associated toxicities have been well documented and screening tools that can be used where resources are limited are welcome.

That children's experience of adverse events reliant on patient reporting often seems to increase as they get older (and gain a vocabulary) is worth noting.

Co-trimoxazole use appears to be a proxy marker in this study for time on ART/exposure to d4T: children taking co-trimoxazole are much shorter on ART ($p<0.001$). There is not likely to be a specific or direct effect of co-trimoxazole use, but the investigators need to finalise the analysis to be sure about this (Remco Peters, personal communication).

Reference

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Lipid profile in children in PREDICT: immediate versus deferred nevirapine-based ART

Polly Clayden, HIV i-Base

PREDICT was a 144-week randomised trial of immediate ART (at CD4 15-24%) versus deferred nevirapine-based ART (at CD4 <15%) conducted in ART-naïve Thai and Cambodian children 1-12 years of age with baseline CD4 between 15-24%. [1]

Suparat Kanjanavanit showed findings from a substudy of PREDICT - in which the children's fasting lipid profile was compared between arms - in an oral presentation at IAC 2012.

The study included data from 263 children. Of these, 129 received immediate ART and 194 deferred starting ART. At the time of analysis, 60 children in the deferred arm had started ART and 143 had not started ART.

At baseline, the children's median (IQR) age was 6.5 (4.1-8.5) years, 58% were girls and 57% were Thai. Their median fasting time was 8 hours. There were no significant differences between study arms in clinical characteristics at week 0, see Table 1.

Abnormal lipid levels were defined as: total cholesterol > 200 mg/dL; LDL-cholesterol > 130 mg/dL; HDL-cholesterol \leq 40 mg/dl and triglyceride > 130 mg/dL.

At week 144, 60 children in the deferred had started ART. At this time point the investigators found dyslipidemia to be significantly less in the immediate arm. They also found the immediate arm had significantly higher total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) but lower triglyceride and TC/HDL ratio than the deferred arm.

In multivariate analysis, the mean differences over 144 weeks between the immediate arm and the deferred arm without ART (n=73) were significant for all lipid parameters, see Table 2.

Table 1: Clinical characteristics at week 0 and 144

Parameters	Week 0		Week 144	
	Immediate	Deferred	Immediate	Deferred
WAZ	-1.3	-1.3	-1.3	-1.4
HAZ	-1.6	-1.7	-1.5	-1.7
CD4 %	19	20	34	24*
CD4 (cells/mm ³)	611	619	977	662*
VL (log ₁₀ c/mL)	4.9	4.7	1.7	3.4*
Dislipidemia %	59	67	37	61*

WAZ= weight for age z-score, HAZ = height for age z-score

* $p<0.05$

Table 2: Treatment effects on lipid profiles

Lipid profiles	Immediate (n=129) vs deferred not started ART (n=143)		Immediate (n=129) vs deferred started ART (n=60)	
	Mean difference (95% CI)	p	Mean diff. (95% CI)	p
Total cholesterol	20.2 (15.9 to 24.5)	<0.001	3.2 (-2.1 to 8.6)	0.24
Triglyceride	-9.8 (-16.8 to -2.8)	0.006	-8.1 (-16.2 to 0.04)	0.05
LDL	9.1 (5.5 to 12.9)	<0.001	-0.7 (-4.0 to 5.5)	0.76
HDL	13 (10.8 to 15.3)	<0.001	4.9 (2.1 to 7.8)	0.001

Dr Kanjanavanit noted that the overall rate of dyslipidemia was reduced from 64% to 37% in immediate treatment arm but increased to 78% in the deferred not starting ART arm.

He also noted that although this comparison was made in a substudy of a randomised trial, the small number of children and short duration of ART in the deferred arm are limitations to the findings.

He concluded, "After 3 years of follow-up, nevirapine-based initiation achieved favourable lipid profile in children with mild to moderate HIV-associated immune deficiency. Less dyslipidemia was found in treatment group compared to deferred group."

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AIDS 2012: HIV PREVENTION

High levels of maraviroc in rectal tissue fail to protect macaques from SIV transmission following rectal exposure

Simon Collins, HIV i-Base

A poster from the group responsible for key animal PK studies looking at tenofovir and/or FTC for PrEP presented a poster with disappointing findings with maraviroc.

These results are important given the investigational use of maraviroc in prevention studies. Despite high levels of penetration in rectal tissue, maraviroc failed to show any impact on the risk of SIV infection.

Results were presented by Garcia-Lerma in an oral poster discussion session from a single dose PK study and a multiple dose SIV exposure study.

The maraviroc PK profile was determined using 12 macaques exposed to a single dose and was similar to human studies, with significantly higher rectal concentrations: peaking at two hours in plasma (median 451 ng/mL) and at 5–48 hours in rectal secretions (median 2,329 ng/mL) and with median AUC₀₋₂₄ 7.5-fold higher (12,720 vs 1,685 ng.hr/mL, respectively). At day 4 maraviroc concentrations in rectal tissue remained more than 20-fold higher than the IC₅₀, and was sufficient to fully occupy CCR5 in PBMCs. The half-life of CCR5-bound MVC in PBMCs was 2.6 days.

The prevention study used a similar design to that used for tenofovir and FTC, dosing 6 macaques with oral maraviroc (44 mg/kg, comparable to the 300 mg human dose) 24 hours prior to rectal exposure and 2 hours post exposure, in a weekly cycle for five weeks, with an additional four macaques as controls.

Despite the strong PK profile there no evidence for prophylactic efficacy: 5/6 treated animals and 3/4 controls became infected over the five weeks. Infections occurred at week 1, 2, 4, 4 and 5 in the animals exposed to maraviroc which were similar to both these and historic controls.

While the study concluded, "that higher doses were needed to see protection" seems optimistic that an effect would necessarily be found, the concern about using a higher than therapeutic dose is likely to limit the interest in further human studies.

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Mechanisms for circumcision to reduce HIV transmission in different penile tissue: target cell differences rather than keratinisation

Simon Collins, HIV i-Base

An intensive study looking at the protective impact on adult male circumcision for reducing the risk of sexual HIV transmission suggested new biological mechanisms for protection.

This study was presented as an oral presentation by Minh Dinh from Northwestern University Feinberg School of Medicine. [1]

Other groups have suggested two mechanisms for protection with both lower keratinisation and a higher number of target cells closer to the tissue surface in the inner compared to the outer foreskin. The current study is a development from previous work from the group that suggested that a reduced keratin layer in the inner foreskin is unlikely to contribute to protection. [2] For the first time, the current study reported evidence for the route of entry to be through the mucous membrane of the glans (penis head) and that circumcision has an impact on target cell distribution in this tissue.

This study used fluorescent immunohistochemistry to stain for HIV target cells and keratin and epifluorescent microscopy and analysed for keratin thickness, viral particles, and viral penetration into penile epithelia in foreskins from 19 donors who were undertaking prophylactic circumcision in Rakai, Uganda. Samples were randomised into three groups and then analysed in a blinded design by separate labs in Chicago and Stockholm.

Both labs were unable to identify differences in keratinisation for the inner and outer foreskin or for the Frenner band (the area between where these different tissues meet).

The group then looked at viral interactions again using fluorescent viral labeling with explants both from US donors undergoing circumcision but also penile tissue post-autopsy, from a US national donation tissue bank, to understand how HIV enters the tissue. While most R5-bound viral particles remained close to the surface, caught in keratinised tissue, this analysis showed a significant difference between viral penetration of the inner foreskin and outer foreskins or shaft tissue ($p=0.02$). An analysis in 14 samples of glans tissue suggested similar difference to inner foreskin. However a 3-fold higher proportion of virions were likely to enter glans tissue compared to shaft tissue in the uncircumcised compared to circumcised samples. Viral penetration increased in proportion to the concentration of Langerhans cells close to the epithelial surface (and this was higher in uncircumcised samples), but were also found at deeper distances from the surface where CD4 cells were commonly found in both tissues.

No difference was seen in urethral tissue between circumcised and uncircumcised samples with little evidence of viral penetration for either group, suggesting that this may not be a major site of infection.

This study answers the suggestion from researchers involved in circumcision research that the groups previous findings may have been confounded by using foreskins donated by 16 US donors who were being circumcised relating to underlying medical conditions. [3]

C O M M E N T

This research is helpful in trying to understand the route of transmission in detail and if validated is of importance not only to people at risk of infection but for production of resources focused on reducing transmission.

A similar approach would help understand the likely risk and mechanism for sexual transmission of hepatitis C, which is particularly poorly understood.

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AIDS 2012: BASIC SCIENCE AND CURE RESEARCH

Towards an HIV cure: Early developments in the field

Muirgen Stack, HIV i-Base

After the announcement of the IAS Towards an HIV Cure scientific strategy at this third IAS pre-conference symposium, held this year from 20-21 July, any advances in the field of cure research will come under a new emphasis.

This strategy outlines the important areas of research where advances needed to be made if a cure (functional or sterilising) is to be realised. [1] Fortunately, some promising cure-related research was presented at AIDS 2012 and this will become a trend that hopefully continues and is expanded upon at further meetings.

Latency, persistence and locating the hiding virus

The mechanisms underlying viral latency are complex and not fully understood. Despite the success of ART, replication competent yet transcriptionally silent HIV-1 provirus goes unnoticed by the immune system. [2] Before new treatments can target the latent reservoirs, the biology underlying persistence needs to be better understood.

Lina Josefsson from the Karolinska institute in Sweden presented results on quantifying which sub types of CD4+ T cells were infected by persistent HIV-1. All patients were on long-term suppressive ART but had either started during acute or chronic infection. [3]

Memory and naïve CD4 T cells in the peripheral blood (PB) were infected 13 and 24 fold times higher respectively, in patients treated during chronic compared to acute infection. Another reservoir of latent HIV is the gut-associated lymphoid tissue (GALT). For patients that started treatment during chronic infection, their effector memory T cells were 6 fold more likely to be infected.

Together, these results suggest that early initiation of therapy reduces the viral reservoir size in the blood and the gut. Although the number of participants in the study was low (n=8), it highlights the importance of the heterogeneity in both how much virus persists and where it resides. Additional research focusing on other plausible reservoirs sites including the central nervous system and kidney (and ideally with patients from different drug regimen backgrounds) is now needed. [4, 5]

Another group led by Charline Bacchus of the Pierre and Marie Curie University further investigated reservoir distribution in patients spontaneously controlling HIV infection after treatment interruption. [6]

The VISCONTI cohort (Virological and Immunological Studies in CONTrollers after Treatment Interruption) enrolled 12 patients who had controlled HIV for a median of 76 months (IQR 67.5-84.5) after interruption of a 3 year (range 1.7-5.9) HAART, initiated within 10 weeks of infection. This group was compared to 8 untreated elite controllers (spontaneously suppressing HIV infection without treatment: 90% with viral load below 200 copies/mL) over 12 (range of 9-14) years. A similar profile of reservoir distribution was seen in both groups, but with differences. In the VISCONTI group, activated CD4 T cells had significantly higher HIV-DNA levels than resting ones, median 2.7 log copies/million cells (range: 2.4-3.4) compared to 2.0 (range: 1.8-2.5), $p=0.005$. HIV-DNA was detected in all CD4 T cell subsets except for 8/12 treatment-naïve patients (TN) CD4+ T cells which were 10 fold less infected than all memory subsets; TN: median 1.5, central-memory (TCM): 2.5, transitional-memory (TTM): 2.6 and effector-memory (TEM): 2.4 log copies/million cells, $p<0.0007$. Whereas in the VISCONTI group, 56% of the reservoir was made up of TTM cells, elite controllers had a more even mix of TCM and TTM cells contributing to their HIV reservoir.

Although the reservoir phenotype of the VISCONTI group is similar to the elite controllers, the fact that they are not identical and yet both groups successfully control the virus is encouraging, and it will hopefully allow for researchers to identify a more general CD4 T cell profile that manages the viral reservoir without ART.

A poster from Maria Jose Buzón from the Ragon Institute in Massachusetts and colleagues showed results from a study looking at the characteristics of a cohort of patients who started treatment early during infection and remained on suppressive HAART for >10 years. [7]

Eight early treated (ET) patients who initiated ART within 90 days of seroconversion were compared to 10 chronic treated (CT) and 37 Elite Controllers (EC). All patients had undetectable viraemia for >10 years. They reported that those from the ET group had significantly lower levels of HIV-1 specific T and B cell responses and lower levels of integrated, total HIV-1 DNA and 2-LTR circles when compared to the CT and EC groups. Both gene expression patterns and miRNA expression profiles were more similar between ET and EC than those of CT. Also, EC and ET had comparable viral reactivation levels, whereas significantly more replication-competent virus was retrieved from CT. The authors concluded, "Prolonged therapy with HAART initiated early during acute infection induces an HIV-1 disease status that in many aspects is reminiscent of the elite controller phenotype".

While these results are supportive of the effectiveness of ART and its early initiation being potentially enough to fully control infection, people identified so early in infection are clearly a small and special sub group. Moreover, as more novel therapeutic approaches are being developed [8, 9, 10, 11, 12, to be reported in the next issue of HTB] and a functional cure being advanced, this will need to overcome now relatively clear physiological disparities between people treatment in chronic early treated infection.

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AIDS 2012: OTHER NEWS

Important publications launched at IAS 2012

Muirgen Stack and Rebecca McDowall, HIV i-Base

The IAS conference was used to launch several publications that each cover important aspects of HIV treatment or access. Here are a few that caught our attention. MSF must get the award for most prolific.

IAS report: Towards an HIV Cure: Global Scientific Strategy

Officially announced at a pre-conference symposium on the 20–21 July preceding the International AIDS conference, the IAS “Towards an HIV Cure” Global Strategy represents a thorough and comprehensive framework for cure-related research in the future.

It aims to use a “bottom-up” approach whereby the scientists themselves dictate research areas and allows for more communication and collaboration between researchers underneath the umbrella of cure research.

The strategy acknowledges the success of antiretroviral therapy (ART) in controlling HIV infection, but recognises that this is not a cure, defined as either “functional” (long term control of HIV in the absence of ART) or “sterilising” (elimination of HIV from the body). Currently, ART fails to eradicate the reservoir of latently infected resting cd4+ T cells, which host stably integrated HIV-1 provirus. This on its own leads to viral persistence but there is also the possibility of on-going low-level replication in other tissues of the body.

The report then identifies seven main research priorities in how best to overcome HIV persistence before a cure (functional or sterilising) can be realised. These are:

- Cellular and viral mechanisms involved in HIV persistence at a molecular level
- Anatomical compartments and cellular sources of HIV reservoirs
- Immune activation and dysfunction in the presence of ART
- Natural models of HIV/SIV control
- Assays to measure persistent infection
- Therapeutic and immunological approaches for eliminating persistent HIV infection
- Enhancement of immune response to control viral replication

At the report launch, Steven Deeks, co-chair of the IAS cure working group, said “Our basic understanding of the mechanisms of HIV persistence in latent reservoirs is far superior than it was a decade ago. We are entering a stage in the epidemic in which we can seriously begin testing drugs that either prevent latency or which force the virus out of its hiding place, making it susceptible to our current drugs.”

The IAS initiative also aims to co-ordinate new donor funding for this research globally.

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http://www.iasociety.org/Web/WebContent/File/HIV_Cure_Full_recommendations_July_2012.pdf (PDF)

Webcast of report launch:

<http://globalhealth.kff.org/AIDS2012/July-22/Towards-an-HIV-Cure.aspx>

A supplementary opinion article can be found in Nature Reviews Immunology 12, 607-614 (August 2012) by Steven Deeks.

JAIDS supplement: HIV and ageing

A review of current knowledge and research concerns relating to HIV and aging, presented as a report to the NIH Office of AIDS Research and published as a supplement in the Journal of AIDS. [1]

Rather than a focus on the recent benefits of HAART that have extended life expectancy by 50 years, the authors are more concerned with the complex interplay of social and medical circumstances that mean that “on average, a 20 year old initiating ART may already have lost one-third of the expected remaining years of life compared to similar HIV uninfected persons”.

The report highlights the concerns about Inflammation, co-infection (including CMV), reviews current data on biomarkers (IL-6, CRP, d-dimer, soluble CD14 and markers of T-cell activation and senescence), highlights current knowledge gaps and suggests priority areas of future research.

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Lancet series on HIV in MSM

The Lancet has published a series of articles highlighting the ongoing growth of the HIV epidemic in men who have sex with men (MSM).

The series explores some of the unique aspects of the epidemic in MSM, which are driving transmission among this population.

The articles cover both the science and culture behind the MSM epidemic. One comment piece examines “The irony of homophobia in Africa”, which is reflected in a review of the recently released film “Call me Kuchu” which looks at the life and death of David Kato in Uganda.

The scientific papers include a review of the “Successes and challenges of HIV prevention in men who have sex with men”. The article emphasises the importance of combining biomedical and behavioural approaches to prevention amongst MSM, and the challenge of implementing these programmes in areas where resources are restricted and legal barriers remain.

Topics covered also include the unique challenges faced by black MSM around the world; stigma and discrimination affecting MSM; and a look at the global epidemiology of HIV infection in MSM.

The full series can be accessed online at:

<http://www.thelancet.com/series/hiv-in-men-who-have-sex-with-men>

MSF report on viral load technology in developing countries

Launched at IAS, this 36-page report argues for the importance of access to viral load testing as part of the expanded access to treatment. Although already recommended in WHO guidelines, the use of viral load testing remains largely unavailable in resource-limited settings.

The report includes an summary and introduction and is divided into four key sections:

- Why the demand and need for routine viral load monitoring is so important
- An overview of current access, including for early infant diagnosis
- How to overcome technological barriers to wider implementations
- Overcoming market barriers

The report is available to download free in PDF format from links on the MSF website.

MSF. Undetectable: how viral load monitoring can improve HIV treatment in developing countries. MSFaccess.org

<http://www.doctorswithoutborders.org/press/release.cfm?id=6130>

Untangling the web of ART price reductions

Essential guide to ART price reductions, launched at IAS, and now in the 15th edition.

This is the leading review of how the majority of the 8 million people in low and middle-income countries are able to access treatment.

The report charts, in real time each year, the success of global donors and negotiators including the Clinton Health Access Initiative (CHAI) to drive generic ART prices to the most affordable levels yet, both for initial and subsequent line combinations.

In addition to reviewing cost implications for future options for scale-up, the resource includes separate information on each major compound and coformulation, including price comparisons for lowest generic costs and appendices that comprehensively include all approved adult and paediatric formulations (generic and originator).



MSF. Untangling the web of antiretroviral price reductions. 15th edition, July 2012.

<http://www.msfaccess.org/content/untangling-web-antiretroviral-price-reductions-15th-edition>

http://www.msfaccess.org/sites/default/files/MSF_assets/HIV_AIDS/Docs/AIDS_report_UTW15_ENG_2012.pdf (PDF download)

Web version:

utw.msfaccess.org

MSF: US trade and IP agreements further threaten global health

MSF access campaign

At IAS , MSF launched a new report on the ongoing negotiations between the United States and the Asia Pacific region for a Trans-Pacific Partnership Agreement (TPP). The report reveals previously secret details about the agreement, which in many ways mirrors the controversial Free Trade Agreement with the EU and India reported in the March-April edition of HTB.

Encompassing eleven countries and slated for further expansion across the Asia Pacific region, the Trans-Pacific Partnership Agreement (TPP) is a regional trade agreement that will “set the standard for 21st-century trade agreements going forward.”

The TPP negotiations are being conducted in secret, but leaked drafts of the U.S. negotiating positions show that the U.S. is demanding aggressive intellectual property (IP) provisions that would roll back public health safeguards enshrined in international trade law in favour of offering enhanced patent and data protections to pharmaceutical companies, making it harder to gain access to affordable generic drugs and hindering needed innovation.

If the U.S.'s demands are accepted, the TPP agreement will impose new IP rules that could severely restrict access to affordable, life-saving medicines for millions of people. Billed by President Obama as “a model not just for countries in the Pacific region, but for the world generally,” the TPP will set a damaging precedent with serious implications for developing countries where MSF works, and beyond.

For more information and to download the full MSF report:

MSF. Trading away health: how the U.S.'s intellectual property demands for the trans-pacific partnership agreement threaten access to medicines (August 2012)

<http://aids2012.msf.org/2012/trading-away-health-how-the-u-s-s-intellectual-property-demands-for-the-trans-pacific-partnership-agreement-threaten-access-to-medicines/>

MSF report for faster scale up

Speed Up Scale-Up: Strategies, Tools and Policies to Get the Best HIV Treatment to More People, Sooner

For over a decade, people living with HIV, treatment advocates, clinicians, and health ministries have been grappling with how to ensure increased access to quality antiretroviral therapy in resource-limited settings. Where are we now?

Although there have been enormous strides over the past decade, constrained budgets and sub-optimal policies that are only slowly changing are impeding the effort to reach all people in need. In addition, too many people are still dying because they do not know they are living with HIV, as well as many people are being diagnosed with HIV late or fall out of care before starting treatment.

This report outlines some of the strategies, tools and policies that have supported the scaling up of treatment during the past decade as well as those that can address persistent or new challenges. The results are presented from a 23-country survey of how consistently these strategies are being implemented. (See Annex 1) The findings demonstrate encouraging progress by some health ministries in adopting many of the enabling policies needed to facilitate scale-up and improve care. Nevertheless, the adoption and implementation of these strategies, tools and policies are lagging in some countries.

The survey results provide a mixed picture: 11 of 23 countries have reached antiretroviral therapy coverage of 60% or more. Some countries have already made or are making strides towards their own national targets of reaching 80% of people in need with antiretroviral therapy. On the other side of the spectrum, six countries are still only reaching one third of the people in need or less. As the international norms for HIV move towards better and earlier treatment and technological advancements in diagnostics are becoming available, it is important to shore up and strengthen the remaining key success factors that risk being compromised: political and financial support dedicated to addressing and reversing the epidemic.

The last 12 years of antiretroviral therapy in resource-limited settings have shown that, when treatment is offered close to home and before people get sick, their chances of survival increase.

Current antiretroviral therapy coverage is only halfway there: meeting the goal means getting an additional seven million people onto life-saving treatment in the next three years and helping them remain in care. Rapidly increasing the number of people living with HIV receiving antiretroviral therapy and supporting retention in care are major challenges, but the potential to start reversing the epidemic by scaling up treatment provides new motivation and represents an opportunity that must be seized.

Source: MSF. Speed Up Scale-Up: Strategies, Tools and Policies to Get the Best HIV Treatment to More People, Sooner (August 2012).

Download the full report:

<http://aids2012.msf.org/2012/speed-up-scale-up/>

UNAIDS report: Together we will end AIDS

Launched just prior to the conference, this report from UNAIDS was stacked high in the UNAIDS booth and is included photographs, graphics and contributions from many people who have key roles in the global response.

Probably the the most useful information is on pages 122-123, just before the ten pages of references, as this contains the individual country data relating to new infections in children, including the latest data on the incidence in women, details on access to treatment and care, and HIV-related mortality.

<http://www.unaids.org/en/resources/campaigns/togetherwewillendaids>

TAG/i-Base Pipeline report 2012

Finally, one of our own publications.

For the third year i-Base have partnered with the New York-based activist group Treatment Action Group (TAG) to produce a combined pipeline review of new drugs, formulations, vaccines, strategies and diagnostics. See the earlier in this issue of HTB for more details.

Available only in electronic versions now - PDF and online.

<http://www.i-base.info/2012-pipeline-report>

We also launched a new dedicated website with TAG that will be updated as new developments are announced:

<http://www.pipelinerreport.org>

CONFERENCE REPORTS

14th International Workshop on Co-morbidities and Adverse Drug Reactions (IWCADR)

19–21 July 2012, Washington

Introduction

This year, the multiple meetings held prior to the IAS conference contributed to slightly lower attendance at this long establish meeting with an interest in the complications in HIV and HIV/HCV coinfection (formerly “the lipodystrophy workshop”).

It is therefore disappointing – and an indication of funding difficulties shared by this and other specialised meetings – that this year none of the usually excellent plenary sessions or any other part of the programme are available as webcasts.

However, the abstract book from the meeting, published as a supplement to Antiviral Therapy, is available with free online access.

<http://www.intmedpress.com/journals/avt/abstract.cfm?id=2261&pid=88>

Reports included in this issue of HTB are:

- Skeletal muscle toxicity and raltegravir
- Proteinuria as a potential early marker of tenofovir-related renal toxicity
- Earlier and greater comorbidities reported in HIV positive cohort

Skeletal muscle toxicity and raltegravir

Simon Collins, HIV i-Base

An Australian study reported higher rates of muscle toxicity associated with raltegravir in asymptomatic patients.

Prompted by higher rates of grade 3/4 creatinine kinase (CK) in registrational studies for raltegravir, and rare cases of rhabdomyolysis, Frederick Lee from St Vincent's, Sydney and colleagues looked at differences in muscle toxicity in 318 HIV positive patients, half who were using raltegravir and half on non-raltegravir combinations.

Muscle toxicity was categorised in four ways: isolated CK elevation, myalgia without muscle weakness, proximal myopathy on examination, or rhabdomyolysis.

Characteristics of the group included: male (98%), white (89%), median age 51 years, median CD4 count 585 cells/mm³ with 91% undetectable (<50 copies/mL). Raltegravir has been used for a mean duration of 28 months. Recent vigorous exercise was reported by 42% and statins by 24%.

A higher proportion of patients on raltegravir reported at least one feature of muscle toxicity (37% vs 19%, $p < 0.01$). Results by category were: CK elevation 14% vs 16% (NS), myalgia without weakness 19% vs 3%, $p < 0.01$ and proximal myopathy 4% vs 0, $p = 0.03$, all raltegravir vs non-raltegravir respectively. No cases of rhabdomyolysis were seen.

Most CK elevations were grade 1 with the single grade 3/4 occurring in the non-raltegravir arm.

In multivariate analysis, only raltegravir use (OR 2.64; 95%CI: 1.57-4.45, $p < 0.01$) and recent exercise (OR 2.26; 95%CI: 1.36-3.77, $p < 0.01$) were independently associated with skeletal muscle toxicity. However, neither raltegravir drug levels nor duration of use were associated with any parameter.

Reference

Lee FJ et al. Skeletal muscle toxicity associated with raltegravir-based combination antiretroviral therapy in HIV-infected adults. 14th IWCADR, 19-21 July 2012, Washington. Oral abstract 015. Antiviral therapy 2012; 17 Suppl 2:A13.

Proteinuria as a potential early marker of tenofovir-related renal toxicity

Simon Collins, HIV i-Base

Researchers from UCL reported on a potential early marker for tenofovir-associated renal toxicity.

Ana Milinkovic and colleagues from University College London, presented results from routine monitoring for tenofovir-related renal toxicity which since 2006 has involved serum creatinine (SCr), eGFR, urine protein (UP/C) and serum phosphate. In patients with abnormal changes, tests for renal tubule dysfunction (including urine retinol binding protein) and phosphate reabsorption capacity are used to diagnose tenofovir-associated renal toxicity.

Abnormal results from the cohort of almost 1300 patients with data were screened for proximal tubular dysfunction including tubular proteinuria and phosphate excretion.

The retrospective case note review identified 103/1293 patients (8%) who had stopped tenofovir, 29 of who (2.2% of the cohort) who discontinued due to renal toxicity. The decision to stop tenofovir in this group and analysis had been based on clinical judgement rather than laboratory results. Median duration of tenofovir use was 1054 days (IQR 834-1266).

Median (IQR) baseline characteristics included: male 82%, white 63%, age 41 years (IQR 34-46), CD4 count 330 cells/mm³ (220-500).

In multivariate analysis, UP/C (per two-fold increase: aHR 3.38; 95%CI 2.69-5.51), SCr (per 10 u/mol increase: aHR 1.36; 95%CI 1.33-1.64) and recent PI use (aHR 3.34; 95%CI 1.24 – 9.41) were associated with tenofovir related renal toxicity.

Of note, half of these patients maintained eGFR levels >75 mL/min/1.73² and elevated UP/C in this group remained predictive leading the authors to conclude that proteinuria is an early marker of tenofovir associated renal toxicity, supporting routine UP/C ratios for patients on tenofovir, even when eGFR remains normal.

Reference

Milinkovic A et al. Proteinuria as an early marker of tenofovir renal toxicity. 14th IWCADR, 19-21 July 2012, Washington. Oral abstract 005. Antiviral therapy 2012; 17 Suppl 2:A5.

Earlier and greater comorbidities reported in HIV positive cohort

Simon Collins, HIV i-Base

A study from Amsterdam reported significantly higher rates of health complications in HIV positive people.

Judith Schouten and colleagues from the Academic Medical Centre in Amsterdam, reported on age-associated non-infectious co-morbidities in 381 HIV positive patients older than 45 years, compared to 349 age, gender and ethnicity matched HIV negative patients seen at a sexual health clinic.

Patients were enrolled consecutively and studied prospectively. Median age was approximately 52 years (IQR 48-60) for both groups. HIV positive people had been positive a median of 12 years (IQR 6-17). Median current and nadir CD4 counts were 573 (IQR 436-748) and 210 (IQR 130-310) cells/mm³, respectively, with 30% having a previous AIDS diagnosis. 91% were on ART (85% with undetectable viral load) for a median of 11 years (IQR 5-15).

HIV positive people were more likely to be current smokers (32% vs 24%) but less likely to be heavy drinkers (3.5% vs 6.9%). Use of recreational drugs was similar (17% used ecstasy, cocaine or cannabis in the prior month). BMI and systolic BP were similar but diastolic BP was slightly higher for the positive group (median 82 vs 79 mmHg, $p < 0.001$).

The rates of comorbidities increased with age in both groups. However, HIV positive patients consistently reported a higher incidence of one or more comorbidity (75% vs 62%) and a higher mean number of co-morbidities (0.87-2.03 vs 0.69-1.73), see Table 1. BMI, use of recreational drugs and alcohol, ethnicity and sexual orientation (MSM) were not found to be independent risk factors.

After adjusting for age, gender and pack years of smoking, HIV positive patients were significantly more likely per five years to have more comorbidities (OR 1.24 per; 95%CI 1.07-1.27, p=0.0003). In the HIV positive group, duration of ART use (OR 1.24; 95%CI 1.06-1.46, p=0.009) and lower nadir CD4 count per 100 less cells (OR 1.12; 95%CI 0.99-1.28, p=0.074), but not duration of infection, were each associated with an increased risk of more complications.

Hypertension, angina pectoris, myocardial infarction, peripheral arterial insufficiency, cerebrovascular disease, cancer and chronic liver disease were all significantly more prevalent in the HIV positive group.

Table 1: Incidence and mean number of non-infectious comorbidities

	HIV positive	HIV negative	p
>/=1 comorbidity	74.5%	61.6%	<0.001
age 45-50	59.8%	49.6%	<0.0001 for trend
age 65+	94.5%	8.5%	<0.0001 for trend
Mean number of comorbidities			
age 45-50	0.87	0.69	
age 65+	2.03	1.73	

C O M M E N T

These results are important and have been highlighted by other groups. However, an appropriate control group is always difficult for HIV studies as HIV positive people are likely to receive a higher level of monitoring and more careful follow-up than age-matched adult attending GUM services.

Even if this study is picking up earlier diagnosis of comorbid conditions than the control group and this is a marker of closer monitoring and care, it still leaves these patients with a higher level of treated conditions and more complex polypharmacy.

References

Schouten J et al. Comorbidity and ageing in HIV-1 infection: the AGEHIV Cohort Study. 14th IWCADR, 19-21 July 2012, Washington. **Oral abstract 024.** Antiviral therapy 2012; 17 Suppl 2:A20.

This study was also presented at the 19th IAS Conference. Abstract THAB0205.
<http://pag.aids2012.org/abstracts.aspx?aid=14739>

CONFERENCE REPORTS

20th International HIV Drug Resistance Workshop

9-13 June 2012, Sitges

Introduction

This international meeting on drug resistance now covers both HIV and hepatitis and usually includes studies presented here prior to other HIV conferences.

Several of the presentations are now posted to the website for the meeting together with a PDF file of the abstract book.

<http://www.intmedpress.com/journals/avt/abstract.cfm?id=2179&pid=88>

Brief reports summarise the following selected studies.

- In vitro resistance profile for BMS-986001
- Defective viral reservoir populations is common in patients on long-term suppressed ART
- Recombination dynamics in case of MDR sub-type D following superinfection with wild-type sub-type B
- First case report of transmission with five-class resistance
- New data on the Berlin patient: interpret with caution

In vitro resistance profile for BMS 986001

Simon Collins, HIV i-Base

New data was presented for an NRTI in development at BMS.

The degree of cross-resistance between commonly used first-line NRTIs leave a role for new drugs in this class, especially if they prove to also reduced toxicity concerns. This is perhaps even more important in countries where failing treatment is currently maintained until clinical failure, as accumulated mutations increase cross-resistance to potential drugs for subsequent treatment.

An NRTI in development with BMS, compound name BMS-986001 (BMS-001) that has a similar structure to stavudine (d4T) but without causing mitochondrial-related toxicities is currently in Phase II studies.

Li and colleagues from BMS presented in vitro drug susceptibility results to a panel of NRTI mutations using the Monogram Phenosense test.

BMS-001 was hypersusceptible to K65R (0.43 fold change) and L74V (0.65 fold change): key mutations associated with tenofovir and abacavir resistance but this reverted to levels similar to wild-type virus in the presence of M184V. In clinical practical, M184V is often the first mutation to occur in combinations that include 3TC or FTC, so the joint mutation is commonly seen. It was also hypersusceptible to the MDR Q151M mutation but this steadily reduced in the presence of other mutations including M184V (from 0.17 fold to 1.24-fold), with one isolate including 151 and 184 mutations dropping to > 40-fold loss in sensitivity.

Susceptibility was significantly reduced by 6-8 fold to virus from common thymidine analogue mutations (TAMs) (M41L, L210W, T215Y or D67N, K70R, T215Y).

The new compound is not able to overcome resistance to the MDR T69SSS with TAMs (> 40-fold).

This profile highlights the potential for a new NRTI that may have a role for patients failing a first-line combination containing tenofovir or abacavir, but results from clinical trials will need to correlate these response in vivo.

Reference

Li P et al. The in vitro cross-resistance profile of the NRTI BMS-986001 against known NRTI resistance mutations. 20th Intl Drug Resistance Workshop, 5-9 June 2012, Sitges. Abstract 2. Antiviral Therapy 2012; 17 Suppl 1:A10.

Defective viral reservoir populations is common in patients on long-term suppressed ART

Simon Collins, HIV i-Base

Fourati and colleagues from Paris analysed PRBC and rectal tissue samples from five patients maintained on controlled ART (range: 7-13 years) with five treatment-naive patients, using the presence of in-frame stop codon mutations in RT as an indicator of replication defective virus.

They reported a high level of defective genomes (median 21%; range 15%-100%) in the treated patients with the percentage inversely linked to the calculated size of the viral reservoir measured by proviral HIV DNA ($r^2=0.24$; $p=0.033$). No similar mutations were found in the naive patients. Most of the changes were related to APOBEC3-induced hypermutations.

The researchers proposed that their finding might support an accumulation of virus that is unable to replicate on ART, reaching a common viral extinction and that future use of proviral HIV DNA in reservoir sites in the context of cure research, should additionally measure whether this is replication competent.

Reference

Fourati S et al. HIV-1 genome is often defective in PBMCs and rectal tissues after long-term HAART as a result of APOBEC3 editing and correlates with the size of reservoirs. 20th Intl Drug Resistance Workshop, 5-9 June 2012, Sitges. Abstract 33. Antiviral Therapy 2012; 17 Suppl 1:A41.

Recombination dynamics in case of MDR sub-type D following superinfection with wild-type sub-type B

Simon Collins, HIV i-Base

While research into reinfection is largely driven by expanding number of case studies, Koning and colleagues from the UK described the dynamics of reinfection with wild-type virus, using single genome sequencing (SGS) in both plasma and semen samples.

Sequential plasmas sampling was performed over 87 weeks, with one semen sample, in a treatment naive patient. The initial sub-type D sample at diagnosis showed RT mutations at D67N, K70R, A98G, K101E, Y181C, G190A, T215L and K219E which was maintained at week 34. At 54 weeks, 18/25 genomes remained similar to baseline, with 1/25 wild-type sub-type B and 3/25 recombinant B/D sub-types with variable resistance.

At weeks 85 and 87, only 2/43 genomes related to the baseline sample, 3/43 were drug-sensitive sub-type B and 39/43 were B/D recombinants, only one of which maintain drug resistant mutations.

The single semen sample at week 87 showed 18/21 of genomes sampled to be sub-type B, and the remaining three B/D recombinants all to be drug sensitive.

No data was presented on subsequent patient treatment history.

Reference

Koning FA et al. Dynamics of recombination in HIV-1 following superinfection described using single genome sequencing. 20th Intl Drug Resistance Workshop, 5–9 June 2012, Sitges. Abstract 62. *Antiviral Therapy* 2012; 17 Suppl 1:A77.

First case report of transmission with five-class resistance

Simon Collins, HIV i-Base

A sobering report of the first case of transmission of five-class resistance was presented by Walworth and colleagues from Monogram, from a patient treated in Washington DC.

The patient was hospitalised in 2010 during acute seroconversion and resistance testing showed mutations associated with reduced susceptibility to drugs from the classes of NRTIs, NNRTIs, protease inhibitors, fusion inhibitors and integrase inhibitors.

The mutation profile included L10Y, I13V, K20I, E35D, M36I, K43T, I62I/V, V82A in protease, M41L, D67N, L74V, V118I, K101E, Y181C, V189I, G190S in RT; G140S and Q148H in integrase and Q40R and N43S substitutions in gp41, with reduced drug susceptibility confirmed by phenotypic testing.

Based on resistance and tropism profiles, the patient was treated with a combination of tenofovir/FTC, darunavir/ritonavir and maraviroc. A good viral response was reported with viral suppression maintained at month 6.

The researchers commented that while this was the first case of five-class resistance, it included the third case of transmitted integrase resistance, and that including integrase in baseline testing would be increasingly important as this class becomes more widely used.

The patient achieved viral suppression at week 12 using a combination of darunavir/ritonavir, tenofovir/FTC, and maraviroc.

Reference

Walworth C et al. Optimised antiretroviral drug selection achieves rapid and sustained suppression of viral replication, despite transmission of HIV-1 exhibiting resistance to five drug classes. 20th Intl Drug Resistance Workshop, 5–9 June 2012, Sitges. Abstract 92. *Antiviral Therapy* 2012; 17 Suppl 1:A112.

An earlier analysis of this case was also presented at the 19th IAS Conference. Abstract THPE063.
<http://pag.aids2012.org/abstracts.aspx?aid=13632>

New data on the Berlin patient: interpret with caution

Richard Jeffreys, TAG

Steve Yuki from UCSF presented new data on the case of Timothy Brown, the “Berlin Patient.”

Yuki described multiple experiments performed by several independent laboratories with the aim of searching intensively for any signs of residual HIV infection in plasma, peripheral blood mononuclear cells (PBMC) and biopsies from the gut and cerebrospinal fluid (CSF). The nature of these analyses is a testament to Brown’s extremely laudable willingness to undergo an array of unappealing procedures in order to advance research into curing HIV.

No infectious HIV was detectable in any sample (including samples containing huge numbers of cells). In most cases, no HIV RNA or DNA could be found either, but there were some exceptions: a minority of samples, analysed by some labs, intermittently tested positive for extremely low levels of HIV RNA. A very small proportion of the rectal samples also tested positive for very low levels of HIV DNA. Genetic sequencing results were not available but the abstract indicates that the RNA positive samples did not show any relationship with each other or the original infecting HIV (a finding perhaps suggestive of PCR contamination). Levels of antibodies against HIV have continued to decline over 18 months of follow up, while CD4 and CD8 T cell counts have reached near normal levels. The researchers make it very clear that because the assays being used are at the limits of their sensitivity and specificity, it cannot and should not be concluded from these data that Brown is still infected. Although it is possible that there is some residual virus present and that Brown is a case of a “functional cure” rather than complete HIV eradication (or “sterilising cure”), further work will be needed to explore that possibility. But it is far more likely that—as the study authors state—these new results are just evidence of the technological challenges associated with looking for miniscule amounts of viral genetic material.

Unfortunately, it is all too easy to envision the mainstream media picking up news of this presentation and wildly misinterpreting it (e.g. “Man Said Cured of HIV Still Infected!”). Alain Lafeuillade, who runs the biannual HIV Persistence Workshop and the HIV Reservoir Portal website, has not helped matters by writing a bizarrely misleading post on the study which suggests that the authors interpretation of the data is wrong and that Brown is either not cured, or—in an even stranger piece of speculation—that he may have been reinfected. The evidence supports neither claim.

In a related development, on 7th June 2012, the scientist Lawrence Petz held a press conference with Timothy Brown at a symposium in San Francisco on the use of cord blood to facilitate stem cell transplants. Petz revealed that around 100 cord blood donors homozygous for the CCR5 delta-32 deletion have been identified (out of 17,000 tested), and one HIV-positive individual in the Netherlands has recently received

such a transplant as part of a course of treatment for another disease. Another similar transplant is to be performed soon for an HIV-positive individual in Madrid. These cases will be carefully followed to see if the beneficial outcome experienced by Timothy Brown can be duplicated.

Source: TAG Basic Science Web Blog (09 Jun 2012)

Ref: Yuki SA et al. Challenges inherent in detecting HIV persistence during potentially curative interventions. International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies, Sitges, Spain, 5-9 June 2012.

ANTIRETROVIRALS

Dolutegravir indicates superiority compared to efavirenz in treatment-naïve patients: top-line results only

Simon Collins, HIV i-Base

Just prior to IAS conference in Washington, a press release from Shionogi-ViiV outlined top-line results from a phase III indicating that the investigational integrase inhibitor had produced superior results compared to efavirenz.

Although not seen as a helpful way to review new clinical data, once primary endpoint results are available, trading laws in the US and some other countries mandate that they are released publicly, in the interest of transparency.

The press release included results from the SINGLE study, specifically that a dolutegravir-based combination demonstrated superiority compared to Atripla in treatment naïve patients. This was based on viral suppression at 48 weeks of 88% vs. 81% (difference 7.4%; 95%CI: +2.5% to +12.3%, p=0.003).

This difference was driven by a lower rate of discontinuations due to side effects in the dolutegravir arm (2% vs. 10%).

Further details are needed when the study is presented or published before any further comment is warranted.

Source: Shionogi-ViiV Healthcare press release. Shionogi-ViiV Healthcare announces positive initial data from phase III study of dolutegravir-based regimen vs Atripla in HIV. (11 July 2012).

FDA update to darunavir label: severe skin reactions

Updates to the darunavir (Prezista) package insert were approved on June 1, 2012 and include the following:

Addition of acute generalised exanthematous pustulosis (an acute skin eruption of characterised by numerous small, sterile pustules) to the warnings and precautions (severe skin reaction) and adverse reactions (postmarketing experience) sections.

Revisions to drugs interactions and clinical pharmacology sections included boceprevir drug-drug interaction information. Specifically, concomitant administration of darunavir/ritonavir and boceprevir resulted in reduced steady-state exposures to darunavir and boceprevir. It is not recommended to co-administer boceprevir and darunavir/ritonavir.

The full updated labeling will be posted on the FDA website.

TREATMENT ACCESS

FDA approval of generic ARVs

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

Drug and formulation	Manufacturer, Country	Approval date
lopinavir/ritonavir oral solution, 80 mg/20 mg/mL	Cipla, India	29 June 2012
efavirenz, 600 mg tablets	Par Formulations	26 June 2012
efavirenz, 600 mg tablets	Edict Pharma, India	25 June 2012

efavirenz, 600 mg tablets	Micro Labs, India	20 June 2102
* abacavir 300 mg tablets (full approval)	Mylan Pharma	18 June 2012
3TC / AZT FDC scored paediatric tablets for oral suspension tablets, 30 mg /60 mg. For pts 3 months and older & weighing > 5 kg.	Cipla, India	15 June 2012
3TC tablets, 150 mg and 300 mg	Micro Labs, India	30 May 2012

* full approval; 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/oa/pepfar.htm>

Source: FDA list serve:

<http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm>

Activists protest at IAS for Global Fund to stick to principles

Global Fund Observer

The Global Fund’s new funding model must be demand driven, and must not place caps on requests from individual countries. This was the message delivered by a group of activists on 26 July at a session on the Global Fund at the International AIDS Conference in Washington, D.C.

The Global Fund is in the process of designing a new model to replace the rounds-based system of funding.

The activists disrupted the start of a 90-minute session on “The Global Fund: The Next Five Years,” just as the first presenter, Global Fund General Manager Gabriel Jaramillo, was about to speak. They chanted “End AIDS, no caps on our lives” and carried signs, one of which read “GF CAPS = DEATH.”

After the activists demonstrated for about two minutes, their spokesperson, Rosemary Mburu, was allowed to address the session. Ms Mburu is coordinator of the Africa Civil Society Platform at World AIDS Campaign.

Ms Mburu said that the world desperately needs a fully funded and strong Global Fund because of the urgent need to massively scale up life-saving services. She said that the activists had a specific message for Mr Jaramillo and others from the Global Fund: “Don’t compromise Global Fund principles when you develop the new funding model.”

Ms Mburu said that donors have advanced proposals for a new funding model that attack the core principle that real country expressions of demand for services should drive proposals - and that argue instead for an arbitrary allocation based on how much money is available at a given point in time. “We reject these proposals,” she said.

“An AIDS-free generation will not be achieved with a Global Fund that sets envelopes for countries and regions, [sets] arbitrary caps on country requests, or creates random lists of fundable interventions,” Ms Mburu said.

Ms Mburu spoke for about three minutes. Mr Jaramillo then began his talk. He said a few words at the outset that might have been directed at the protesters, though they could also have been directed to the audience in the hall. Mr Jaramillo said, “In my 18 months of navigating global health, I have met a lot of people but I have to say you are truly the best. You have made such a wonderful contribution to the world. Sometimes I think that you are not even conscious of [the magnitude of your contribution].”

Later in the session, after the presentation by Nadia Raffi, regional coordinator of the Civil Society Action Team for the Middle East and North Africa Region (and the only civil society representative on the panel), Ms Raffi invited representatives of the protestors onto the stage to ask some of the panel members to sign a pledge to uphold the demand-driven principles of the Global Fund. The precise wording of the pledge was as follows:

“Demand-driven pledge. At the International AIDS conference on 26th July, I commit as the world prepares to embark on a course to end AIDS and as the Global Fund reviews its grant-making model, that I will defend the demand-driven Global Fund, and oppose any measure that

undermines scale-up, resource mobilization or universal access. In particular, I will oppose proposals to create ceilings or envelopes that cap countries' ambition when applying to the Global Fund."

The activists asked four people to sign the pledge: Mr Jaramillo; Eric Goosby, US AIDS Ambassador; Mireille Guigaz, Ambassador of France for the Fight Against HIV and Communicable Diseases - all presenters - and Rachel Ong, communications focal point for the Communities Delegation on the Global Fund Board, and co-moderator of the session. Mr Jaramillo, Ms Guigaz and Ms Ong all signed the pledge; Dr Goosby declined.

When GFO asked the (US) Office of the Global AIDS Coordinator why Dr Goosby had declined to sign the pledge, a spokesperson said that the US is working closely with other stakeholders to develop a new funding model in the spirit of the new Global Fund five-year strategy and the founding principles of the Fund. "These discussions are ongoing, and the US will join in the dialogue on all options raised in that forum... Ultimately, the US will work with the Global Fund and its stakeholders to adopt a new funding model that will ... save the most lives..."

Source: Don't compromise your principles in the new funding model, Global Fund told. Global Fund Observer (GFO) Issue 191, 3 August 2012.

<http://www.aidspace.org>

The Global Fund: The Next 5 Years

<http://pag.aids2012.org/session.aspx?s=58>

EU parliament rejects anti-counterfeiting trade agreement: allows continued access to generic medicines

MSF Press release

On 4 July 2012, MSF issued a press release, summarised below, that welcomed the rejection by members of the European Parliament today of the Anti-Counterfeiting Trade Agreement (ACTA) put before them by the European Commission.

"We are relieved that the EU Parliament has struck down ACTA", said Aziz ur Rehman, Intellectual Property Advisor for the MSF Access Campaign. "The way it was written, ACTA would have given an unfair advantage to patented medicines, and restricted access to affordable generic medicines to the detriment of patients and treatment providers alike."

ACTA was purported to protect against counterfeiting across a number of industries, including for medicines, where it was held up as a way of blocking potentially harmful 'counterfeit' medicines. MSF strongly supports efforts to ensure that generics meet accepted international standards, however ACTA's overbroad definition of 'counterfeiting' and its excessive enforcement provisions left too much room for error. Legitimately produced generic medicines could have been seized and detained, hindering access for people who rely on these medicines to survive.

The stringent provisions in ACTA would also have targeted third parties – including treatment providers like MSF – by exposing them to the risk of punitive action in trademark and patent infringement allegations.

Following the rejection of ACTA, the European Commission should review similarly harmful intellectual property provisions being pursued in other agreements, including in free trade negotiations. One such current negotiation is with India, one of the world's biggest exporters of generic medicines, often referred to as 'the pharmacy of the developing world'.

"The EU Trade Commissioner Karel de Gucht should take heed - the vote on ACTA has shown that these harmful policies are unacceptable to European parliamentarians and some EU member states. The Commission should rethink its approach on intellectual property enforcement measures in free trade and other agreements", Mr ur Rehman said.

Source: MSF press release. (4 July 2012)

<http://www.msfaaccess.org/about-us/media-room/press-releases/eu-parliament-rejects-acta-allowing-continued-access-generic>

US trade deal threatens access to medicines

MSF Access Campaign

At the IAS conference in Washington, MSF launched a new report on the ongoing negotiations between the United States and the Asia Pacific region for a Trans-Pacific Partnership Agreement (TPP).

The agreement in many ways mirrors the controversial Free Trade Agreement with the EU and India (reported in the March-April edition of HTB).

Encompassing eleven countries and slated for further expansion across the Asia Pacific region, the Trans-Pacific Partnership Agreement (TPP) is a regional trade agreement that will "set the standard for 21st-century trade agreements going forward."

The TPP negotiations are being conducted in secret, but leaked drafts of the U.S. negotiating positions show that the U.S. is demanding aggressive intellectual property (IP) provisions that would roll back public health safeguards enshrined in international trade law in favour of offering enhanced patent and data protections to pharmaceutical companies, making it harder to gain access to affordable generic drugs and hindering needed innovation.

If the U.S.'s demands are accepted, the TPP agreement will impose new IP rules that could severely restrict access to affordable, life-saving medicines for millions of people. Billed by President Obama as "a model not just for countries in the Pacific region, but for the world generally," the TPP will set a damaging precedent with serious implications for developing countries where MSF works, and beyond.

For more information and to download the full MSF report please see:

Source: MSF. Trading away health: how the U.S.'s intellectual property demands for the trans-pacific partnership agreement threaten access to medicines (August 2012)

<http://aids2012.msf.org/2012/trading-away-health-how-the-u-s-s-intellectual-property-demands-for-the-trans-pacific-partnership-agreement-threaten-access-to-medicines/>

SIDE EFFECTS

Theratechnologies withdraw EU application for tesamorelin (Egrifta)

Simon Collins, HIV i-Base

On 22 June 2012, Theratechnologies, the Canadian-based company responsible for developing tesamorelin, a growth hormone releasing factor (GHRF) that reduces central visceral fat, released a press release relating to regulatory issues. [1]

Foremost of these was the announcement that filing for approval in the EU has been withdrawn, meaning that although approved in the US, European patients will not be able to access this option in the near future.

The brief detail cited lack of safety data (>48 weeks) concerning the increased levels of insulin-like growth factor (IGF-1) and the lack of cardiovascular endpoint to evaluate the risk/benefit ratio.

Community commentary of the company studies have also highlighted the inadequacy of the trial design for regulatory studies, which involved discontinuing treatment in all patients at the end of the study. This resulted in the unethical issue of withdrawing successful treatment from responders, but also ensuring that no longer term safety or management data continue to accrue during follow-up, while regulatory submissions were ongoing. [2]

The press release also referred to further data required on long-term safety by the Canadian regulatory agency, that the company needs to answer within 90 days and a manufacturing deficiency relating to the regulatory decision in Brazil

The FDA approved tesamorelin in the US in November 2010.

C O M M E N T

While tesamorelin is far from an ideal treatment, and may only be suitable for a minority of patients with lipohypertrophy, in the absence of effective treatment, it is disappointing that European patients will be further denied access, especially as European patients participated in the research.

However, it also raises the issue of disparity of approaches by the US and European regulatory agencies.

The FDA have approved a range of treatment to mediate metabolic complications, none of which have received EU licenses, even within a limited and narrow indication.

References

Theratechnologie Press Release. Theratechnologies Provides Regulatory Update on Tesamorelin. (22 June 2012).

http://www.theratech.com/sites/default/files/news_release_en/th-06222012-en.pdf (PDF)

FDA approves tesamorelin for reduction of central fat accumulation. HTB November/December 2010.

<http://i-base.info/htb/14188>

Recent studies on HIV, ART and osteoporotic fracture risk

Muirgen Stack, HIV i-Base

Two studies published earlier this year in the journal AIDS added to the accumulating data on the complex relationship between bone health, HIV and antiretroviral treatment (ART).

Tenofovir associated with increased fracture risk

In the first, Roger Bedimo and colleagues reported on the relationship between osteoporotic fracture risk and cumulative exposure to ARVs. They reported that cumulative exposure to tenofovir was independently predictive of increased risk of osteoporotic fracture (12% higher risk per year of exposure) after controlling for traditional osteoporotic risk factors and concomitant ART. [1]

This was a retrospective analysis from patients treated from 1988 to 2009 in the US Veterans Health Administration clinical case registry. ICD-9 diagnostic codes were used to identify osteoporotic fractures (defined as wrist, vertebral or hip fracture) after patients had been diagnosed with HIV. Cumulative ART exposure (drug or class) was defined from initial prescription to the first recorded fracture.

Multivariate analyses used two models: model 1 (MV1), controlled for age, race, tobacco use, diabetes, chronic kidney disease (CKD), hepatitis C virus (HCV) and BMI; model 2 (MV2), controlled MV1 variables and concomitant exposure to other antiretroviral drugs.

From over 56,600 patients identified in this predominantly male (98%) cohort, 39,277 (69.4%) had at least 1 month of antiretroviral therapy (ART) exposure with the total ART exposure in the cohort being 164,414 person-years (PY). A total of 951 individual patients sustained osteoporotic fractures. Multiple fractures were censored after the first event.

Patients with osteoporotic fracture had a slightly higher median age than those without (46 vs. 44 years), were more likely to be white (57% vs. 45% of those without fracture), a BMI below 20 (49% vs. 33%) and have HCV co-infection (51% vs. 31% ($p < 0.0001$ for all comparisons)).

Tenofovir exposure (46,062 PY) was associated with a yearly hazard ratio for osteoporotic fracture of 1.08 (95% CI 1.02-1.15, $p < 0.001$). Exposure to abacavir, AZT or d4T or NNRTIs were not significantly associated with increased risk of osteoporotic fracture in univariate or multivariate models.

For the 32,439 patients who entered the cohort in the HAART era, tenofovir exposure (38,009 PY) was associated with a yearly hazard ratio (HR: 95%CI) for osteoporotic fracture of HR 1.13 (1.05-1.21, $p = 0.001$) in MV1 and HR 1.12 (1.03-1.21, $p = 0.011$) in MV2. Boosted protease inhibitor exposure PI/r (32,109 PY) was associated with HR 1.08 (1.01-1.15, $p = 0.026$) in MV1 but was not significant at HR 1.05 (0.97-1.13, $p = 0.237$) in MV2. Exposure to abacavir, AZT, d4T or NNRTI was again not significantly associated with increased risk of osteoporotic fracture in either model.

Concomitant exposure to both tenofovir and PI/r was associated with a greater osteoporotic fracture risk (HR 1.16; 95%CI 1.04-1.30) than exposure to either tenofovir without PI/r (HR 1.11, 95%CI 1.01-1.21) or PI/r without tenofovir (HR 1.10; 95%CI 1.01-1.22).

Of the protease inhibitors, only lopinavir/ritonavir (15,319 PY) was associated with significantly increased osteoporotic fracture risk in MV1 (HR 1.13; 95%CI 1.04-1.22, $p = 0.005$) and barely in MV2 (HR 1.09; 95%CI 1.00-1.20, $p = 0.051$).

ART (including tenofovir) protective of fracture risk

The second study was a nested case-control study by Linda Mundy and colleagues and reported a reduced risk of fracture in HIV positive people on ART (including tenofovir). [2]

This was a nested case-control design in a cohort of almost 60,000 HIV positive people (approximately 25% women) enrolled from 1997 to 2008 in a US medical insurance database. ART was prescribed to 51% of patients at some point and was more common from 2003-2008 (72%) than 1998-2003 (29%). Cumulative ART exposure was again derived from prescription history. During this period, 2,411 individuals were identified with closed non-traumatic fractures according to ICD-9 codes and were matched by age and sex to 9144 HIV positive controls without fractures.

Variables included in the analysis included excess alcohol use, low physical activity, low body weight, hepatitis C virus (HCV) infection, excess steroid use and treatment for osteoporosis with bisphosphonates.

In this study, fracture risk was significantly reduced in people exposed to ART (OR 0.64, 95% CI 0.58-0.71; $p < 0.0001$). Furthermore, reduced risk for fracture was associated with exposures to both NRTI and NNRTI drug classes, with a pattern of incremental reduction of risk with increased duration of exposure. A null effect was associated with those exposed to protease inhibitors (PI), but this effect was reduced after extended exposure of 18 months or more in a subset of patients.

Fracture risks were also reported for individual drug exposure. Reduced risk was reported for efavirenz, FTC, 3TC, tenofovir and AZT. Increased risk was reported for darunavir, delavirdine and saquinavir. After an initial increase in risk, nevirapine, ddI, nelfinavir, ritonavir and d4T were associated with a reduced risk after increasing the duration of exposure. Null or uncertain risk for fracture was associated with amprenavir, atazanavir, enfuvirtide, fosamprenavir, indinavir, lopinavir, tipranavir, and T-20 (although limited data was available for some of these drugs).

A sub-analysis of 8,879 cases enrolled in care after 2001, assessed the exposure-response relationship to abacavir and tenofovir, two drugs that have previously been associated with altering BMD levels. No statistically significant association was reported even after 12 months of cumulative exposure to either drug. Fracture risk after 12 months of exposure to tenofovir was not significant (aOR 1.08 95% CI 0.83-1.40).

In the discussion the authors note the complexity of estimating time-dependent drug-specific risks over different time periods, especially given the dynamics of bone metabolism with age. However, ART exposure, including by class and drug was generally protective of fracture risk suggesting an overall benefit of treatment. Although the number of fractures with darunavir was low, the associated was notable (aOR=1.93, 95% CI=1.05-3.56; global P-value=0.043) and may warrant further study.

Comparing the studies

Both studies evaluated a similar number of patients and used the same diagnostic codes to identify reported fractures through retrospective methods. Antiretroviral use was ascertained through prescription history and both studies included fracture risk variables in their analysis.

There were differences however, as Bedimo et al, failed to include prior fracture events in their results, which is an important absence (Mundy et al found this to be significantly higher, statistically as a prediction of subsequent fracture risk). However, Bedimo et al only used reported vertebral, hip and wrist fractures (selected on the basis of their likelihood of being related to osteoporosis) whereas Mundy et al identified any non-traumatic fractures and grouped them as cases, limiting the inference that all were osteoporotic in origin. Neither study evaluated BMD so none of the reported fractures can be proven to be definitively osteoporotic.

The Bedimo et al study period was 21 years and included the distinction of ARV use during the HAART and pre HAART eras, whereas the Mundy et al study period was only 11.25 years.

Bedimo et al included age, race, tobacco use, diabetes, BMI, HCV co-infection and cumulative ARV exposure as variables. Sex was not included as 98% of the cohort was male.

Mundy et al included a much larger number of variables into their analysis; age, sex, geographic census region, year of enrollment, excess alcohol use, low physical activity, HIV-related conditions (CDC category A/B/C), prior fractures, low body weight, lipodystrophy, hepatitis B/C virus, and prescription drug exposures (proton pump inhibitor, glucocorticosteroid excess, vitamin D/calcium, bisphosphates) against ARV drug exposure. However, race and tobacco use were included.

Mundy et al evaluated a wider variety of ARV drugs on fracture risk, including all of the main classes whereas, Bedimo et al analysed a smaller selection but crucially were able to study their effects on fracture risk over a longer period of time.

The primary result and conclusion from Bedimo et al was that tenofovir remained independently predictive of osteoporotic fracture risk (12% higher risk per year of exposure) after controlling for traditional osteoporotic risk factors and concomitant antiretroviral drug used during the HAART era.

Despite finding a statistically significant result for tenofovir use increasing fracture risk, Bedimo et al failed to find a statistically significant result on cumulative ARV use (per year of exposure) increasing fracture risk in their multivariable analysis 0.99 (0.95-1.04; p=0.77).

C O M M E N T

These findings are not necessarily contradictory, nor supportive. As both HIV infection itself and ARV use has been associated with increasing fracture risk and lowering BMD, it may be that two physiological effects are happening but not being recorded in the data. Retrospective analyses from cohort database, especially over such a long period with likely underreported of both events and lifestyle factors has well described limitations.

ART lowers the impact of the HIV infection on the body, but is used over time, as BMD reduces due to ageing. Until clear causality is established, it is difficult to weight specific risk on certain ARVs, particularly when other more established risk factors are added into the analysis and the statistical significance of each ARV on fracture risk starts to decline.

The caution on using tenofovir in patients with highest risk of fracture (previous history of fracture, osteoporosis, FRAX score) is still probably warranted. [3]

The START study that randomises patients in early infection (CD4 >500 cells/mm³) to either immediate or deferred (until CD4 <350) ART is already two-thirds enrolled. The bone sub-study in START, with both biomarker and DEXA results will produce a prospective dataset to help answer many of these increasingly important questions.

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PREVENTION

FDA approve Truvada to reduce the risk of sexual transmission

FDA press release

On 16 July 2012, the US Food and Drug Administration approved Truvada (tenofovir/FTC) to reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners. [1]

The indication specifies "Truvada is to be used for pre-exposure prophylaxis (PrEP) in combination with safer sex practices to prevent sexually-acquired HIV infection in adults at high risk. Truvada is the first drug approved for this indication".

Truvada for PrEP is meant to be used as part of a comprehensive HIV prevention plan that includes risk reduction counseling consistent and correct condom use, regular HIV testing, and screening for and treatment of other sexually-transmitted infections. Truvada is not a substitute for safer sex practices

The PrEP indication means Truvada is approved for use as part of a comprehensive HIV prevention strategy that includes other prevention methods, such as safe sex practices, risk reduction counseling, and regular HIV testing.

As a part of this action, FDA is strengthening Truvada's Boxed Warning to alert health care professionals and uninfected individuals that Truvada for PrEP must only be used by individuals who are confirmed to be HIV-negative prior to prescribing the drug and at least every three months during use to reduce the risk of development of resistant HIV-1 variants. The drug is contraindicated for PrEP in individuals with unknown or positive HIV status.

Approval was based on two large, randomised, double-blind, placebo-controlled clinical trials. The iPrEx trial in 2,499 HIV-negative men or transgender women who have sex with men and with evidence of high risk behavior for HIV infection and the Partners PrEP trial in 4,758 heterosexual couples where one partner was HIV-infected and the other was not (serodiscordant couples). Result from both studies have been widely reported (including in HTB).

As a condition of approval, Gilead is required to collect viral isolates from individuals who acquire HIV while taking Truvada and evaluate these isolates for the presence of resistance. Additionally, the company is required to collect data on pregnancy outcomes for women who become pregnant while taking Truvada for PrEP and to conduct a trial to evaluate levels of drug adherence and their relationship to adverse events, risk of seroconversion, and resistance development in seroconverters.

C O M M E N T

Within two weeks of this FDA decision, the NEJM published three further PrEP studies. All are available as free access. [2, 3, 4]

Although these have previously been presented at conferences over the last year (and reported in HTB), the full studies are important due to the varying level of protection.

The TDF2 and Partners PrEP studies, reported an efficacy rate of 62% to 75% but the FEM-PrEP study was discontinued early because of a lack no evidence for protection was observed.

Reduced adherence may contribute to the FEM-PrEP results, but these results have not yet been explained.

The journal also included an editorial reviewing the future of PrEP. [5]

References

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BASIC SCIENCE

Role of cell-to-cell transmission in sustaining the HIV reservoir

Richard Jeffreys, TAG

A new study by Marc Permanyer and colleagues, published online recently by the Journal of Virology, disputes the interpretation of results suggesting that cell-to-cell transmission facilitates ongoing viral replication in the face of antiretroviral therapy. [1]

The earlier research, from the laboratory of David Baltimore, was published as a high profile paper in August 2011 in the journal *Nature*. This paper proposed that cell-to-cell transmission might represent a mechanism that sustains the reservoir of HIV-infected cells in people on long-term ART. [2]

The essence of the disagreement relates to the method used to measure cell-to-cell HIV spread in a laboratory culture system. The original study used a modified HIV that expresses a green fluorescent protein (GFP) tag, and assessed whether the tag became detectable in cells as a surrogate for viral replication.

Permanyer's work shows that transfer of HIV from cell-to-cell, as measured by GFP, does not necessarily equate to continuation of the viral replication cycle. In the presence of ART, the transfer is shown to be abortive because replication is blocked.

The researchers conclude: "data on cell-to-cell spread should be taken with caution as it is crucial to correctly distinguish and measure abortive virus transfer or surrogate markers of infection (LTR-driven GFP) from effective viral replication."

Source:

TAG Basic Science Web Blog (29 Jun 2012)

References

1. Baltimore J et al. Nature, August 2011.
2. Permanyer M et al. Antiretroviral agents effectively block HIV replication after cell to cell transfer. J Virol. 2012 Jun 13. [Epub ahead of print] <http://jvi.asm.org/content/early/2012/06/08/JVI.010444-12.abstract>

FILM REVIEWS

ACT-UP in film: “How to survive a plague” and “United in anger”

Simon Collins, HIV i-Base

The IAS conference in Washington also included the opportunity to see two new films on early HIV activism in the US.

On the first evening of the conference, a few blocks south of the conference centre, a preview screening took place for a film that tracked the history of ACT-UP from the first meetings through to the arrival of the first effective treatments.

The film tells the story of how people came together to organise to overturn the way that research, drug regulation, medicine and science worked in the US, fighting ignorance, indifference and prejudice. It is that simple and dramatic. And many activists who followed, myself included, recognise that little of the current work we are involved in would have been possible without their achievements.

The film was directed by David France, who tracked down more than 700 hours of archived footage from 30 different collections, and edited this with recent interviews from early activists including Peter Staley, Mark Harrington, David Barr, Garance Franke-Ruta, Spencer Cox, Larry Kramer, Gregg Bordowitz and Gregg Gonsalves. Many others, just as crucial in the struggle, did not make it. As you are drawn into the story you meet people who leave you to finish the journey without them.

ACT-UP came from a crisis that is difficult for anyone who was not there at the time to imagine now - but it did not come with the first cases, or even in the first years. By the time the group was founded in New York in 1987, six years after the first deaths from AIDS, 40,000 people had died in the US and 500,000 people had died globally.

But the same month that the group formed, AZT, a previously existing compounded developed with considerable public funding, was approved as the first treatment. The manufacturers set the price higher than any other current medication at \$10,000 a year, and an ACT-UP demonstration managed to close trading on the floor of the New York stock exchange, forcing Boroughs-Wellcome to drop the price by 20%.

Other actions used media attention to force political change. These included unrolling a giant replica condom over the home of the homophobic Republican senator Jesse Helms, closing the FDA with thousands of demonstrators to change in the mechanism for regulatory approval for life-threatening conditions, holding a “die-in” in St Patricks Cathedral in response to Catholic directives against using condoms, and in 1996, scattering on the White House lawn the ashes of their friends and lovers as a last act of protest.

But the change came not just from shouting and protests - though that potential brought muscle to the groups demands. Behind the scenes, ACT-UP members became sufficiently expert at research and science, to be able to draft the first strategic agenda for HIV research and some of the first industry trials and taking the stage of International Conferences to launch this.

They were able to get the FDA to overturn the decision to refuse approval for a drug called DHPG (proven to save the eyesight of people with CMV, later called ganciclovir). And they forced open the secretive world of FDA committees - “why should science be shrouded in secrecy?” so that public involvement set new standards. Even when scientists recognised that nothing was certain the interactions with the activist led to personal responses that “we have no right to say we can’t do this”.

These examples show how ACT-UP’s mix of public protest and forcing dialogues with health officials, scientists and drug companies lead to faster, more effective, more affordable treatment. People organised together to say when things were not good enough.

In a panel discussion after the screening, director David France described how reactions to the film vary: “for those under 40 everything is new and for those older they are watching home movies”. He made the film “to correct a misdirection that not everything was about loss. It was a period of immense creativity, activism and change”. For all the noise and press, these activists were also quiet, considered, tactical, strategic.



Poster still from *How To Survive a Plague*.



Early ACT-UP members attending the screening of *How To Survive a Plague*: (l-r) Sam Avrett, David Barr, Moisés Agosto, Mark Harrington, Garance Franke-Ruta and Gregg Bordowitz.

One activist emphasised that although the film ended in 1996, what happened after this was even greater, involving treatment activists who changed the world under much harder conditions. David Barr was one of a handful of ACT-UP members involved in ACT-UP's Treatment and Data group who went on to found the Treatment Action Group - a group that continues today to be one of the leading HIV treatment policy organisations in the US.

Having spend many years developing support for international HIV projects, and still visibly moved from having watched the film in which he was featured, he found the 2012 IAS conference a difficult experience: "The meeting is full of good people saying the right things, but there is no passion here. The scientific breakthroughs over the last two years are so dramatic. Treatment as prevention closes the circle, but the rhetoric of "a world without AIDS" will not make anything happen. Everything is really just falling apart, and if it falls apart now we will never get it back together. Activists need support and money. If we want any of this to work - treatment as prevention - we need community activism and yet we have little or no funding. Just let the Russian activists here talk about what they face every day - what they are doing now is just as brilliant as anything we did."

This is something he returns to: "The need for activism is not just about being angry, but about being strategic so we will see this through. For many people HIV is now seen as a career. We were doing this for personal reasons - not to help other people as a goal in itself. We had our own personal agenda. Personal motivation drove everything."

A second film chronicling the history of ACT-UP called "United in Anger: A history of ACT-UP" was screened in the Global Village at the IAS conference.

It is produced by Jim Hubbard and Sarah Schulman of the ACT-UP oral history project and based on many of the extensive interviews with over 140 activists. Transcriptions are available online including from many of the activists included in both films.

This film is a profile of ACT-UP to establish its place in history rather than the more intimate reflections from one group of activists. It includes more HIV positive women and other campaigns including the the four-year drive to change the US CDC definitions for AIDS-defining illnesses to include infections that specifically affected women, without which they were excluded from public assistance programmes.

Both films are important. See them to understand and appreciate our history. See it to learn and to be inspired that change can happen and, finally, to document and tell your own histories afterwards.

Links:

How to Survive a Plague, director David France.

<http://www.howtosurviveaplague.com/>

"United in Anger: A history of ACT-UP", director Jim Hubbard.

<http://www.actuporalhistory.org/interviews/index.html>

<http://www.unitedinanger.com/>

ON THE WEB

Free full text online articles:

PLoS Medicine (July 2012)

This month, PLoS Medicine includes a broad range of HIV related papers.

The ethics of switch/simplify in antiretroviral trials: non-inferior or just inferior?

Andrew Carr, Jennifer Hoy, Anton Pozniak

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001240>

Paper discussing the limitations and ethics for antiretroviral switch studies using the MONET and SWITCHMRK studies are examples.

Treatment of young children with HIV infection: using evidence to inform policymakers

Andrew Prendergast, Di Gibb et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001273>

Paper evaluating the evidence for a change in policy for the treatment of young HIV positive children and infants, including when to start wand optimal choice of combination.

HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa

Jeffrey Eaton et al.

Article discussing modelling approaches to the use of ARV treatment as prevention.

<http://www.ploscollections.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001245>

Accompanied by ten discussion papers.

<http://www.ploscollections.org/article/browseissue.action?issue=info%3Adoi%2F10.1371%2Fissue.pcol.v07.i18>

Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis

Amitabh Suthar, Stephen Lawn, Reuben Granich et al.

In a systematic review and meta-analysis, Amitabh Suthar and colleagues investigate the association between antiretroviral therapy and the reduction in the incidence of tuberculosis in adults with HIV infection.

<http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001270>

FUTURE MEETINGS

Conference listing 2012/13

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.

52nd ICAAC

9–12 September 2012, San Francisco, USA.

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

16th Annual UK Resistance Meeting

20th September 2012, London

<http://www.mediscript.ltd.uk/Resistance2012.htm>

BHIVA Autumn Conference 2012

4th - 5th October 2012, London

<http://www.bhiva.org>

3rd Intl Workshop on HIV and Ageing

5–6 November 2012, Baltimore, USA.

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

11th International Congress on Drug Therapy in HIV

11–15 November 2012, Glasgow

<http://www.hiv11.com>

20th Conference on Retroviruses and OIs (CROI) 2013

28 February–6 March 2013, Atlanta, all to be confirmed.

<http://retroconference.org>

19th Annual (BHIVA) 2013

16th - 19th April 2013, Manchester

<http://www.bhiva.org>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website: 2012 update

The i-Base website has been recently redesigned to meet access standards for PDA, iPad, tablet, Windows 8 and touch screen access.

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

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

All i-Base publications are available online, including editions of the treatment guides. The site gives details about 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 200,000 pages from 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 (April 2012)
- HIV testing and risks of sexual transmission (February 2012)
- HIV and quality of life: side effects & complications (July 2012)
- 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

Text from activists from 25 countries and 50 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. Information to support this is available on the i-Base website.

In addition, PDF files of some of the translated publications are available online.

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

<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, Spanish and Turkish.

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>

by sending an email to: subscriptions@i-Base.org.uk

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**However you chose to donate to i-Base,
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- HIV Treatment Bulletin (HTB) every two months by e-mail (PDF file) by post
- HIV Treatment 'Passports' - Booklets for patients to record their own medical history
1 5 10 25 50 Other _____
- 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 (April 2012)
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 (July 2012)
1 5 10 25 50 Other _____
- Guide To HIV and hepatitis C coinfection (March 2009)
1 5 10 25 50 Other _____
- Clinical 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
1 Sheet 1 pad 5 pads 10 pads Other _____
- Phonline support material (please specify quantity of each)
A3 posters _____ A5 leaflets _____ A6 postcards _____ Small cards _____

Please fax this form back, post to the above address, or email a request to HIV i-Base:

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