ISSN 2040-1450 (Print)

htb+ south
HIV treatment bulletin+south

htb south : volume 5 number 3

july–september 2012

CONTENTS

Published by HIV i-Base

htb south

HIV TREATMENT BULLETIN SOUTH

HTB South is a quarterly journal published by HIV i-Base.
http://www.i-Base.info

To order copies send an email to: subscriptions@i-Base.org.uk

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HIV i-Base receives unconditional educational grants from Charitable Trusts, individual donors and pharmaceutical companies.All editorial policies are strictly independent of funding sources. HIV South is supported by The Monument Trust. Nathan Geffen is renumerated from this grant.

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

EDITORIAL

This issue of HTB South includes the wealth of data presented before and during the 19th IAS World AIDS Conference in Washington DC in July 2012.

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.

Two prevention studies looking at maraviroc in macaques and mechanisms for the benefit from medical male circumcision are respectively disappointing and illuminating. We also include an overview of cure research presented at the meeting – which had a high profile including an interesting satellite – and studies looking at PK of old and new TB drugs, particularly when given with ART.

Southern African HIV Clinician's Society

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

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

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

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

http://www.sahivsoc.org

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Also preceding the main conference was the 14th International Workshop on Co-morbidities and Adverse Drug Reactions (IWCAR). 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-morbiditiy plus a higher number of co-morbidities in HIV positive people compared to negative controls.

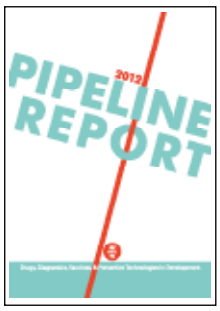
Finally, for a change of scenery for the conference coverage, we include reports from Sitges in June, where 20th International HIV Drug Resistance Workshop was held. From this meeting we have – among others – a further report of in vitro data for BMS-98600, this time showing its resistance profile, and 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. And TB drug development is advancing, which Nathan Geffen describes.

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

HTB SOUTH SUPPLEMENTS

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 Jefferys 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 incuded 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:

- New booster - cobicistat as an alternative to ritonavir
- Dolutegravir vs raltegravir in treatment-naive patients: 48 week results from the SPRING 2 study
- Elvitegravir vs raltegravir: 96 week phase III results in treatment experienced patients
- 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 from raltegravir registrational studies
- First report: atazanavir-related cholelithiasis (gall stones)
- 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
- Tenofovir prophylaxis for neonates
- Efavirenz levels variable in children in the CHAPAS-3 study
- Lipid profile in children in PREDICT: immediate versus deferred nevirapine-based ART
- High prevalence of peripheral neuropathy in children taking d4T in rural South Africa
- BCG vaccination at birth induces CD4 cell activation in HIV exposed infants
- Pharmacokinetics of old and new TB Drugs
- 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
- Towards an HIV cure: Early developments in the field

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-naive 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 (Ctau = 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 coinfected 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 occured 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 phophokinase (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-naive adults: 48 week results from SPRING-2 (ING113086). 19th International AIDS Conference. 22-27 July 2012, Washington. Late breaker oral presentation THLBB04.

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 coinfected 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) expect 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 to the FDA and EMA for a decision on regulatory approval as a single agent.

References

1. Elion R et al. Efficacy and safety results from a randomized, double blind, active controlled trial of elvitegravir (once-daily) versus raltegravir (twice-daily) in treatment-experienced HIV-positive patients: long term 96-week data. 19th International AIDS Conference. 22-27 July 2012, Washington. Oral abstract TUAB0105.
   http://pag.aids2012.org/Abstracts.aspx?SID=202&AID=5823
   http://pag.aids2012.org/flash.aspx?pid=1386

2. Molina J-F et al. Elvitegravir once-daily is non inferior to raltegravir twice-daily in treatment experienced patients: 48 week results from a phase 3 multicenter, randomized, double blind study. 19th International AIDS Conference. 22-27 July 2012, Washington. Oral late breaker abstract WELBB05.
http://pag.ias2011.org/Abstracts.aspx?SID=44&AID=4757
3. Margot NA et al. Low rates of integrase resistance for elvitegravir and raltegravir through week 96 in the phase 3 clinical study GS-US-183-0145N. 19th International AIDS Conference. 22-27 July 2012, Washington. Poster abstract TUPE050.
http://pag.aids2012.org/abstracts.aspx?aid=19167

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 Cmax concentration and at 200 uM 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 uM 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 deoxypyridinoline 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
1. Wang F et al. The HIV NRTI BMS-986001 does not degrade mitochondrial DNA in long term primary cultures of cells isolated from human kidney, muscle and subcutaneous fat. 19th International AIDS Conference. 22-27 July 2012, Washington. Poster abstract TUPE042.
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2. Guha M et al. Absence of renal and bone toxicity in non-clinical studies of BMS-986001, a nucleoside reverse transcriptase inhibitor (NRTI) of human immunodeficiency virus (HIV). 19th International AIDS Conference. 22-27 July 2012, Washington. Poster abstract TUPE041.
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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<001. 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

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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 add 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

Mills A et al. Once-daily maraviroc in combination with ritonavir-boosted atazanavir in treatment-naïve patients infected with CCR5-tropic HIV-1 (study A4001078): 96-week results. 19th International AIDS Conference. 22-27 July 2012, Washington. Oral abstract TUAB0102.

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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 efavrienz 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 comparitor arms, especially when a composite efficacy and tolerability endpoint is likely to show differences compared to efavirenz.

Reference

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   http://pag.aids2012.org/abstracts.aspx?aid=12576

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 pharmacovigilence 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 underdone 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 laperoscopic 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 n 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 coinfected 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.
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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 AUC0-t and AUC 0-IFN fell within the conventional bioequivalence range of 80 -125%, while for Cmax it was just outside. For ritonavir (RTV), AUC0-t and Cmax 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.

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.

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 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.

References

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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% (IQR18.4-26) 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 to18 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 the in 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) AUC0-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 Ct these values were, 1.00 (90% CI 0.833 – 1.21) and 0.397 90.298 – 0.528).

Despite lower Ct 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 chlolesterol (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 Casaerean 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 Shiau 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 (± 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 ≥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.

Reference

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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 onging.

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 ≤ 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/mm3)	611	619	977	662*
VL (log10 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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BCG vaccination at birth induces CD4 cell activation in HIV exposed infants

Polly Clayden, HIV i-Base

Almost a third of infants in sub-Saharan Africa are HIV exposed, through delivery or breastfeeding.

In this region young infants are often routinely vaccinated at birth with BCG to protect them from disseminated TB. Live attenuated BCG vaccine is known to be safe and effective in uninfected children but may cause CD4 T cell immune activation, which could increase susceptibility to HIV and disease progression. Since 2007, BCG vaccination is contraindicated for HIV-infected infants in WHO guidelines.

In a late breaker presentation at IAS 2012, Heather Jaspan presented results from a South African study to assess CD4 cell activation and inflammatory cytokines in peripheral blood of HIV-exposed infants BCG vaccinated at birth (in accordance with South African immunisation guidelines) versus at 8 weeks old.

The study was conducted in Khayelitsha, a township with 30% antenatal HIV prevalence. Infants enrolled were those who had a normal pregnancy and delivery and no TB contacts. Infants were randomised to either the early (n=62) or delayed (n=56) arm. Those in the early arm were a median of 3 days old at vaccination compared to 56 days in the delayed arm, p <0.0001.The median maternal CD4 count at delivery was similarly about 350 cells/mm3 in both arms and about 15% of children were breastfed.

At 6 weeks infants in the early arm had significantly higher HLA-DR expression on CD4 T cells than those whose BCG vaccination was delayed, p=0.024. They also had significantly higher CCR5, HLA-DR and CD38 co-expression on CD4 T cells, p=0.01. There was no difference in CD8 T cell activation between the early and delayed arms.

The CCR5 agonist, MIP-1b (CCLA) was significantly higher at 6 weeks in unvaccinated infants, unadjusted p=0.036. But the investigators found no differences in plasma IFN-a, IFN-g, MCP-1, TNF-a, IL-8, GMCSF or IP-10 levels, nor in PBMC IFN-a , IFN-g, RANTES, TNF-a, IL-8, IL-10, TGF- b, OAS or IP-10 mRNA levels, between vaccinated and unvaccinated infants.

When the investigators looked at factors predicting CD4 T cell activation at 6 weeks, only timing of BCG was significant, adjusted coefficient -.463 (95% CI -.771 to -.154), p=0.004.

This finding has important implications for timing of BCG vaccine and use of live, replication-competent bacteria as vaccine vectors in HIV-exposed, breastfed infants.

C O M M E N T

The majority of the infants in this study were formula fed, which, until recently, was standard of care in Western Cape.

Although breastfeeding is recommended now in the context of either maternal ART or infant prophylaxis, women who are not on fully suppressive therapy or infants who are not receiving prophylaxis might be at additional risk of HIV acquisition with early BCG vaccination. More research is needed.

Reference

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AIDS 2012: TUBERCULOSIS

Pharmacokinetics of old and new TB Drugs

Polly Clayden, HIV i-Base

Several studies at IAS 2012 showed pharmacokinetc (PK) data for older and investigational TB drugs, particularly in the context of treating HIV.

Efavirenz and rifampicin

ART and TB treatment must be given together particularly in people with advanced HIV but doing so is complicated by drug-drug interactions. Rifampicin upregulates several cytochrome P450 enzymes and has been associated with a decrease of approximately 30% trough levels of efavirenz (Cmin), when the two drugs are given together. Conversely, in African people particularly, CYP2B6 polymorphisms have been associated with paradoxical increases in efavirenz levels.

The reports of reduction in exposure led the FDA to recommend a dose increase earlier this year from 600mg to 800 mg once daily of efavirenz when co-administered with rifampicin for people weighing >50 kg. Clinical data have not shown reduced virologic suppression with 600 mg efavirenz plus rifampicin.

STRIDE (US Adult AIDS Clinical Trials Group A5221) was an international randomised trial of immediate (2 weeks after starting TB treatment) versus early (8 to 12 weeks) ART among HIV positive people with CD4 <250 cells/mm3 treated for TB. Participants were stratified to those <50 versus >50 cells/mm3 CD4. For people with <50 cells/mm3 CD4, immediate ART resulted in lower rates of AIDS and death compared to early ART but immediate ART did not result in a reduction of AIDS and death overall.

Annie Luetkemeyer from the trial group showed findings from a PK analysis of STRIDE participants receiving 600 mg efavirenz, regardless of weight, plus rifampicin-based TB treatment. [1]

In this substudy, efavirenz Cmin was determined using high performance liquid chromatography with a lower limit of detection of 0.1 mg/L. Samples were obtained 20-28 hours post-dose at weeks 4, 8, 16 and 24 on RIF, and weeks 4 and 8 off rifampicin, in participants with no missed doses for 3 days prior to sampling.

There were a total of 780 participants and 543 provided one or more efavirenz PK value. At baseline they (n=543) were a median age of 34 years, weight 52.8 kg, BMI 19.4 kg/m2 and CD4 count 64 cells/mm3. Seventy four percent were black, 20% Hispanic, 5% white and 1% Asian.

When the investigators looked at the effect of weight on efavirenz Cmin in participants on rifampicin, they found they had a median of 1.96 (IQR 1.24 to 3.79) mg/L overall. The difference in efavirenz Cmin between those weighing more or less than 50 kg was not significant. But for those weighing less than 60 kg the median efavirenz Cmin was 2.02 (IQR 1.29 to 4.09) mg/L compared to 1.68 (IQR 1.07 to 3.06) mg/L in participants above this weight, p=0.02.

There were no significant differences in efavirenz Cmin on versus off rifampicin across all weight comparisons. There was a difference however for black patients on rifampicin (n=367) who had a median efavirenz Cmin of 2.1 mg/L compared to off rifampicin (n=269) when this value was 1.8 mg/L, p=0.01. Comparisons in other ethnic subgroups were not significant but the numbers were small.

Concomitant ART and TB treatment did not effect viral load suppression <400 copies/mL. By week 48, 75.8% of participants were suppressed (n=780, but Dr Luetkemeyer remarked that this was similar in the substudy). There was no statistically significant difference in proportions of participants who were suppressed comparing those above and below 50 kg. But a significantly higher proportion of participants weighing over 60kg had a suppressed viral load compared to those weighing less, 81.9% versus 73.7%, p=0.02. Dr Luetkemeyer noted that higher weight was a marker for better health overall in the study.

When the investigators looked at efavirenz Cmin outside the therapeutic window they found subtherapeutic concentrations (<1 mg/L), were not associated with rifampicin and occurred in 27.3% versus 26.2% on and off respectively, p=0.72. Nor were they associated with weight.

Supratherapeutic efavirenz Cmin (>4 mg/L), observed in 19.6% on versus 18.8% off rifampicin, p=0.76, was not associated with rifampicin either. However, the proportion of black participants with supratherapeutic concentrations on rifampicin was significantly greater than in white participants, 22.9% versus 3.9%, p=0.02.

This finding is likely to be due to genetic differences in metabolism. Data from genetic evaluations of CYP2B6 variants were not presented.

Dr Luetkemeyer concluded that these data do not support weight based increase of efavirenz during rifampicin-based TB treatment.

Efavirenz and rifampicin in pregnancy

In the same session, Kelly Dooley from the TSHEPISO study group described the PK and pharmacodynamics (PD) of efavirenz among pregnant women. [2]

Efavirenz is being used more and more in pregnancy. In Soweto, where the TSHEPISO study is being conducted, about 1 to 2 % of HIV-positive pregnant women have active TB, yet there are few data describing the combined effect of pregnancy and rifampicin on efavirenz levels.

TSHEPISO is an ongoing prospective cohort study of HIV positive pregnant women with (n=250 cases) and without TB (n=500 controls). Women are enrolled at 13 to 34 weeks gestation. Women (n=150) with and without TB, receiving once daily efavirenz-based ART at 600 mg will enrol in an efavirenz PK/PD substudy, with their infants. Dr Dooley showed preliminary results from 76 women and 70 infants evaluated in this substudy to date.

Sampling is performed at 37 weeks gestation or at delivery and then six weeks post-partum. Efavirenz levels are also measured in cord blood at delivery and in infants at 7 days. Plasma concentrations are determined by liquid chromatography-tandem mass spectrometry

Women also have CYP286 genotyping and are categorised as extensive, intermediate, slow or very slow metabolisers. Maternal viral load is measured at delivery and in infants at six weeks of age.

The case (n=33) and control (n=43) study participants were similar at enrollment with median values of approximately: 30 years of age, 30 weeks gestation and 300 cells/mm3 CD4. There were differences between the groups in the proportion with a viral load less than 20 copies/mL: 28% and 58% in the cases and controls respectively. This difference is probably explained by the delay in starting ART among those needing treatment for TB. At delivery the median time on efavirenz was 12 and 21 weeks for the cases and controls respectively, and delivery occurred at approximately 38 to 39 weeks in both groups. Distribution of CYP286 metaboliser status was also similar between the groups.

The median maternal efavirenz Cmin pre/intrapartum (n=59) was 1.4 (IQR 0.99 to 1.89) mg/L, at this time point 25.4% had an efavirenz Cmin of <1 mg/mL. At 6 weeks post partum (n=50), these values were 1.68 (IQR 1.22 to 2.7) mg/L and 20%.

Comparing on (n=30) and off (n=46) rifampicin, efavirenz Cmin were respectively 1.76 (IQR 0.89 to 3.13) and 1.52 (IQR 1.14 to 2.02) mg/L. Proportions of women with an efavirenz Cmin of <1 mg/mL were 29.1% and 17.1%.

By metaboliser status, 56.3% extensive, 5.7% intermediate, 16.7% slow and 0% very slow metabolisers had a Cmin of less than <1mg/L.

Like the study above, this analysis showed no significant differences in efavirenz Cmin on versus off rifampicin across all weight comparisons. The median Cmin of efavirenz was 1.91 in women both above and below 60kg on rifampicin, but a smaller proportion of the women who weighed <60 kg had Cmin <1mg/L, 20% versus 31.6%. Women off rifampicin weighing <60kg had a median efavirenz Cmin of 1.33 (IQR 1.12 to 1.64) mg/L compared to 1.55 (IQR 1.13 to 2.07) mg/L in those >60 kg; 11.1% and 16.7% had a Cmin < 1mg/L, respectively.

Cord blood samples were available for 45 infants and had a median efavirenz concentration of 1.15 (IQR 0.628 to 1.91) mg/L, of these 4 (8.9%) were below the limit of quantification (BLQ). At 7 days samples were available for 57 infants and the median efavirenz concentration was BLQ (IQR BLQ to 0.079) mg/L; 35/57 (61.4%) were BLQ. Quantifiable values were related to larger cord blood concentrations. Cord blood and maternal pre-partum concentrations were highly correlated (r=0.93).

At delivery 70% of cases and 83% of controls had a viral load <20 copies/mL, p=0.24. Of women receiving efavirenz for at least 12 weeks at delivery, 82% of cases and 93% of controls had viral load <20 copies/mL, p=0.26. There were no vertical transmissions among women receiving efavirenz at delivery

Raltegravir as a possible alternative to efavirenz

Raltegravir might offer an alternative to efavirenz for people needing concomitant HIV and TB treatment. This antiretroviral is not metabolised by CYP450, however rifampicin does induce the UGT 1A1 pathway and a previous study in healthy volunteers showed 61% and 40% reductions in raltegavir Cmin and AUC. This was partially compensated by a dose increase of raltegravir from 400 mg to 800 mg twice daily.

The Reflate Study (ANRS 12 180) is investigating the efficacy of these two doses of raltegravir compared to efavirenz in people also receiving rifampicin-based TB treatment in France and Brazil.

Nathalie De Castro from the study group presented 24-week data from Reflate - a multicentre, open-label, randomised, phase 2 trial. [3] Antiretroviral naïve HIV positive adults were randomised to receive raltegravir, at 400 mg or 800 mg twice daily, or efavirenz 600 mg once daily, in regimens with tenofovir and 3TC, having started TB treatment. The primary endpoint was the proportion of participants with viral load <50 copies/mL at week 24 using a modified ITT TLVOR analysis. The trial was 80% powered to show >70% success at this time point.

A total of 179 people were screened and 155 randomised - 52 to raltegravir 800 mg, 51 to raltegravir 400 mg and 52 to efavirenz 600 mg. At baseline the majority (73%) of participants were men, with a mean age of 38 years, a median viral load of approximately 5 log copies/mL and median CD4 count of 140 cells/mm3. The majority (85%) had pulmonary TB and about half were confirmed cases; participants received rifampicin-based TB treatment for a median of 6 weeks before starting ART.

At week 24 78% (95% CI 67 to 90), 76% (95% CI 65 to 88) and 63% (95% CI 49 to 76) participants had viral load <50 copies/mL in the raltegravir 800 mg, 400 mg and efavirenz arms respectively. The majority of treatment failures were virological and this occurred in 4, 12 and 15 participants, in the raltegravir 800 mg, 400 mg and EFV arms respectively. Adverse events leading to treatment discontinuation occurred in 3 participants in the raltegravir 800 mg and 2 in the efavirenz arms; there were 2 deaths in each of these respective arms (4 overall).

There was slightly more raltegravir, 3TC and tenofovir resistance in the 400 mg (4/5) than 800 mg (1/2) arm - but only tiny numbers were analysed. Resistance was present in 4/6 of the participants analysed who received efavirenz. All arms had greater than 150 cells/mm3 CD4 increase in CD4.

The investigators concluded that raltegravir seems to be a suitable alternative to efavirenz for HIV-TB co-infected patients and the optimal dose has yet to be defined based on the PK sub-study and 48 week follow-up data

Bedaquiline and rifapentine not recommended together

Dan Everitt from the TB Alliance presented data from a drug-drug interaction study of bedaquiline (TMC 207) to evaluate the effect of rifapentine on bedaquiline PK. [3]

Bedaquiline) is a diarylquinoline in development to treat drug-sensitive and drug-resistant tuberculosis. The innovator company, Janssen submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) in June 2012, seeking accelerated approval for the use of bedaquiline as an oral treatment, to be used as part of combination therapy for pulmonary, MDR-TB in adults.

It is being studied in novel combinations with the aim to minimise adverse interactions with ART. Drug-drug interaction studies have been conducted with nevirapine - which did not significantly affect bedaquiline exposure - and efavirenz - which decreased its exposure by 18% with 14 days co-administration in healthy volunteers.

A previous evaluation showed exposure of bedaquiline decreased by 52% after 7 days of rifampicin - a potent inducer of CYP3A4. And exposure of M2 decreased by 25%. In vitro and in vivo studies suggested the induction potential of CYP3A4 might be less with rifapentine.

This was a two-period, single-sequence drug interaction study in two groups of healthy subjects. The first period evaluated the PK of bedaquiline and its M2 metabolite after a single 400 mg dose. The second period evaluated the effects of repeated doses of either rifampicin or rifapentine on the PK of bedaquiline and M2. Subjects took 600 mg rifapentine (Group 1) or 600 mg rifampicin (Group 2) once daily for 22 days. A single 400 mg dose of bedaquiline was given on day 10 of the second period followed by 14 day PK sampling.

A total of 32 subjects were enrolled and 29 completed the study. Rifapentine reduced both the AUC and Cmax of bedaquiline giving 62.2% and 42.8% mean ratios respectively. The effects on M2 were similar.

Given this reduction in exposure of over 50%, the TB Alliance and Janssen will not be conducting further studies of bedaquiline with either rifampicin or rifapentine and recommend that they are not given together.

No clinically relevant interactions between delamanid and lopinavir/ritonavir or tenofovir

Delamanid (OPC-67683), a novel nitro-dihydro-imidazooxazole derivative, in phase 3 of development by Otsuka for the treatment of MDR-TB, including in people with HIV receiving ART. Delamanid is metabolised by plasma albumin and to a lesser extent CYP3A4.

Tenofovir is not metabolised by CYP enzymes and does not affect CYP3A4. Lopinavir/ritonavir is generally contraindicated with drugs metabolised by CYP3A because of potent CYP3A inhibition by ritonavir and with potent CYP3A inducers that may reduce lopinavir efficacy. Delamanid and its major metabolites neither inhibit nor induce CYP enzymes.

In a poster authored by Anne Paccaly and colleagues on behalf of the sponsor, findings were shown from a phase 1, open-label randomised, multiple dose parallel group trial investigated the drug-drug interaction potential of delamanid 100 mg twice daily and tenofovir or lopinavir/ritonavir at standard doses. In this trial, healthy volunteers aged 18 to 45 years (similar numbers of men and women) were assigned to treatment groups: delamanid (n=11), tenofovir (n=12), lopinavir/ritonavir (n=11), delaminid and tenofovir (n=13), delaminid and lopinavir/ritonavir (n=12), for 14 days to reach steady-state exposure.

Samples were taken pre-dose, days 12-13 and day 14 (full PK profile). Delamanid and metabolite plasma concentrations were determined by ultraperformance liquid chromatography-tandem mass spectrometry and ARVs by high performance liquid chromatography-tandem mass spectrometry. PK parameters and geometric mean ratios for Cmax and AUCt with 90% CI were determined.

The evaluation found that delamanid did not affect tenofovir, lopinavir or ritonavir drug exposure. Tenofovir had no effect on delamanid exposure, while a slightly higher (20%) delamanid exposure was seen with lopinavir/ritonavir, possibly related to CYP3A inhibition by RTV. Delamanid metabolites were not affected by tenofovir nor markedly affected by lopinavir/ritonavir. No changes in drug exposure occurred were considered to be clinically relevant.

C O M M E N T

The first efavirenz presentation above ended with a welcome discussion on toxicity as Dr Luetkeymeyer was asked whether data was collected on CNS side effects as some people had "astronomically high" efavirenz levels. She explained that the investigators were looking at discontinuations, of which there were 18 in the substudy, and these were expected to be associated with CNS toxicity. Five of the participants who discontinued had efavirenz levels in the toxic range. But she noted that this represented only 5 of 92 patients with toxic levels discontinuing as a result. She explained that: "In many clinical studies, especially in resource limited settings people will do a lot to continue their ART and suffer a lot of side effects. Obviously we don't recommend this but they often feel that it is their only chance to get these meds." Hopefully these remarks will resonate with researchers and implementers, as so often, side effects, particularly those that depend on patient reporting, are under managed or ignored in poor (and rich) settings, despite much evidence to suggest their occurrence. The investigators are looking at patients with toxic levels who did not discontinue efavirenz.

The data on efavirenz-based ART and TB treatment in pregnancy are welcome as this is happening more and more. Women need to initiate ART early enough to have time to achieve a suppressed viral load by delivery and earlier initiation of ART is now recommended in the presence of TB treatment.

Based on the findings of these efavirenz/rifampicin interaction studies, the FDA recommendation should be revisited.

Raltegravir might well be an interesting alternative to efavirenz in the setting of treatment for HIV/TB coinfection, but for most countries with a high burden of TB its exorbitant price and limited availability might make this a merely theoretical option. Raltegravir costs over R800 per month (including VAT) in the South African private sector.

The development of bedaquiline with other TB drugs is ongoing. The NC-003 study - which will combine bedaquiline with combinations of PA-824, clofazinamine and pyrazinamide and compare them to standard of care (isoniazid, rifampacin, pyrazinamide and ethambutol), - starts in September in South Africa. The Janssen phase 3 study will permit HIV positive people on ART to enroll, including people receiving ritonavir boosted PIs and efavirenz who will be closely monitored.

It is important that sponsors developing the new TB drugs continue to look at possible drug-drug interactions with other old and new TB drugs and ART. The data from the drug-drug interaction study with delamanid and efavirenz will be presented at the upcoming ICAAC meeting.

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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 indentify differences in kerantinisation for the inner and outer foreskin or for the Frener 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 uretheral 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-naive 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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http://pag.aids2012.org/Abstracts.aspx?AID=19162
9. Hofmann-Sieber H et al. Towards HIV eradication: eradication of HIV-1 proviral DNA by Tre-recombinase in HIV-positive humanized mice. Oral abstract TUAA0302.
http://pag.aids2012.org/Abstracts.aspx?SID=276&AID=11812
10. Henrich T.J. et al. Long-term reduction in peripheral blood HIV-1 reservoirs following reduced-intensity conditioning allogeneic stem cell transplantation in two HIV-positive individuals. Oral abstract THAA0101.
http://pag.aids2012.org/abstracts.aspx?aid=6016
11. Kitchen S et al. In vivo suppression of HIV antigen specific T cells derived from engineered hematopoietic stem cells. Oral abstract TUAA0303.
http://pag.aids2012.org/Abstracts.aspx?SID=276&AID=19110
12. Trautmann L. Novel approaches: treatment and HIV pathogenesis. Immunopathogenesis and its treatment. Symposia Session. 23 July 2012, 2.30-4.00pm, Washington.
http://pag.aids2012.org/flash.aspx?pid=1677

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 asymtomatic 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), mylagia without weakness 19% vs 3%, p< 0.01 and proximal myopathy 4% vs 0,

p=0.03, all raltgravir 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 ptoential 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 tbule dysfunction (includingurine retinaol 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/1.73^2 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 rountine 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 comorbiditiy (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 comorbididity	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 (r2=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 suppresion 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 Yukl from UCSF presented new data on the case of Timothy Brown, the "Berlin Patient."

Yukl 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 publically, in the interest of transparency.

The press release included results from the SINGLE study, specifically that a dolutegravir-basred 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 dolutegrvir 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/oia/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 Rafif, 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 Rafif 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.aidspan.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.msfaccess.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)

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EPIDEMIOLOGY

New studies show the complexity and importance of HIV epidemiological modelling

Nathan Geffen, CSSR

In Isaac Asimov's Foundation science fiction series, which is set far in the future, mathematical modelling of human society has reached such a sophisticated level that the protagonists can predict the fall and rise of their civilization thousands of years into the future. The series' main mathematician is even able to determine a set of interventions that will shorten the period of barbarism between the collapse of his society and the rise of the next one.

Alas, in 2012, we are barely able to predict the future trajectory of a single disease in one country a few years into the future.

It might seem unlikely that mathematical models can generate controversy that ultimately even involves the president of a country. Yet when the Actuarial Society of South Africa (ASSA) published their AIDS models in the early 2000s, public debate followed because contrary to the AIDS denialist views of then President Mbeki, the ASSA models showed that millions of people in South Africa had HIV, that hundreds of thousands of people were dying annually of AIDS, life-expectancy had plummeted and that, in the absence of antiretroviral treatment (ART), the worst was yet to come.

Mathematical models of epidemics estimate important information such as the prevalence, incidence and effect on life-expectancy of an epidemic disease at time-points for which there have been no direct measurements. They usually tell us about the state of an epidemic now and in the future under different scenarios.

Model myths

It is seldom that people outside the field have a good understanding of the details of mathematical models. Models often seem mystical. Perhaps this is why there is a myth that epidemiological models are just mathematics and not based on real-world measurements.

But this is not true. Good models have a large number of parameters that have to be set using the best available peer-reviewed data, for example the risk of a sexual act resulting in HIV transmission, or the effect of ART on a person's infectiousness. Once all the parameters are set models must be calibrated against reliable epidemiological data, so that their outputs match what is known about the epidemic. This is analogous –albeit much more complex-- to calibrating a scale before you stand on it. You make sure that the scale points to zero, so that when you stand on it, it will not understate or exaggerate your weight. Likewise, a good mathematical modeller will make sure that if the countrywide HIV epidemic was measured in a reliable survey to be, say 9%, in 2001, that when the model is run, it calculates close to 9% prevalence for 2001. If it does not, then the modeller has to revisit the model's parameters and calculations. It is hard work and good modelling is a highly skilled undertaking.

There is also a belief that models are entirely dependent on the assumptions and biases of the people who develop them, which is partially true, and therefore have no value, which is not true. A household budget is a mathematical model, and most readers of this article have no doubt done one. If done carefully, they are based on real-world measurements and they predict future expenditure quite well most of the time. Most of us find them very valuable. At the risk of hyperbole, the difference between a household budget and the most sophisticated mathematical models of the HIV epidemic is merely complexity.

A comparison of models

Today there are new controversies in HIV demographic modelling, albeit much more interesting and rational than the AIDS denialist response to the models of the early 2000s. In 2009 Reuben Granich and his colleagues published the results of their model in the Lancet. They predicted the HIV epidemic in South Africa could be eradicated by 2050 if universal voluntary testing and immediate treatment for all people with HIV were introduced. [1] But using different treatment-uptake assumptions, Wagner and Blower used the same model and reached different conclusions. They published the results of their model in a paper titled, "Voluntary universal testing and treatment is unlikely to lead to HIV elimination". [2]

PLoS Medicine has published a set of articles that look at the cost and effectiveness of using antiretroviral treatment to reduce HIV incidence. These papers debate the assumptions, methodologies and conclusions of mathematical models and consequently the affordability and benefits of treatment as prevention.

One of these papers was co-written by the developers of 12 different epidemiological models, including the Granich one. Jeffrey Eaton, Timothy Hallett and colleagues explain, "Each of these models has predicted dramatic epidemiologic benefits of expanding access to ART, but models appear to diverge in their estimates of the possibility of eventually eliminating HIV using ART, the cost-effectiveness of increasing the CD4 threshold, for treatment eligibility, and the benefits of immediate treatment compared to treatment based on the current World Health Organization eligibility guidelines. Directly comparing the models' predictions is challenging because each model has been applied to a slightly different setting, has used different assumptions regarding other interventions, has been used to answer different questions, and has reported different outcome metrics." [6]

The aim of the research described in the paper was to systematically compare the 12 models by standardizing a set of antiretroviral treatment scenarios and reporting a common set of outputs. The intervention scenarios were consistently implemented across the different models with the purpose of controlling "several aspects of the treatment programme and isolat[ing] the effects of model structure, parameters, and assumptions …"

Three variables were controlled across the models and systematically varied: CD4 threshold for starting treatment, proportion of people eligible who access treatment and retention of people on treatment.

PLoS Medicine's editor explained the methodology, "To exclude variation resulting from different model assumptions about the past and current ART program, it was assumed that ART is introduced into the population in the year 2012, with no treatment provision prior to this, and interventions were evaluated in comparison to an artificial counterfactual scenario in which no treatment is provided. A standard scenario based on the World Health Organization's recommended threshold for initiation of ART, although unrepresentative of current provision in South Africa, was used to compare the models."

The methodology of the twelve models varied greatly. For example:

- They used two different modelling methods. Four used microsimulation. In these models, each individual in a population is simulated. Random events that affect their risk of HIV infection are applied to them. This is the most computationally intensive of the modelling methods. Microsimulations can take hours or even days to produce results. The remaining eight models, "stratify the population into groups according to each individual's characteristics and HIV infection status and use differential or difference equations to track the rate of movement of individuals between these groups."
- Ten of the models explicitly provide for both sexes and heterosexual HIV transmission.
- Six of the models include age, but the extent "to which age affects the natural history of HIV, the risk of HIV acquisition, and the risk of HIV transmission varies amongst these."
- One model simulates the HIV epidemic in Hlabisa, KwaZulu-Natal, while the remaining models deal with the national South African epidemic.

The models were compared under three different CD4 cell count thresholds: CD4 count ≤ 200 cells/mm3, ≤350 cells/mm3 and treatment for all irrespective of CD4 count. The proportion of eligible individuals who eventually initiated treatment was also varied as follows: 50%, 60%, 70%, 80%, 90%, 95%, and 100%. So was the percentage of people retained on treatment after three years, excluding those who died, as follows: 75%, 85%, 95%, and 100%.

Outcomes of the different models

The estimates of adult male HIV prevalence in South Africa in 2012, if there was no ART, ranged from 10% to 16% across the models. Female prevalence ranged from 17% to 23%. Male incidence ranged from 1.1 to 2.0 per 100 person-years and female incidence ranged from 1.7 to 2.6.

Under the scenario where no treatment is provided, the models varied in their predictions about the future trajectory of the epidemic, ranging from almost no change in HIV incidence to a 45% reduction in incidence over the next 40 years. All the models predicted that treatment would reduce incidence by a large percentage over the no treatment scenario. Their estimates varied, but by a narrow range. For example, if 80% of HIV-positive individuals started treatment a year after their CD4 count drops below 350 cells/mm3 and 85% remain on treatment after three years, the models' estimates of the drop in incidence ranged from 35% to 54% lower eight years after the introduction of ART compared to not providing ART at all. The number of person-years of ART per infection averted over eight years ranged between 5.8 and 18.7. As expected, the further into the future the models went the more they diverged. This scenario, incidentally, reflects current WHO treatment guidelines coupled with the UNAIDS definition of universal access.

Effect of ART on incidence in South Africa

The authors then did a separate analysis using seven of the models to determine the effect of the actual ART rollout in South Africa on incidence by comparing it with a no-treatment scenario. Models either used their own existing calibrations of the number of people on ART in South Africa or were calibrated using estimates of the number of adults starting and on ART in each year from 2001 to 2011.

All of the models predicted that ART has reduced incidence. The estimates ranged from 17% to 32% lower in 2011 than in the absence of ART. Interestingly, the models give widely different estimates of the effect of ART on prevalence. For example a model by Jeff Eaton and colleagues, as well as Leigh Johnson's STI-HIV model, estimate that prevalence is 8% higher than it would have been without treatment, while the Granich model and another by Christophe Fraser and colleagues calculates that massively reduced incidence results in no net change in prevalence at the current point in time. It is worth recalling that an increase in prevalence does not mean a failed response to the HIV epidemic. On the contrary, the only way prevalence can decrease is if more people die than are infected. Since ART keeps people alive, it is unsurprising that several models predict an increase in prevalence. Incidence, not prevalence, is the measure of the success of prevention efforts.

Test and treat

The impact on incidence of a CD4 threshold of 200 cells/mm3 versus 350 cells/mm3 versus treatment with very high rates of HIV screening and removal of CD4 eligibility–the latter known as the test and treat approach–were also compared across the 12 models, but there were not consistent results here. Some models showed that that moving from 200 to 350 would not make a substantial difference, but that moving from 350 to treating everyone did, while others found that moving from 350 to treating everyone made little difference.

In an intervention treating all HIV-positive adults with 95% access and 95% retention, only three of nine models predicted that HIV incidence would fall below 0.1% per year by 2050, the virtual elimination threshold proposed by Granich and colleagues.

Explaining the differences between models

The authors put forward three hypotheses to try and explain the differences between their models. These were (1) differences in the fraction of transmission that occurs after people become eligible for ART in the no-treatment scenario, (2) differences in how effective ART is at reducing transmission and (3) different assumptions about what happens to patients who drop out of care. These hypotheses were tested and only accounted for some of the differences in model outcomes.

Although the models estimates diverge, collectively they help policy makers and provide tentative estimates of how successful antiretroviral treatment will be at reducing incidence. Also, they were not all designed to answer the identical questions.

The effectiveness of treatment as prevention is a question that will have to be answered more definitively with clinical trials as well as observational studies of actual practice. Over the next few years, cluster controlled trials in South Africa, Zambia, Tanzania and Botswana will hopefully provide these answers.

In the same PLoS Medicine collection, there is an interesting debate between Kimberly Powers, William Miller, and Myron Cohen on the one hand, and Brian Williams and Christopher Dye on the other, followed by a commentary by Christophe Fraser. One side argues that widespread treatment will have a massive effect on HIV incidence, while the other argues that it will be compromised by the high transmission rate during primary infection. Interestingly, Myron Cohen who was the lead investigator on HPTN 052, the trial that showed a 96% reduction in HIV incidence amongst sero-discordant couples if the HIV-positive partner was put onto early treatment, takes

the view that high levels of transmission during early infection will "compromise the effectiveness of HIV treatment as prevention." [4]

The future of mathematical modelling

It is important to realize that disease modelling at the level of sophistication seen in these models is a relatively new field, made possible by the tremendous increase in computer power over the last few decades. Microsimulations in particular stretch the capabilities of even today's computers and computer programmers. The widely different methodologies and assumptions used should be seen as the pioneering efforts in a new science. Hopefully over time, and as the predictions of models are compared to what actually happens, modellers will be able to identify techniques that are robust and standardize the science. Just as the 95% confidence interval and the correspondence of a p-value less than 0.05 with significance are part of a standard part of medical statistics today, similar standard concepts might emerge in the modelling field. And just as R and STATA are standard software tools used by the vast majority of medical statisticians, so there will hopefully one day be standard tools for both deterministic and microsimulation mathematical models.

An effort to standardise modelling is already underway. Wim Delva and colleagues have published an article in the same PLoS Medicine collection which summarises extensive discussions between mathematical modellers. They describe nine principles for mathematical modellers and those who depend on HIV models to make policy decisions. [5] The (edited) principles are:

1. The model must have a clear rationale, scope and objectives.
2. The model structure and its key features must be explicitly described.
3. The model parameters must be well-defined and justified.
4. The way the model has been calibrated must be explained and justified.
5. The model's results must be clearly presented including uncertainties.
6. The model's limitations must be described.
7. The model must be contextualised. In other words previous studies must be referenced and the similarities and differences must be explained. Differences in the results of the model and previous models must be described.
8. The model must provide epidemiological impacts that can be used for health economic studies.
9. Models must be described in clear language.

These principles surely apply to all disease modelling, not just HIV.

Disease modeling is important. Models help us understand the relative contribution of different factors to the present state of the epidemic and they give us some understanding of what will happen in the future under different interventions. They are valuable for making policies with short and medium-term impacts. Longer-term projections, such as to the year 2050, are less useful given that so many unpredictable technological and demographic changes are likely to occur over such a long time. Besides their practical value, disease modelling is a fascinating theoretical field with some elegant mathematics and computer algorithms.

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Thanks to Leigh Johnson, Jeffrey Eaton and Timothy Hallett for their advice.

TUBERCULOSIS

Important advances in TB drug development

Nathan Geffen, CSSR

Three recent studies have significantly advanced TB drug development.

Delamanid for MDR TB

Delamanid (formerly known as OPC-67683) is a nitroimidazole and is one of two new drugs in this class used to treat TB. It inhibits the synthesis of mycolic acid, a component of the TB bacterium cell wall. It is being developed by the Japanese pharmaceutical company, Otsuka.

In June the company published the results of a large Phase II trial in the New England Journal of Medicine. The trial took place in Philippines, Peru, Latvia, Estonia, China, Japan, Korea, Egypt, and the United States. Patients were randomly assigned to receive a standard background MDR TB drug regimen plus either delamanid 100mg twice daily (n=161), delamanid 200 mg twice daily (n=160) or placebo twice daily (n=160) for eight weeks in hospital. Delamanid is taken with food.

All participants had been diagnosed with multi-drug resistant TB. Nearly all were HIV-negative. The median age was 35. Baseline BMI was 19.6. Nearly 70% of participants had lung cavities. All patients had been previously treated for TB. Of the 481 patients, 402 were sputum-positive using MGIT.

One patient died of TB. Eighteen, 14 and 15 people withdrew from the delamanid 100mg, delamanid 200mg and control arms respectively. Fourteen patients, evenly distributed across the arms, discontinued the study drug because of adverse events.

Except for QT interval, there were no significant differences in adverse events between the arms. QT interval was higher in the 200mg group (13.1%) than in the 100mg group (9.9%), which was higher than the placebo group (3.8%). There were no clinical events associated with QT interval.

Delamanid exposure increased less than proportionally with the dose. The half-life plasma concentration of delamanid was 38 hours after patients stopped taking the drug.

The main finding of the study was that patients who received delaminid 100mg and 200mg had a 45.4% and 41.9% sputum conversion rate (using MGIT) respectively after two months compared to 29.6% in the placebo arm (p=0.008 for the 100mg and p=0.04 for the 200mg comparisons).

The authors explain that a second large, randomised, controlled trial of six months of treatment with delamanid as part of a full background drug regimen and including patients with HIV on ART has started. It is designed to provide data on 30 months of follow-up of patients.

Possible shorter TB regimen using PA-824

One of the aims of the TB Alliance is to develop shorter, more effective and safer TB treatment regimens. But there are many possible drug regimens, especially with several new agents in the pipeline, and each can take years to test. Iteratively adding single agents to the standard regimen and testing these in clinical trials would be an extremely costly and time-consuming way to identify an optimal new regimen. The question then is how to identify the most promising regimens for large, long, expensive trials.

Andreas Diacon of Stellenbosch University and a team from several research institutions published an article in the Lancet describing a phase 2a trial. This has received wide publicity because it has provided a clever way forward for identifying new TB regimens to take into large trials. [2]

TB patients at hospitals in Cape Town were randomised to several regimens. The effect of the regimens was measured using 14-day early bactericidal activity (EBA). This was done to identify the most promising regimen (or regimens) to test further. EBA was measured using MGIT from sputum samples collected daily from patients.

To be included patients had to be 18 to 65 years old. They had to weigh 40 to 90kg, be smear-positive, have a chest radiograph consistent with TB and be able to produce sputum.

The following regimens were tested:

1. Bedaquiline 700mg on day 1, 500mg on day 2 and 400mg daily thereafter.
2. The same as above plus PA-824 200mg daily.
3. The same as the bedaquiline alone regimen plus pyrazinamide 25mg/kg daily.
4. PA-824 200mg daily plus pyrazinamide 25 mg/kg daily.
5. PA-824 200mg daily, pyrazinamide 25 mg/kg daily and moxifloxacin 400mg daily.
6. Standard isoniazid, rifampicin, pyrazinamide, ethambutol regimen dosed according to body weight.

PA-824 is a new TB drug being developed by the TB Alliance. Like delanamid, it is a nitroimidazole.

Of the 173 patients screened, 85 were included in the trial. Of these 15 were randomly allocated to each arm, except for the standard regimen, to which 10 were allocated.

Half the patients reported adverse events, though most were mild and not drug-related. Fourteen patients completed their regimens in arms 1 to 4, 12 completed regimen 5 and all 10 completed the standard regimen. Five of the seven withdrawals were due to elevated ALT. One PA-824-moxifloxacin-pyrazinamide patient had a QT interval that met withdrawal criteria. One had an altered consciousness experience due to newly diagnosed neurocysticercosis. All of these (except the patient with neurocysticercosis) withdrawals were asymptomatic.

All patients had TB that was susceptible to the treatment regimens they were on.

The key finding of the trial was that the mean 14-day EBA of the PA-824-moxifloxacin-pyrazinamide regimen (0.233, standard deviation 0.128) was significantly higher than the bedaquiline regimens (bedaquiline 0.061 [SD: 0.068], bedaquiline-pyrazinamide 0.131 [SD: 0.102], bedaquiline-PA-824 0.114 [SD: 0.050]).

The PA-824-moxifloxacin-pyrazinamide EBA was not significantly different from the PA-824-pyrazinamide (0.154 [SD: 0.040]) and standard regimen (0.14 [SD: 0.094]).

The authors conclude that the PA-824-moxifloxacin-pyrazinamide regimen is potentially suitable for treating drug-sensitive and MDR TB. They propose further clinical trials for this regimen. But they also state that the bedaquiline-PA-824 and PA-824-pyrazinamide had comparable EBAs with the standard regimen and therefore "could become important building blocks of future regimens". They make the important point that, a "regimen not containing isoniazid and rifampicin would represent a substantial step towards a new regimen with low interaction potential suitable for both fully drug-susceptible and MDR tuberculosis. With this study the path to the construction of new regimens becomes clearer."

PNU-100480

Sutezolid (PNU-100840) is a new oxazolidinone. This is the same class of drug as linezolid. These drugs prevent bacterial proteins from being made by interfering with an enzyme that binds with bacterial ribosomes. [3]

The 2012 i-Base/TAG Pipeline Report explains that sutezolid appears to be more potent against TB than linezolid in vitro, in ex vivo whole blood cultures, and in mice. The report also explains that a whole-blood study predicted that sutezolid, SQ109 and bedaquiline, would be additive and should be tested as part of a novel regimen. [4]

The results of a phase 2 study conducted in South Africa were described in an oral abstract by Robert Wallis of Pfizer and colleagues at the IAS 2012 conference. Sputum positive patients were randomly assigned to, either sutezolid 600mg twice daily (n=25), 1200 mg once daily (n=25), or the standard South African first-line regimen (isoniazid, rifampicin, ethambutol and pyrazinamide, n=9) for the first 14 days of treatment. Only 7% of the patients were HIV-positive (not yet on ART) and 20% were women. [5]

All volunteers completed the trial. There were no treatment-related serious adverse events. There was also no effect on the QT interval. Seven patients on the sutezolid arms had transient asymptomatic ALT elevations.

At baseline, the mean log colony forming units per millilitre (CFU/ml) was 6.95. The mean time to detection using MGIT was 116 hrs. Using 90% confidence intervals, all three treatment arms reduced colony forming units and increased time to MGIT detection significantly, but the standard regimen improvements were significantly greater. The actual reductions are depicted graphically in the abstract and so the exact values are not given. These appear to be approximately as follows:

- Time to MGIT detection: approximately 75 hours longer for the sutezolid regimens versus 160 hours for the standard regimen.
- CFU/ml reduction: approximately 1.2 log for sutezolid versus 2.8 log for standard.

The authors concluded that further studies of the drug are warranted.

C O M M E N T

This is one of the most exciting and fast-moving periods in TB drug development since the 1960s. Delamanid has arguably leapfrogged bedaquiline to the front of the new drug pipeline. But both are important. Both drugs must be put swiftly through the remaining studies needed for regulatory approval, which includes providing plans for paediatric development, and both drugs must be made available for pre-approval access to patients with drug-resistant TB who are being treated at well-run TB facilities. They also need to be tested together. The Global TB Community Advisory Board has written to Otsuka raising these issues and Otsuka has replied. This correspondence can be downloaded from the TB Online website (see refs). [6-7]

Except for delamanid, the regimens and drugs discussed here are several years away from coming to market. The pace from drug discovery to market for new TB drugs is far too slow. Bedaquiline has been in development since at least 2004 and is still not approved anywhere. According to the Working Group on New TB Drugs the current annual budget for sutezolid is tiny, $250,000 to $1,000,000. The annual budget for PA-824 is significant, $10 million, but nothing close to what would be spent on a blockbuster drug.

Although the TB drug development pipeline has improved, the difference in pharmaceutical expenditure on this disease versus more profitable ones highlights the neglected disease problem, which is that pharmaceutical companies and research institutions fail to develop sufficient drugs for diseases that almost exclusively affect poor people.

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SIDE EFFECTS

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 indentified in this predominently 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 weigh, 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 contradictive, 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 pubished 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]

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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 subrogate 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.01044-12.abstract

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, Altanta, all to be confirmed.

http://retroconference.org

19th Annual (BHIVA) 2013

16th - 19th April 2013, Manchester

http://www.bhiva.org

HIV i-BASE

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

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

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

All i-Base publications are available online.

http://www.i-base.info

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

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

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

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

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

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

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

HIV i-Base

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

However, any donation that your organisation can make towards our costs is greatly appreciated.

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

REFUNDS FROM THE TAX MAN

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

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