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EDITORIAL

Welcome to the March/April edition of HIV Treatment Bulletin.

This issue largely features our first coverage from the annual Conference of Retroviruses and Opportunistic Infections, which this year attracted over 4000 delegates to Seattle.

Much of the conference is available as web casts and references in HTB also link to the study abstracts.

Further coverage will continue in the next issue, with pre-press articles available online.

HTB SUPPLEMENT

A new edition of the i-Base Introduction to Combination Therapy is included as a supplement to this issue of HTB.

Revised annually, this free guide is an introduction to treatment for people who are newly diagnosed, thinking of starting treatment or already on treatment. This non-technical resource is based on national and international treatment guidelines and is written in every day language.

The guide includes information on how treatment works, when to start, treatment choice, adherence, resistance, avoiding side effects and includes a full colour pill chart.

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

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

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

<http://www.surveymonkey.com/s/978R8F9>

CONFERENCE REPORTS

19th Conference on Retroviruses and Opportunistic Infections (CROI)

5–8 March 2012, Seattle

Introduction

The Conference on Retroviruses and Opportunistic Infections (CROI) conference is probably the most important annual scientific HIV meeting and it is also one of the most accessible for people who are unable to attend the meeting.

Most of the presentations are available to watch free online without registration. This includes web casts of the opening lectures, oral presentations and poster discussions.

Abstracts and PDF files for many of the full posters are also online.

<http://retroconference.org>

With over 1100 studies presented, we will split coverage over two issues of HTB. This issue includes reports on cure research, antiretrovirals, paediatrics, prevention studies and some hepatitis coinfection. The next issue will include PMTCT, women's health, treatment access, TB, opportunistic infections, side effects and other complications. Some of these early reports will be posted online prior to the print edition.

This issue includes:

- Cure research takes centre stage: proof of concept for activating the latent reservoir
- Quad fixed-dose integrase combination: phase 3 studies at week 48
- Dolutegravir studies continue to show promise
- Tenofovir prodrug: 10 day monotherapy study sets dose at 25 mg for easier coformulation
- Paediatric formulations of ARVs: including an exciting new class
- Lower malaria risk in children receiving lopinavir/ritonavir-based compared to NNRTI-based ART
- High prevalence of d4T-associated lipodystrophy including lipoatrophy in children
- Lopinavir/ritonavir monotherapy in children
- Stopping treatment after early ART in infants
- Treatment interruptions in children PrEP: PK modeling of daily TDF/FTC (Truvada) provides close to 100% protection against HIV infection
- Risk of HIV reinfection may be similar to risk of initial HIV infection

- Case report: homozygous CCR5 delta-32 protection overcome by infection with X4 virus
- No association between atazanavir and MI or stroke in D:A:D
- Hepatitis C: telaprevir and boceprevir in coinfection
- Herpes Zoster vaccine safe and effective in HIV positive people
- High dose flu vaccine improves antibody responses in HIV positive people

CROI 2012: CURE RESEARCH

Cure research takes centre stage: proof of concept for activating the latent reservoir

Simon Collins, HIV i-Base

For the last two years the major HIV conferences, including CROI and the International AIDS Society (IAS) have included cure research prominently in the main programme. This is new and significant.

At CROI in 2010, Anthony Fauci, head of the US National Institute of Allergy and Infectious Diseases (NIAID) announced that the US government would be launching new funding for cure research. [1]

Many of the researchers in this field have been working on a cure years, some for decades. But the new drive for this research to receive better funding is clearly an important factor in how quickly future progress will be made.

The new funding may, in part at least, have also been driven by the responsibility that America has assumed as the largest donor for global HIV treatment programmes. Over the last ten years, ARV access in low and middle-income countries has increased from less than 0.5 million people in 2002 to over 6.5 million people in 2012. A long-term alternative to lifelong treatment is therefore likely to be an economic as well as a medical necessity. While current cure research uses specialised and expensive procedures, as with all new developments, including ARVs, high initial costs would hopefully be driven down to become more widely affordable.

The IAS has also been developing a leadership role to coordinate global funding for cure studies and to hopefully focus on a research map that will minimise duplication. [2] The IAS organised workshops prior to each of its last two conferences and another is planned prior to the Washington meeting in July 2012. [3] Several community workshops, including one before CROI this year have also contributed to broadening awareness of the potential for a cure. [4, 5]

In addition to an oral abstract session this year, CROI included several helpful presentations of the current research in the preconference workshops for young investigators, particularly the overview by John Mellors and the talk on animal models for latency by Vincente Planelles. [6, 7]

The Berlin cure

Whether through mediated immunity (referred to as a functional cure) or eradication (a sterilising cure), the ability to overcome lifelong treatment has always been an ultimate goal, even while the focus for recent years shifted to achieving more effective, tolerable and durable treatments.

The first report of a cure following stem cell transplantation from a donor who was naturally resistant to HIV infection (he was homozygous for the delta-32 deletion in CCR5) was at CROI in 2008 [8] and increasing press coverage since had made this a highly publicised case, and brought optimism to cure research.

The mechanism responsible for curing Timothy Brown (a.k.a. the Berlin Patient) who has been off treatment now with no evidence of HIV for over four years has not been isolated to a single component from a complex and risky set of procedures.

In addition to myeloablative chemotherapy and total body irradiation to kill both HIV infected and uninfected immune cells, he received antithymocyte globulins, cyclosporin, mycophenolate acid (MMF) and gemtuzumab (anti-CD33) that would also have killed HIV-infected and uninfected cells, followed by allogeneic stem cell transplants from a donor homozygous for delta-32 mutation, which should have reseeded an immune system resistant to CCR5 HIV infection, he developed graft vs host disease (GVHD) indicating he had accepted the donor immune system. These procedures have a 25% mortality risk and he underwent each procedure twice as the course was repeated.

An oral presentation at CROI reported on ten patients on suppressed ART who underwent autologous (self-donated) hematopoietic stem cell transplantation for AIDS related lymphoma, which is a less risky procedure than that used by Tim Brown. Unfortunately, persistent HIV viraemia was still detected in 9 of 10 patients post-transplant, with a median viral load of 1.5 copies/mL (range: <0.2 to 26) and median total HIV-1 DNA of 554 copies/million PBMCs (range: <0.4 to 2179). 2-LTR circles were detectable post-transplant in only 2 of 10 patients (range: 1 to 7 copies/million PBMC). The only patient with undetectable plasma viral load had the highest levels of HIV-1 DNA and 2-LTR circles. Additionally, plasma viraemia persisted in a patient with undetectable HIV-1 DNA in PBMC. Although the authors concluded that this showed that the CCR5 delta-32 donor was essential in the Berlin case, patients in their study also did not have total body irradiation, graft vs. host disease, and were reinfused with their own stem cells, which could have included HIV-infected T-cells. [9]

A further US study is about to open of allogeneic stem cell transplant in HIV positive people with bone marrow failure with the hope that 1 or 2 of the 15 patients may also be able to be matched to a delta-32 donor to see if the Berlin case can be repeated. [10]

This will involve overcoming the difficulty of finding and matching a delta-32 donor who is also compatible on 8 HLA types. At the community cure meeting prior to CROI, John Zaia from the City of Hope Cancer Centre near Los Angeles described an initiative to develop an inventory

of cord blood stem cell donors as an international resource, and to date, out of 13,000 donors tested, 90 have been identified as being homozygous for the CCR5 delta-32 deletion. [5]

First activation of latently infected resting T-cell reservoir in vivo

While many aspects of this research are controversial, there is broad consensus on the need for a strategy to overcome the reservoir of long-lived, latently infected, resting CD4 cells that harbour integrated HIV and that are not reached by current ART.

Most notably, an oral presentation at CROI included results from a proof of concept study that viral latency might be overcome. David Margolis from the University of North Carolina presented results in an oral late breaker presentation that the use of a single dose of the histone deacetylase (HDAC) inhibitor vorinostat (suberoylanilide hydroxamic acid, SAHA) is able to activate latently infected resting CD4 cells. [11] In 2005, Margolis presented results from using another HDAC inhibitor, valproic acid, to stimulate the latent reservoir.

Of the 11 human histone deacetylase, HDACs 1, 2, and 3 are the primary enzymes that limit activation of HIV integrated into cells by producing a barrier that maintains latency. Vorinostat is a selective inhibitor of HDAC 1, 2, and 3 that has been shown to induce HIV expression from latently infected resting cells *ex vivo*. However, vorinostat, although approved as a cancer treatment also has mutagenic properties.

In this proof of concept study, the change in the latent reservoir was determined by measuring cell associated HIV RNA specifically in the resting cell population. This involves harvesting approximately four billion lymphocytes from each aviraemic patient by leukopheresis that are treated with magnetic antibody beads to leave 200-1000 resting CD4 cells that can be tested by RNA PCR.

Six study participants had baseline measures of activation, that were tested *ex vivo* after exposure to vorinostat and that demonstrated that a change was measurable in all patients. Each patient also undertook a single 200 mg safety dose and a separate single 400 mg dose of vorinostat for a PK study to decide the timing for the second leukopheresis used to determine efficacy.

Following a second, therapeutic 400 mg dose, all six patients responded with a highly significant mean 4.8 fold increase (range 1.5-10-fold) of RNA expression in resting CD4 cells ($p < 0.01$). The treatment was well tolerated with no reported side effects associated with vorinostat and none greater than grade 1. Of note, and perhaps surprisingly, no increases in HIV plasma RNA were detected using a single copy/mL test.

The study concluded that is the first demonstration of activation of latent resting HIV-infected CD4 cells *in vivo*. However, these results are still preliminary. While the proof-of-concept is exciting, Margolis suggested that this might be seen as the equivalent of a "ddC moment in relation to HAART".

Additionally, other molecules may be more effective compounds to activate latency and *in vitro* data suggesting panobinostat as more active than vorinostat were presented in a poster. [12]

Earlier in the same conference session Liang Shan reported that latently infected resting CD4 cells treated with vorinostat survived despite viral cytopathic effects, even in the presence of autologous CD8 cells from most patients on ART concluding "that stimulating HIV-1-specific CTL responses prior to reactivating latent HIV-1 may be essential for successful eradication efforts and should be considered in future clinical trials". [13]

Treatment during early infection

Theoretically, the easiest targets for cure research might be those patients diagnosed earliest in their infection, who promptly start treatment and who maintain suppressed viraemia for many years.

Although the latent cell reservoir is established within weeks of infection and is likely to be slowly reduced after years on effective ART, in nearly all patients, viraemia rapidly returns within weeks if treatment is interrupted. Even when HIV is reduced to being present in less than 1 in 1.7 billion cells, this is sufficient for systemic infection to quickly be reestablished (within two months) if treatment is stopped. [14]

While levels this low might question the importance of a treatment to target the viral reservoir, they can so far only be achieved with very early treatment and/or many years of viral suppression. The need to reduce the viral reservoir more quickly will be a concern for everyone else who started ART during chronic infection.

Rapid viral rebound without treatment has been widely reported in numerous treatment interruption studies. However, several small cohorts have also reported viral control in a minority of patients, usually in those who initiated treatment in acute infection and maintained undetectable viral load for several years.

Last year at CROI, the ANRS Visconti study reported small numbers of patients who started treatment in early infection (after seroconversion, median viral load >100,000 copies/mL), maintained viral suppression for >3 years on treatment and who have subsequently controlled viraemia off treatment for >6 years. [15] This year at CROI similar cases were reported in posters by two other groups.

Maria Salgado and colleagues reported a single case of a patient who initiated treatment during seroconversion (viral load >750,000 c/mL, western blot indeterminate) for three years and after stopping ART has since maintained viral load suppressed to <50 copies/mL off-treatment for more than nine years. Initial and current viral isolates are dual CCR5/CXCR4 tropic and fully replication-competent *in vitro*. Minimal viral evolution has been detected over the 11 years.

He is reported to currently have low titers of neutralising antibodies to heterologous and autologous HIV-1 isolates, and his CD8+ T cells do not have potent HIV suppressive activity suggesting a mechanism other than CTL-mediated suppression reported in elite controllers. [16]

Alain Lefeuvre from General Hospital, Toulon (who is also one of the key organisers of the International HIV Persistence Workshop that has been meeting every two years since 2003) reported that 17% (8/45) of a cohort of patients treated at seroconversion for a median of 2.2 years (range 1.8 to 4.0) have remained off treatment for more than 10 years, two of whom remain suppressed to <20 copies/mL (median 2,500 copies/mL for the other six). The 37 people who restarted treatment (due to confirmed CD4 decline to <350 cells/mm³) did this after a

median of 5.0 years (range 3.0-8.0) off-treatment. The study suggested the protective mechanism could be related to early ART reducing the HIV reservoir but also emphasised that such responses seem to be rare. [17]

A poster from Joseph Margolick and colleagues reported small differences in viraemia between people diagnosed in early infection (within a year of infection) and randomised to immediate treatment (n=57) year and those who did not start early treatment (n=24). However, study numbers were very low at the evaluation point (24 months after stopping treatment of 24 months after diagnosis) due to ~20% loss to follow-up and exclusion of people who restarted treatment for other reasons. [18]

Generally small differences were also reported from early treatment in the larger SPARTAC study that randomised almost 400 people (diagnosed within 6 months of infection) to deferred ART or immediate treatment for either 3 months or 12 months, and who then stopped treatment. [19]

However, in the context of eradication research, two oral presentations suggested that early treatment, while too late to prevent the establishment of the viral reservoir, might reduce the pool of latently infected cells.

Maria Buzon and colleagues estimated the size of the viral reservoir in patients treated for more than ten years who initiated ART within 3 months of infection (n=9) and compared levels integrated and total HIV DNA levels to people who started treatment during chronic infection (n=26) and to elite controllers (n=37). [20]

Integrated and total DNA levels were significantly lower in both primary treated (p=0.06 and p=0.001, respectively) and elite controllers (p=0.003 and p<0.0001, respectively) compared to those treated in chronic infection. In addition, the ratio between total and integrated HIV-DNA was significantly lower in early treated and elite controllers (both p=0.04 vs chronic) with no differences between acute and EC groups.

Although patient numbers were small, differences were also reported when comparing how soon treatment had been started with patients treated during Fiebig stage III or IV vs stage V having significantly lower levels of both total and integrated HIV DNA after two years.

An oral presentation by Alan Perelson from the Los Alamos National Laboratory used mathematical modelling to look at the impact of early treatment of 27 people treated during acute infection on the size of the latent reservoir, and the relationship of both to initial viral load and target cell ability. [21]

This study also reported that earlier ART, including earlier during primary infection, had a measurable impact related to the initial size of the reservoir, with patients who already started with very low levels of resting cell infection (who also had low levels of peak viral load) experiencing less change in the reduction of resting cell decay. The model also suggested that CD4 T cell increases in response to successful ART was not increasing the viral reservoir.

Research into a functional cure

Other groups are focusing on immunological interventions that would support a functional rather than eradicating cure.

Pablo Tebas from the University of Pennsylvania, presented additional safety and efficacy results from the use of zinc finger nuclease (ZFN) modification of CD4 cells (using SB-738) to a CCR5-deleted phenotype (in development by Sangamo BioSciences). [22]

This process involves harvesting cells by apheresis, treating them with SB-738 to produce 13-35% of cells with CCR5-deletions *in vitro*. The cells are then expanded, cryopreserved and 5-30 billion cells are reinfused into the donor patient.

Results were combined from three studies: one in ART responders (baseline CD4 >450 cells/mm³) who subsequently interrupted treatment (group 1, n=6) and two in immune non-responders (baseline CD4 <500 cells/mm³) who have not interrupted treatment (group 2, combined n=15). Initial results from these studies were presented at CROI and ICAAC conferences last year.

Most patients were male, white, mean age 48, with a long history of HIV infection (median 12 and 18 years in group 1 and 2 respectively). Mean CD4 count and CD4:CD8 ratio were 921 (±222) cells/mm³ and 1.4 (±0.6) in group 1 and 335 (±89) cells/mm³ and 0.7 (±0.3) in group 2.

Duration of follow-up is now a mean 325 days (range 90 – 738 days).

After infusion, CD4 cells increased by about 1500 cells/mm³ in group 1 (n=6), these then decreased during the treatment interruption but which remained significantly above baseline during follow-up. CD4 responses in group 2 involved an increase of about 500 cells/mm³ which then dropped by about 200-300 which then remained stable out to over a year in the patients who did not interrupt treatment. The expansion of CD4 cells was associated with increases in IL-2, IL-7 and IL-15.

The CD4:CD8 ratio increased significantly in both groups, normalising and remaining at approximately 1.0 throughout follow-up in the group 1 and increasing to approximately 2.5 for the six patients in group 2 decreasing during the treatment interruptions but then remaining stable.

The modified cells continued to be detected through follow-up at 2% of circulating CD4 cells at 48 weeks for most patients. Levels were higher during the treatment interruption for group 2 and then dropping to 2%. Circulation of cells to other tissue sites was confirmed by multiple rectal biopsies where levels of the CCR5-modified cells were comparable to those in blood or higher throughout follow-up.

During the treatment interruption viral load rebounded over the first 8 weeks to around 100,000 copies/mL in a similar way to other interruption studies dropping by one log during the last 4 weeks off-treatment to levels that were generally higher than pre-ART. After three months, when treatment was restarted, viral load became undetectable again in all six patients. One person, later found to be heterozygous for the delta-32 mutation, had a lower rebound (to 10,000 c/mL) and then resuppressed viral load to undetectable by week 8 and remained undetectable off treatment until restarting as per protocol at week 12.

This group used a new method to measure changes in the viral reservoir based on levels of HIV DNA sensitive to low copy numbers (although unable to distinguish between integrated DNA and 2-LTR circles). They reported no detectable change in 4/6 patients with one person having a transient 4-fold increase at week 12 and 20 during the interruption but returning to baseline levels and one person experiencing a 9-fold increase that returned to baseline 16 weeks after restarting treatment.

Side effects were mild and transient, mainly within 24 hours of the infusion (mild chills, fever, headache, fatigue) but included one report of arthritis lasting a few days and abnormal garlic-like body odour.

Next steps include using immunomodulatory drugs such as cyclophosphamide to promote engraftment and increase the percentage of modified cells and studying other patients who are heterozygous for the delta-32 deletion.

Several studies presented studies where pegylated interferon (peg-IFN) was added to ART prior to stopping HIV treatment and continuing peg-IFN. The results suggested that viral rebound was delayed by the peg-IFN via an immune-mediated rather than antiviral mechanism, but these were small studies with short-term follow up (12 and 24 weeks). [23, 24, 25]

C O M M E N T

The timeline for a cure at this meeting was optimistically referred to as being at least ten years. HIV is a tricky puzzle: the virus is resilient and the range of immune responses is complex. Nevertheless, these advancements in several key and linked areas are crucial advances.

Several networks are encouraging collaborative research in order to be able to compare and evaluate different approaches. [26, 27]

Numerous compounds that are already licensed are already being looked at for their potential to overcome latency. These include prostratin, lonomycin, thapsigargin (a calcium pump inhibitor), PMA, typhostin-A (a non-selective typhosin phosphate inhibitor), CD3/CD8 antibodies for TCR signaling, PLA, toll like receptor 7 (TLR7 including GS-9620) and protein kinase-C (PKC) agonists. Several companies including Gilead and Merck are already screening for and have identified other potential HDAC inhibitors.

The important of informed community participation in partners in this research is particularly important given the ethical considerations for study volunteers. If a mechanism is discovered to cure HIV more widely, it may still only work in some patients.

With current treatment able to nearly normalise life expectancy, a cure has a high bar to overcome. Some of this research will involve asking people on stable treatment to interrupt therapy and some of the interventions will have potentially greater toxicity than their current ART. At least for the foreseeable future, the potential risks in these initial studies are likely to outweigh any personal benefits.

Treatment during primary infection early treatment may put someone at a preferential state to respond to parts of a strategy to cure HIV, and some people diagnosed this early may want to take this decision. Because the latent pool is smaller in such patients, those initiating ART during acute HIV may be the best candidates for pilot studies attempting HIV eradication.

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CROI 2012: ANTIRETROVIRALS

Quad fixed-dose integrase combination: phase 3 studies at week 48

Simon Collins, HIV i-Base

The fixed dose, single-pill, four-drug formulation of elvitegravir/cobicistat/tenofovir/FTC, developed under the name Quad, is likely to be closest to regulatory approval (and has an FDA hearing in May).

At CROI, results were presented from two randomised, double blind, placebo controlled Phase 3 studies. One study comparing Quad to efavirenz/tenofovir/FTC (Atripla) was an oral session and another comparing Quad to atazanavir/ritonavir plus tenofovir/FTC was a poster. [1, 2]

The primary endpoints in both studies were the proportion of patients with undetectable viral load (< 50 copies/mL) at week 48 by intention-to-treat analysis, with non-inferiority defined by a lower margin of -12% and that included patient stratification by baseline viral load above and below 100,000 copies/mL. Virological efficacy was around 90%, tolerability was good and discontinuations were notably low in all arms and Quad was found to be non-inferior compared to the comparator combinations in both studies.

Study 236-0102 compared Quad to Atripla enrolled 700 treatment-naïve patients in the US and Puerto Rico and Paul Sax from Brigham and Women's Hospital, Boston, presented the results. [1]

Baseline characteristics included: mean age 38 years and low median viral load (31,000 copies/mL) although one third of participants started at >100,000 c/mL. Mean CD4 count was just under 400 cells/mm³ with 12% of participants starting below 200, 32% starting at both 200 to 350 and 350-500 and 23% starting at >500 (percentages for Quad arm but similar to Atripla). The study was largely male (88%) with ethnicity 61% white, 31% African Americans and 8% other. Less than 5% of participants in each arm had either HBV or HCV coinfection.

Discontinuations before week 48 were similar in 11% vs 13% in the Quad vs Atripla arms for broadly similar reasons.

Viral load was suppressed to undetectable in 88% vs 84% patients (difference +3.6%, 95%CI -1.6 to +8.8) meeting criteria for non-inferiority, with 7% of patients in each arm having virological failure and 5% vs 9% having missing data (all Quad vs Atripla, respectively). Responses by subgroup (viral load, CD4, race, sex, age and adherence level) were not significantly different but trended to favour Quad. CD4 increases favoured the Quad arm with +239 vs +206 cells/mm³ respectively (p=0.009).

Approximately half of the patients in each arm failed with mutations associated with resistance to either integrase inhibitors (mainly E92Q) or NNRTIs (mainly K103N) in 8/14 vs 8/17 respectively.

Most side effects were reported as mild (grade 1) with statistically significant differences including more nausea in the Quad arm (21% vs 14%) and more abnormal dreams (15% vs 27%), insomnia (9% vs 14%), dizziness (7 vs 14%) and rash (6% vs 12%) in the Atripla arm.

Discontinuations related to side effects occurred due to rash (0 vs 1.4%), renal abnormalities (1.4% vs 0), depression (0.3% vs 0.9%), abnormal dream (0 vs 0.6%) in the Quad vs Atripla arms respectively with 3% in each arm stopping due to both fatigue and paranoia.

The most frequent grade 3 or 4 laboratory abnormalities occurring in greater than five patients in each arm were broadly similar and generally low including creatinine kinase (5% vs 11%), AST (2% vs 3%), ALT (1% vs 3%), GGT (2% vs 5%), neutrophils (2% vs 3%), amylase (2% each arm) and haematuria (2% vs 1%), all in Quad vs Atripla respectively.

Serum creatinine increased by approximately 0.1-0.2 mg/dL by week 2 in the Quad arm which was maintained through to week 48 compared to no change with Atripla ($p < 0.001$).

Increases in fasting total cholesterol, LDL and HDL cholesterol were significantly greater in the Atripla compared to the Quad arms but there was no difference between groups in the more clinically significant TC:HDL ratio or in triglycerides (+ 7 mg/dL in each arm).

The second Quad study, called 236-0103, compared Quad to atazanavir/ritonavir plus tenofovir/FTC (Truvada). It enrolled 708 treatment-naïve patients and results were presented by Edwin DeJesus in a poster. [2] Baseline characteristics were broadly similar to the 236-0102 study: mean age 38 years, 90% male, and 74% white. CD4, viral load and hepatitis coinfection were also similar, with 40% of participants having viral load $\geq 100,000$ copies/mL. Exclusion criteria for this study included eGFR < 70 mL/min.

Virological efficacy (< 50 copies/mL) at week 48 was 92% vs 88% (difference +3.5%, 95%CI -1.0% to +8.0%) in favour of Quad, which met criteria for non-inferiority. In patients with baseline viral load $\geq 100,000$ copies/mL, response rates were 85% vs 82% (NS). Virologic failure (FDA snapshot algorithm) was 5%, in both arms. Median CD4 increases were similar at + 207 vs 211 cells/mm³ and discontinuation rates for side effects were 4% vs 5% (both in Quad vs atazanavir/r arms, respectively).

Side effects occurring in $\geq 5\%$ of patients, were similar in each arm, apart from elevated bilirubin levels which were significantly higher in the atazanavir/ritonavir arm. Discontinuations occurred due to diarrhoea (4% vs 5%), pyrexia (1% vs $< 1\%$), nausea (1% vs 0), nausea, vomiting and fatigue (each $< 1\%$ vs 1%) and jaundice, dizziness, ocular icterus and drug eruption (each 0 vs $< 1\%$). The most frequent grade 3 or 4 laboratory abnormalities occurring in at least 2% in either arm were broadly similar including creatinine kinase (6% vs 7%), haematuria (4% vs 2%), AST (2% vs 3%), ALT (2% vs 2%), amylase (2% each arm) and increased bilirubin (1% vs 58%), all in Quad vs atazanavir/ritonavir arms respectively. Serum creatinine increased by approximately 0.08 mg/dL by week 2 in the Quad arm which was 0.12 mg/dL at week 48 compared to 0.05 with atazanavir/ritonavir ($p < 0.001$). Median change in CLCr from baseline was -12.7 mL/min in Quad and -9.5 mL/min ($p < 0.001$). Lipid increases were similar for TC, LDL and HDL cholesterol (all $p = NS$) but triglycerides increased by less in the Quad arm (+5 vs +23 mg/dL, $p = 0.006$).

Median changes in bone mineral density were similar in each group. Spine changes reduced by about 3% at week 24 and remained stable, with reductions at week 48 of -2.45% vs -3.48% ($p = 0.25$ for between arm comparison). Reductions at the hip were continuous slopes for both combinations of about -1.5 vs -2.0% at week 24 and -2.87 vs 3.59% at week 48 ($p = 0.12$).

In an answer to a question about clinical management of increases in serum creatine, in reference to increases seen in both Quad studies, Paul Sax stated that a statistical analysis of the data suggested that an increase of 0.4 mg/dL or greater was a cut-off for concerns about potential tenofovir renal tubular toxicity.

When asked whether paired cystatin C in serum would distinguish between tenofovir and cobicistat associated changes Sax said that this was a possibility, but that it might be affected by other HIV-related factors. The question of cost was also raised in the context of results that had not demonstrated superiority, perhaps related to study size.

C O M M E N T

Quad has already been submitted for regulatory approval to Western regulatory agencies with an FDA decision expected by August 2012.

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Dolutegravir studies continue to show promise

Simon Collins, HIV i-Base

Results from the SPRING-1 dose-finding study of dolutegravir/abacavir/3TC compared to efavirenz/tenofovir/FTC (Atripla) were presented in a late-breaker oral session and were broadly similar at 96 weeks to 48 week results for the 50 mg arm. [1]

Two hundred and five subjects were randomised to receive dolutegravir at 10 mg, 25 mg or 50 mg once daily compared to efavirenz. Participants were 86% male, 80% white, 26% $> 100,000$ copies/mL viral load, and 67% used tenofovir/FTC as the nucleoside backbone.

At week 96 the proportion of subjects with viral load < 50 copies/mL (TLOVR) was 79%, 78% and 88% in the 10 mg, 25 mg and 50 mg arms respectively vs 72% in the efavirenz arm. Virological failure occurred more frequently in the lower dose arms: in 13% ($n = 7$), 8% ($n = 4$), 4% ($n = 2$)

and 8% (n=4) of the 10 mg, 25 mg, 50 mg and efavirenz arms respectively but these were low study numbers and half these patients who counted as failure by TLOVR analysis resuppressed to below 50 copies/mL by week 96. No mutations associated with resistance to integrase inhibitors or NNRTIs were seen in these patients.

CD4 increases were not statistically different at week 96: +338 cells/mm³ for the combined dolutegravir arms vs +301 cells/mm³ for efavirenz ($p = 0.155$).

Only two people discontinued dolutegravir due to side effects (one in each of the 25 mg and 50 mg arms) compared to five in the efavirenz group. Side effects were lower in the dolutegravir arms although serious side effects were similar. The only grade 3/4 lab abnormalities were single cases of ALT elevation associated with acute hepatitis C. No differences in renal markers were observed between the two groups.

A second oral presentation reported from a phase 1 pharmacokinetic study in HIV negative people that an increased dolutegravir dose (50 mg twice-daily) overcomes an interaction with rifampin. [2]

Five other posters expanded the profile of this important new integrase inhibitor.

These included:

- Exciting results on a paediatric granule formulation that produced higher levels compared to the oral tablet in HIV negative volunteers used oral or dissolved irrespective of liquid. [3]
- Results from a single dose pharmacokinetic study in HIV positive adults with mild-moderate liver impairment suggested that dolutegravir could be used without dose modification in these patients. [4]
- Reporting a higher genetic barrier to resistance *in vitro* that may differ by HIV subtype and identification of mutations R236K and H51Y in subtype B. [5]
- Similar potency against raltegravir-associated mutations in HIV-2 as HIV-1 [6]

C O M M E N T

The oral presentation of the SPRING-1 study was uncharacteristically understated: “dolutegravir has some attributes that might make it interesting for use in combination therapy” before listing once-daily dosing, no boosting, low PK variability, few expected drug interactions, potentially distinct resistance profile to raltegravir and high potency at a low milligram dose.

Further studies with this compound will be followed closely together with the back-up GSK-1265744 compound that may be used at even lower milligram doses (5-10 mg). Low milligram compounds have the potential as less expensive options to PI-based combinations in low-income countries, if patent issues are overcome.

Currently, a fixed dose formulation of dolutegravir with abacavir and 3TC has completed initial PK studies.

On 2 April, as this issue of HTB went to press, top-line results were released from the SPRING-2 phase 3 study in treatment-naive adults reporting dolutegravir to be non-inferior to raltegravir. [7]

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Tenofovir prodrug: 10 day monotherapy study sets dose at 25 mg for easier coformulation

Simon Collins, HIV i-Base

Further data on the development of a tenofovir prodrug from Gilead (compound name GS-7340) were presented by Peter Ruane MD from Los Angeles. [1]

This compound is expected to have higher potency at much lower concentrations in all cell types with EC50s compared to the current formulation of tenofovir disoproxil fumarate (TDF) of 0.003 vs 0.015 uM in PBMCs and 0.014 vs 0.06 uM in macrophages. Last year at CROI a similar dose finding 10-day monotherapy study reported viral load reductions of about -1.0 log at 50 mg and 150 mg doses, compared to 0.5 log with TDF, with plasma concentrations of GS-7340 that were 88% lower and intracellular concentrations 4-fold higher compared to TDF.

This current study randomised 38 treatment-naïve or experienced (but tenofovir sensitive) patients to 10 days GS-7340 monotherapy using 8 mg, 25 mg and 40 mg with placebo and TDF arms as controls. The primary endpoint was the time-weighted average change in viral load (DAVG) at day 11.

Baseline characteristics included: age 38 years, 97% male and 50% white/38% African American. The mean viral load and CD4 counts were 31,000 copies/mL and 478 cells/mm³ respectively.

DAVG results were -0.76, -0.94, -1.13, -0.48 and -0.01 log copies/mL in the 8 mg, 25 mg, 40 mg, TDF and placebo arms respectively with median viral load reductions -1.08 (8 mg); -1.46 (25 mg); -1.73 (40 mg), -0.97 (TDF) and -0.07 (placebo). There were significant differences between both the 25 mg and 40 mg arms when compared to TDF, but not for the 8 mg dose.

Plasma tenofovir exposures across the GS-7340 groups were approximately 80 to 97% lower compared to TDF with intracellular concentrations in PBMCs 7-fold higher in the 25 mg dose and 20 fold higher with the 40 mg dose.

There were no clinically significant laboratory abnormalities or drug-related serious adverse events, no discontinuations and no evidence of resistance over the 10 days.

Phase 2 studies that are already ongoing or soon to enroll are using the 25 mg dose for development in two fixed dose formulations. One substitutes GS-7340 for TDF in Quad with elvitegravir, cobicistat and FTC (in study 292-0102) and a second in coformulation with darunavir, cobicistat and FTC to be the first once-daily single-pill PI combination (in study 299-0102).

C O M M E N T

The discussion after this presentation included surprise that the dose selected for development was to be based on such a small short study and that the greater virological efficacy in the 40 mg group was not going to be explored further. Also that this decision was largely driven by the ease of coformulation with the lower milligram dose.

Another question was whether increased intracellular concentrations of GS-7340 accumulated in renal tubule cells. Although no renal concerns were seen after 10 day exposure this will be an important aspect of further studies. *In vitro* data in MT-2 cells, PBMCs and macrophages did not find concerns from increased levels of intracellular diphosphates. CNS penetration of GS-7340 is expected to be similar to tenofovir DF and it may also have activity against HBV.

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CROI 2012: PAEDIATRICS

Paediatric formulations of ARVs: including an exciting new class

Polly Clayden, HIV i-Base

International guidelines recommend universal and immediate treatment of HIV-infected neonates, which poses a significant challenge given the lack of suitable formulations in this age group.

Three posters at CROI showed novel “sprinkle” formulations of two integrase inhibitors and a protease inhibitor.

Dolutegravir

Dolutegravir (DTG) is a promising integrase inhibitor currently in phase 3 of development. The compound is interesting for several reasons: once daily dosing for treatment naïve patients, low milligram dose (50 mg, so potential for co-formulation and low cost), adequate plasma exposure without boosting, few expected drug interactions, an expected different resistance profile to raltegravir and a very comprehensive development plan. 96-week phase 3 data was also presented at CROI 2012 (see above).

The developers - a partnership between Shionogi & Co and ViiV Healthcare - plan to study the compound in all paediatric age groups down to young infants, a population woefully short of appropriate antiretroviral formulations. DTG is currently being studied in children 6 – 18 years in IMPAACT P1093.

Parul Patel and colleagues presented findings from an evaluation of the single dose pharmacokinetics (PK) in healthy adults of a new oral granule formulation of DTG, in development for infants and young children. [1] The granules were given with and without 30 mL of various liquids and compared to the current tablet formulation given with 240 mL of tap water.

This was a single-centre, randomised, open-label, 5-way crossover study in 20 healthy adult subjects. Subjects received a single dose of DTG 50 mg as the phase 3 tablet and in 10 g of granule given: direct to mouth with no liquid; with purified water; with mineral water containing high calcium concentrations (Contrex); or with infant formula milk. All formulations were administered in fasting state.

The study treatments were separated by seven days. Safety evaluations and serial PK samples were collected over 48 hours in each dosing period. The PK parameters of DTG were estimated using noncompartmental methods; geometric least squares (GLS) mean ratios and 90% CI were generated to compare treatments. Taste was assessed using a questionnaire that examined bitterness, sweetness and colour.

The investigators reported DTG exposures of the granule formulation were all moderately higher than the tablet formulation with or without liquids (55% - 83% and 62% - 102% for AUC 0-INF and C_{max} respectively, see table 1). Exposure was highest when the granule formulation was given with formula milk.

Inter-subject variability from the granule formulation was modest with a coefficient variation for AUC of 31-43%. DTG was well tolerated and there were no withdrawals due to AEs. The subjects rated the taste as acceptable for all treatments.

Table 1: Comparison of PK parameters of dolutegravir

Granule comparison to tablet	GLS mean ratio (90% CI)	
	AUC 0-INF	C _{max}
Direct to mouth	1.58 (1.46 - 1.71)	1.62 (1.49 - 1.77)
With purified water	1.57 (1.45 - 1.69)	1.66 (1.52 - 1.81)
With mineral water	1.55 (1.43 - 1.67)	1.65 (1.51 - 1.79)
With formula milk	1.83 (1.69 - 1.98)	2.02 (1.86 - 2.20)

These data indicate that the DTG granule formulation can be given without restriction on the type of liquid or can be given alone. The taste was not considered to be a barrier to further development although the investigators noted that children's preference could be different to that of adults. The granule formulation is being studied further in children in IMPAACT P1093.

Raltegravir

The integrase inhibitor raltegravir (RAL) is approved as a 400 mg film-coated tablet for use in adults and for children aged 6 to 18 weighing > 10 kg, and 100 mg and 25 mg chewable tablets are approved for children > 2 to <12 years old at a maximum dose of 300 mg. [2]

The paediatric programme is ongoing in IMPAACT P1066 and an oral granule formulation is being studied in the youngest children and babies. Stephen Spector and colleagues from the study team presented intensive PK, and preliminary 24 weeks safety and efficacy data from cohort IV - 6-month- to <2-year-olds - receiving the RAL oral granule formulation. [3]

Nine HIV-infected children were enrolled in a dose-finding study. Entry criteria included HIV RNA >1000 copies/mL and either prior ART experience PMTCT failure. The children received weight-based RAL oral granule suspension at ~6 mg/kg, every 12 hours.

Intensive PK was performed between day 5 and 12 after which the site investigators optimised the children's background regimen. A dose was selected for continued study using an AUC_{12 hr} targeted design (geometric mean [GM] target range of 14 to 25 µM*h) with C_{12h} target to exceed the RAL IC₉₅ (31 nM). Virologic suppression was defined as HIV RNA <400 copies/mL or ≥1 log drop from baseline at 24 weeks.

One child's PK data were excluded due to absorption issues. Of the remaining 8 children: 67% were male; 78% black; mean (SD) age, 13 months

(6.3); log₁₀ RNA, 5.68 copies/mL (0.95); CD4 percent, 21% (9%); CD4 count, 1338 cells (822); weight, 8.3 kg (2.6), dose, 5.94 mg/kg (0.42).

The investigators reported geometric mean values of: AUC_{12hr}, 20 uM*h; C_{max}, 10.7 uM; and C_{12h}, 115 nM. These PK values are achieved study targets and are similar to those observed in 2 to < 12 year old children receiving chewable tablets. Of the 9 children enrolled, 3 had 16 grade ≥3 adverse events of which 2 were considered related to RAL.

- Patient 1: 3 low ANC and 7 reports of elevated lipase with concurrent acute Epstein-Barr virus (EBV) infection.
- Patient 2: dyspnea non drug-related; concurrent drug related elevated bilirubin and hypoglycaemia.
- Patient 3: low ANC, non drug-related.

One child had grade 1 spitting up after taking the study drug.

At week 12, 78% (95% CI 40 to 97%) of the 9 children achieved virologic suppression. The children had a median gain in CD4 percent of 5% (95% CI -3 to 7%) and CD4 cells of 687 (95% CI -297 to 1237) cells/mm³ at week 12. By 24 weeks (n=7), 85% achieved virologic suppression and CD4 gain (n=8) was 5.3% (95% CI -4.0 to 18.8%) and 446 (95% CI 13 to 696) cells/mm³.

The 6 mg/kg every 12 hours dose was chosen for continued study in this age group.

Lopinavir/ritonavir

A sprinkle formulation of lopinavir/r (LPV/r) – Lopimune - has been in development by the generic manufacturer Cipla for some time. The sprinkle formulation (40/10 mg LPV/r) consists of a finite number of mini tablets in a capsule, which is opened and sprinkled on soft food.

Jaideep A Gogtay and colleagues showed results from a randomised crossover PK study in healthy adults comparing a single dose of sprinkles from 10 capsules of LPV/r and a single dose of 5 mL Kaletra oral solution (each mL containing 80 mg lopinavir and 20 mg ritonavir).

Both formulations were administered with about 150 g porridge and 240 mL water. Blood samples were taken pre-dose and serially up to 36 hours and were analysed using a validated LCMS/MS method. PK parameters were calculated using a non-compartmental method using drug concentrations versus time profile.

Twelve subjects completed the study (ie the minimum sample size acceptable to regulatory authorities). Their PK parameters are shown in table 2.

For LPV the Ln-transformed 90% confidence interval of the least square mean of the LPV/r sprinkles and solution for the PK parameters AUC_{0-t} and AUC_{0-IFN} fall within the conventional bioequivalence range of 80 -125% while for C_{max} it falls just outside. For RTV AUC_{0-t} and C_{max} fall just outside the range but AUC_{0-∞} falls within it. However, the investigators noted that the differences were not large. Based on this pilot PK study, the sprinkle formulation is now being studied in HIV-infected children.

Table 2. PK parameters of lopinavir/ritonavir administered as sprinkles and oral solution

Drug	Formulation	AUC _{0-t} (hr.ug/mL)	AUC _{0-IFN} (hr.ug/mL)	C _{max} (ug/mL)
Lopinavir	Sprinkles	86.98	92.99	6.82
	Solution	84.57	89.26	6.28
	Ln-transformed 90% CI (T/R)	87.19 – 120.52	87.76 -122.54	91.31 – 131.02
Ratio of least square mean T/R	Ln-transformed	102.51	103.71	109.38
Ritonavir	Sprinkles	6.69	6.86	0.79
	Solution	6.23	6.38	0.77
	Ln-transformed 90% CI (T/R)	88.23 – 125.15	88.63 -124.6	80.4 – 135.96
Ratio of least square mean T/R	Ln-transformed	105.08	105.09	104.55

C O M M E N T S

These data represent great strides in paediatric drug development and, if approved, these formulations will offer important treatment options for the youngest age group. Integrase inhibitors would mean a new therapeutic class for young children that might overcome some of the shortcomings of the currently available drugs. The sprinkle formulation of LPV/r, is now being studied in CHAPAS 2 and also as part of a programme by Drugs for Neglected Diseases initiative (DNDi) to come up with an affordable regimen appropriate for children under two.

Data to guide the dosing of children less 3 years for efavirenz (EFV), the preferred first line anchor drug for older children and adults, remains elusive. A poster at this meeting showed that CYP2B6 genotype strongly influences EFV PK and safety in this age group. [5] Aggressive dosing (~40 mg/kg) produced therapeutic EFV concentrations in most (68%) children less than 3 years with GG/GT genotype, however, this leads to excessive exposure in those with TT genotype. These data suggest that optimal use of EFV in children less than 3 years requires pretreatment genotyping, and the study protocol has been amended to include this at screening. A related poster showed data from model predicting the PK of EFV in children with different CYP2B6 genotypes, with simulations that indicate that genotype-guided dose optimisation could be used in paediatric patients. [6] Although EFV could be important for use in HIV/TB coinfecting infants, complex genotype screening, the risk of resistance from NNRTI exposure in PMTCT and the probability that boosted PIs will be universally recommended in RLS make it an unlikely option in this age group.

For older children, Abbott has developed a low dose tablet of LPV/r (100/25 mg). Another paediatric PK poster showed data from a small study of 8 children aged 4.5 to 9 years designed to evaluate the comparability, efficacy, and tolerability in stable patients switching to this tablet from the oral solution. [7] PK analysis showed mean LPV AUC and C_{max} ratios between liquid and tablet formulations to be 1.01 and 1.02, indicating that overall, the concentrations achieved with the different formulations were essentially the same.

And recently there have been some important FDA approvals including tenofovir and raltegravir for children two years of age and above and darunavir for those three years and above, which we reported in the February edition of HTB. [8, 2, 9] Also for etravirine for children of six and above, including a new scored 25 mg tablet for paediatric use (see later in this HTB). Paediatric approval from the EMA is awaited for these drugs and unlike the US tenofovir is not approved for the 12 to 18 years age group. For details see Table 3.

For RLS it is hoped that first line treatment for children above three can be aligned with adults and dosed according to weight bands with tenofovir/3TC/EFV using suitable FDCs. A further children's PK poster showed that tenofovir given in combination with 3TC/EFV achieved comparable plasma exposure to that achieved in adults. [10] The investigators also noted that concerns remain about bone and renal toxicities with this drug.

A final poster on paediatric PK reported from a study revealing lower than expected darunavir and etravirine concentrations when the two were given together to older children and adolescents 11 years of age and above. [11] The study highlights both the importance of studying drugs in combination - to determine the contribution of drug-drug interactions - and in different populations, in this case to determine whether the results are age-related. Whether these findings will affect clinical response requires further study.

Overall the data presented at CROI (and recent FDA approvals) shows promise for paediatric HIV treatment in the near future.

Table 3: Paediatric antiretroviral pipeline

Compound	Company	Class	Formulation and dose	Status and comments
Atazanavir (ATV)	Bristol-Myers Squibb	PI	Oral powder 50mg sachet Capsule 100, 150, 200, 300mg	Ongoing phase 2 in naïve and experienced children with or without RTV from 3 months to 6 years of age.
Darunavir (DRV)	Janssen	PI	Oral suspension 100 mg/mL 75 and 150 mg tablets.	FDA approved > 3 years of age (waiver for children < 3). Dosage of DRV and RTV is based on body weight and should not exceed the treatment experienced adult doses. DRV/RTV ratios vary according to weight and treatment experience.
Dolutegravir (DTG)	Shionogi / ViiV	INI	Older children tablets 10, 25, 50mg. Granule formulation being evaluated.	Phase 1&2 from 6 weeks to 18 years of age. Ph 1 PK completed. Exposure of granules with different liquids exceeded that of tablets in healthy adults so can be given without liquid restriction or directly to mouth.
Elvitegravir/cobicistat (EVG/COB) Quad (EVG/COB/TDF/FTC)	Gilead	INI / booster / FDC	To be decided. Solid and liquid forms in development, separately and co-formulated as Quad (solid tablet only).	EVG treatment experienced 12 to 18 years of age. Integrated plans for paediatric studies under discussion.
Etravirine (ETR)	Janssen	NNRTI	Dispersible tablets. 25 mg (scored), 100mg.	FDA approved for experienced children >6 years weighing >16 kg. Phase 1&2 naïve /experienced 2 months to 6 years of age planned.
Lopinavir/ritonavir (LPV/r)	Cipla	PI	Sprinkles. 40/10 mg (equivalent to 0.5 mL liquid).	Similar PK to liquid in healthy adults. PK in children being evaluated. Sprinkle regimen for use in infants <2 years in RLS in development.
Maraviroc (MVC)	Pfizer / ViiV	CCR5 inhibitor	Oral suspension 20 mg/mL	Phase 4. Experienced CCR5 tropic 2 to 12 years.
Raltegravir (RAL)	Merck	INI	Oral granules for suspension 6mg/kg (100 mg sachet) 100 mg and 25 mg chewable tablets	FDA approved 400 mg tablet for children aged 6 to 18 weighing > 10 kg, and chewable tablets for aged > 2 to <12 at a maximum dose of 300 mg. Awaiting EMA approval Granules Phase 2, 2 weeks to 2 years of age. Achieved good target exposure in 6 months to <2 years of age, similar to that with older children. Neonate passive PK study.
Rilpivirine (RIL)	Tibotec / Janssen	NNRTI	Oral granules 2.5mg base/g	Phase 2 planned in children 0-12 children years of age.
Tenofovir (TDF)	Gilead	N(t)RTI	Oral powder 40 mg /1 g 150 mg, 200 mg and 250 mg tab	Recently FDA approved for 2 to <12 years of age. Awaiting EMA approval for 2 to 18 years of age.

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Lower malaria risk in children receiving lopinavir/ritonavir-based compared to NNRTI-based ART

Polly Clayden, HIV i-Base

Children with HIV in sub-Saharan Africa have significant morbidity and mortality risk from malaria. Interventions including bed nets and cotrimoxazole are not sufficient to decrease the risk in this population.

HIV and malaria parasites both encode aspartic class proteases, offering the possibility that HIV protease inhibitors (PIs) might have antimalarial properties. Furthermore, *in vitro* studies have demonstrated some activity against *Plasmodium falciparum* with PIs.

In an oral presentation, Jane Achan from Uganda presented findings from a study conducted by investigators from Makerere University College of Health Sciences and Infectious Diseases Research Collaborations in Kampala and the University of California, San Francisco, to compare the efficacy of lopinavir/ritonavir (LPV/r)-based and NNRTI-based ART regimens on malaria risk reduction in HIV positive children.

The study was a randomised open label trial of 170 children with a median age of 3 years of age (range 2 months to 6 years) conducted in Tororo, Uganda between September 2009 and July 2011. The children were either, ART-naïve (approximately 70%) and eligible for treatment, or receiving NNRTI-based ART and virologically suppressed (<400 copies/mL). They were randomised to receive either NNRTI- or LPV/r-based ART and followed for 2 years. All children received bed nets and cotrimoxazole and treatment for uncomplicated malaria with artemether-lumefantrine, the standard of care in Uganda and many African countries.

Following malaria diagnosis, the children attended the clinic on days 1, 2, 3, 7, 14, 21 and 28. Lumefantrine levels were measured on day 7 as this has been shown to be an independent predictor of malaria.

The analysis was ITT and the investigators compared the incidence of malaria between the study arms using Poisson regression.

Dr Achan reported a 41% reduction in malaria associated with LPV/r-based ART, see Table 1.

Table 1: Comparison of malaria risk NNRTI vs LPV/r

Malaria	NNRTI			LPV/r			IRR (95% CI)	p-value
	Events	PYAR	Incidence	Events	PYAR	Incidence		
All	176	78.2	2.25	109	82.3	1.32	0.59 (0.36-0.97)	0.04
Complicated episodes	2	78.2	0.026	2	82.3	0.024	0.80 (0.06-11.16)	0.87

PYAR= person years at risk

When the investigators looked at possible explanations for this reduction, they found a 29% non-significant direct effect of LPV/r on the children's first episode of malaria HR 0.71 (95% CI 0.45-1.12), p=0.14. An evaluation of the risk of recurrent malaria following treatment with artemether-lumefantrine, however, found LPV/r associated with a 54% reduction in risk HR 0.4 (95% CI 0.22 -0.76), p=0.004.

Median lumafantane levels on day 7 were 926 (IQR 473 – 1910) ng/mL vs 200 (IQR 108 – 510) ng/mL in the LPV/r vs NNRTI arms respectively, $p < 0.001$, which Dr Achan explained might be associated with the boosting effect of ritonavir.

Dr Achan summarised the possible reasons for the lower risk observed in the LPV/r arm as follows:

- PK effect of LPV/r on lumefantrine leading to a prolonged post treatment prophylaxis effect following treatment with artemether-lumefantrine.
- Direct antimalarial effect of LPV/r.
- Antiparasitic synergy between LPV/r and lumefantrine.

She concluded: "This study highlights the possibility of pharmacoenhancement as a tool for reducing the burden of malaria in highly endemic settings."

C O M M E N T

These data are interesting. Conversations after the session suggested that this study adds to the argument for recommending LPV/r-based ART for all infants and young children, but the issue of resistance was also raised with one drug in a combination having a prolonged half-life.

Ref: Achan J et al. Significant reduction in risk of malaria among HIV+ children receiving lopinavir/ritonavir-based ART compared to NNRTI-based ART, a randomised open-label trial. 19th CROI, 5–8 March 2012, Seattle. Oral Abstract 26.

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High prevalence of d4T-associated lipodystrophy including lipoatrophy in children

Polly Clayden, HIV i-Base

Data describing lipodystrophy in children from sub-Saharan Africa are extremely limited. However use of d4T is widespread among children receiving ART in the region: in 2008 to 2009 approximately 90% of children on ART were taking d4T.

Two posters at CROI 2012 described substantial rates of lipodystrophy in South African children aged 3-12 and less than 2 years respectively.

Steve Innes and colleagues from the Children's Infectious Diseases Clinical Research Unit (KID-CRU), Tygerberg Children's Hospital and Stellenbosch University Cape Town performed a cross sectional study of 100 of 300 children on ART at the Tygerberg Family HIV Clinic and 34 HIV-negative controls. [1]

In this study, two clinicians graded fat changes visually using a standardised scale and a dietician took anthropometric measurements of trunk and limb fat. DXA was performed in a sub study of 42 patients and 34 controls. The duration of ART use was recorded.

Using linear regression models the investigators compared fat distribution captured by DXA and anthropometrics among children who were HIV negative, HIV positive with lipoatrophy and HIV positive without lipoatrophy, adjusted for age and sex. The risk factors for clinical lipoatrophy were evaluated by logistic regression.

This reported prevalence of lipoatrophy was 36% (95% CI 26 - 45%). DXA and anthropometrics confirmed significant, substantial extremity fat loss in children with clinical lipoatrophy.

Mean adjusted DXA total limb fat was 2.7 kg (95% CI 2.4 – 2.9), 1.7 kg (95% CI 1.4 -2.1) and 2.3 kg (95% CI 2.1 – 2.6) in HIV negative, HIV positive with lipoatrophy and HIV positive children without lipoatrophy respectively, $p = 0.001$. Limb fat vs limb lean ratios were respectively, 0.63 (0.56 – 0.7), 0.36 (0.25 – 0.46) and 0.62 (0.54 – 0.7), $p = 0.0001$.

Mean adjusted anthropometrics found biceps skin-fold thicknesses of 5.5 mm (5.0 – 5.9), 4.2 mm (3.6 - 4.7) and 5.3 mm (4.9 – 5.7), in HIV negative, HIV positive with lipoatrophy and HIV positive children without lipoatrophy respectively, $p < 0.0001$. Triceps skin-fold thicknesses were respectively 8.7 mm (8.1 – 9.4), 7.1 mm (6.2 – 7.9) and 8.9 mm (8.3 – 9.6), $p < 0.0001$.

The investigators noted that diagnosis by visual grading correlated well with anthropometry and DXA, which are not commonly available in developing countries.

In multivariate analysis, controlling for age, sex and CD4 percentage, the greatest risk factor for clinical lipoatrophy was duration of d4T use, $p = 0.0008$. Cumulative d4T use was also associated with reductions in biceps and triceps skin-fold thickness, $p = 0.008$. Each additional year of accumulated d4T exposure gave an odds ratio of 1.9 (95% CI 1.3 – 2.9), $p = 0.002$.

The investigators wrote: "The prevalence of lipoatrophy is higher in our cohort than non-African cohorts. Our data identify cumulative d4T exposure as the greatest risk factor for lipoatrophy, highlighting the urgent need for all children to transition to alternative medication."

Stephanie Shiao and colleagues from the NEVEREST study team described the prevalence of lipodystrophy and associated patterns of regional fat distribution and metabolic alterations in young children who had started ART at less than 2 years of age. [1]

They performed an evaluation of 156 vertically infected children who started ART at Rahima Moosa Mother and Child Hospital, Johannesburg with lopinavir/ritonavir (LPV/r) + 3TC + d4T, and were randomised to either continue LPV/r ($n = 85$) or switch to nevirapine (NVP) ($n = 71$), while continuing 3TC + d4T. This was done on exit from the NEVEREST 2 trial after approximately 4 years on ART.

Clinicians assessed the children visually for signs of lipodystrophy, including lipoatrophy and lipohypertrophy. Anthropometrics, bio-impedance analysis, viral load, CD4, fasting total cholesterol, HDL, LDL, and triglycerides were measured. Measurements of regional fat - including trunk-extremity skin-fold ratios were estimated. Outcomes were compared across lipodystrophy groups defined as, lipodystrophy, possible lipodystrophy and no lipodystrophy.

The investigators used multiple linear regression to assess differences in arm, trunk and leg fat across lipodystrophy groups, adjusted for total fat, sex and age.

They found, of 156 children with a mean age 5.1 who initiated ART at a mean age of 10.7 months, 13 (8.4%) children were defined as having lipodystrophy, 18 (11.5%) as having possible lipodystrophy and 125 (80.1%) as no lipodystrophy. All 13 children defined as having lipodystrophy had lipoatrophy and 6 also had signs of lipohypertrophy.

There were no differences in age, sex, age at ART initiation, duration of ART, weight-for-age z-scores, height-for-age z-scores, body mass index, or proportion of children with a viral load <50 copies/mL among the three lipodystrophy groups.

There was no difference in the proportion of children with lipodystrophy between those who remained on LPV/r and those who switched to NVP, respectively 7.1% vs 9.9%, $p=0.51$.

The children with lipodystrophy had significantly less body fat than children with no lipodystrophy, measured by mean (\pm SD) skin-fold sum, 34.1 mm (\pm 5.7) vs 42.0 mm (\pm 11.1), $p=0.0016$. Children with lipodystrophy had greater trunk-arm 0.53 mm (\pm 0.07) vs 0.50 mm (\pm 0.05), $p=0.028$ and trunk-leg skin-fold ratios 0.61 mm (\pm 0.07) vs 0.55 mm (\pm 0.06), $p=0.004$, than children without lipodystrophy.

Lipid concentrations were similar across groups, except for mean triglycerides level which was greater for children with lipodystrophy compared to those without, 101 (\pm 45) vs 80 (\pm 34) mg/dL, $p=0.045$. The proportion of children with triglycerides >150 mg/dL was greater for children with lipodystrophy and those with possible lipodystrophy compared to those without, respectively 23.1% vs 4.8% and $p=0.04$ 22.2% vs 4.8%, $p=0.023$.

"A substantial portion of young children who initiated d4T-containing ART before two years of age have lipodystrophy as classified by clinical criteria..." the investigators concluded, adding: "Lipodystrophy can be cosmetically stigmatising and adversely affect adherence to ART. Finding a substantial proportion of young children with lipodystrophy has implications for future adherence, especially during adolescence when awareness of physical appearance is greatly heightened."

C O M M E N T

These reports are concerning and the rate reported by Innes et al particularly is high compared to other (generally anecdotal) reports from other parts of Africa. This may be because children were properly evaluated, although it is not clear whether there was blinding to laboratory results when the clinical diagnosis was made but visual grading correlated well with anthropometry and DXA.

In South Africa, where FDCs are not generally used, the 1 mg/kg doses of d4T will usually be rounded up using stand alone products resulting in a dose at least equivalent 40 mg in adults (Steve Innes, personal communication), so the effects might be less or occur over a longer duration of exposure with a lower dose.

This possibility in children has been used to argue for a controversial study in adults, of lower dose (20 mg) d4T, which, the investigators hope, will mitigate the drug's toxicity. As is usual in adult studies, Innes et al identified "cumulative d4T exposure as the greatest risk factor for lipoatrophy" and since d4T toxicity is both dose and time dependent - as we have stated before - it seems most unlikely that this could be reduced to acceptable levels in this way and there are better solutions on the horizon. [3, 4, 5]

A Thai study suggests that some lipodystrophy in children may be reversible after substitution with another NRTI and results from CHAPAS 3 will clarify whether this occurs. [6] But for the proportion for whom it is not reversible, as Shiao et al wrote, this can be stigmatising and adversely affect adherence to ART, particularly during adolescence when awareness of physical appearance is particularly sensitive (though when is it not?). Adult guidelines have for many years stressed that lipoatrophy is better to avoid than to treat. Children should also therefore be protected from this side effect.

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Lopinavir/ritonavir monotherapy in children

Polly Clayden, HIV i-Base

Induction/maintenance strategies in children are frequently discussed but underexplored and documented.

A poster authored by Pope Kosalaraksa and colleagues from the HIV-NAT 077 study team showed week 144 results for virologically suppressed Thai children switching to lopinavir/ritonavir (LPV/r) monotherapy.

In this study children with two consecutive viral load results <50 copies/mL at least 3 months apart while receiving double PI-containing second line regimens for at least 12 months were switched to LPV/r monotherapy. Virological failure was defined as two viral load results ≥ 500 copies/mL or three of ≥ 50 copies/mL. Children failing LPV/r monotherapy resumed treatment with their previous double PI regimen. The primary endpoint was the proportion of children with virological suppression <50 copies/mL at 144 weeks.

There were 40 children enrolled in the study, of which 90% received saquinavir as their second PI and the remainder indinavir. 3TC was used by 28%, AZT by 10% and EFV by 5%. At the time of enrollment the children were a median age of 11.7 (IQR 10.2-13.5) years, weight of 29.4 (IQR 24.1 – 40.20) kg and CD4 percentage 27% (IQR 23.5-29.5%) cells/mm³.

None of the children had disease progression over 144 weeks of follow up, one child died in a car accident and two were lost to follow up.

At 144 weeks 31/37 (83.8%) were virologically suppressed. The proportion of children remaining on monotherapy with virological suppression was 22/24 (92%). Eleven children experienced virological failure with lopinavir monotherapy with a median viral load measurement of 1740 (IQR 598-21,450) copies/mL. No major LPV/r mutations (L10F, M46I, L76V, V82A) were reported among 10/11 children who failed and genotype testing. When they resumed their previous double PI regimen, 7/11 (63%) children had virological suppression at week 144.

In multivariate analysis viral load at switch to LPV/r monotherapy of ≥ 50 copies/mL was the only predictor of failure, OR 4.4 (95% CI, 1.3-14.8). Although all children had <50 copies/mL at screening, 10% had ≥ 50 copies/mL at baseline. Sex, CDC class, CD4 percent nadir, CD4 percent at switch and adherence by pill count were not associated.

There were no significant changes in CD4 percent, fasting cholesterol, triglyceride, and glucose from baseline.

The investigators noted that frequent viral load monitoring is needed for early detection of virologic failure with this strategy.

C O M M E N T

This study shows a high rate of failure in about a third of children who switched to LPV/r monotherapy. Whether there are children that could benefit from this induction/maintenance strategy (probably not treatment experienced) remains an interesting question in RLS, where starting with a LPV/r-containing regimen in infancy is gaining momentum in settings with concerns about cost and NRTI toxicity.

Looking at darunavir/r monotherapy vs darunavir/r in a triple regimen and also once vs twice daily is currently under discussion for PENTA 17.

Ref: Kosalaraksa P et al. Lopinavir/ritonavir monotherapy in HIV⁺ children; week 144 results. 19th CROI. Seattle WA. March 5-8 2012. Poster abstract 962.
<http://www.retroconference.org/2012b/Abstracts/43511.htm>

Stopping treatment after early ART in infants

Polly Clayden, HIV i-Base

In an oral late breaker, Mark Cotton presented the final results from the Children with HIV Early Antiretrovirals (CHER) trial.

Interim results from CHER, announced in 2007, demonstrated the need for early ART in HIV-infected infants and influenced guidelines worldwide. The standard of care is now universal treatment for infants less than one year (and in WHO guidelines in children up to two years), initiated as early as possible.

In the study, infants <12 weeks of age with CD4 percent $\geq 25\%$ were randomised to receive deferred ART (ART-Def), immediate ART stopping after 40 weeks (ART-40W) or immediate ART stopping after 96 weeks (ART-96W). The recommendation that enrolment to ART-Def cease and all children be assessed to start ART was made by the DSMB in June 2007, as starting ART immediately reduced deaths by 75%. All children received treatment with lopinavir/ritonavir (LPV/r) + 3TC + AZT.

Treatment initiation in the deferred arm and re-initiation in the other two were in accordance with previous WHO guidance at a threshold of CD4 percent <25% in infants and <20% after infancy or with clinical disease progression. The primary endpoint was death or progression to CDC severe B or CDC C disease. All analyses were intent-to-treat using time-to-event methods.

A total of 377 infants were enrolled in CHER between 2005 and 2007. They were a median age of 7.4 weeks with a CD4 percent of 35% at baseline and 341 (91%) completed the study. Median follow up was 249 weeks (4.8 years) and the maximum was 309 weeks (5.9 years). The overall proportion of follow up time on ART in the three study arms were 81%, 70% and 69% in ART-Def, ART-40W and ART-96W respectively.

Approximately 75% in the ART-40W and 65% in the ART-96W arms re-initiated treatment by 240 weeks. The median time to starting ART in ART-Def was 20 (IQR 16-25) weeks and to restarting ART after interruption in ART-40W and ART-96W was 33 (IQR 26-45) and 70 (IQR 35-109) weeks, respectively. Difference between the two deferred arms was 37 (95% CI -11 to 85) weeks, p=0.13. By the end of the trial only 7 children had switched to second line antiretroviral therapy.

When the investigators looked at the total primary endpoints in the study they found 39 (25%) in ART-Def, 31 (25%) in ART-40W and 25 (20%) in ART 96-W. This was mainly due to at least double the number of deaths in ART-Def compared to the other two arms: 22 (18%), 11 (9%) and 9 (7%) in ART-Def, ART-40W and ART-96W respectively. Dr Cotton noted that there were no cases of regimen limiting toxicity.

Time to primary outcome compared to ART-Def, showed 23% fewer events in ART-40W, 42% fewer in ART-96W and 35% fewer in the two arms combined. Hazard ratios (HR) relative to ART-Def were ART-40W, 0.73 (95% CI 0.46-1.17), $p=0.19$; ART-96W, 0.58 (95% CI 0.35-0.96), $p=0.05$ and ART-40W/ ART-96W 0.65 (0.43 – 0.98), $p=0.04$.

Progression to CDC B or C or death was also reduced by 50% and 60% respectively. HR relative to ART-Def were ART-40W, 0.5 (95% CI 0.3-0.8), $p=0.005$ and ART-96W and 0.4 (95% CI 0.3-0.7), $p=0.0003$. There were 43, 27 and 18 events in the ART-Def, ART-40W and ART-96 arms respectively. For encephalopathy there were 9, 5 and 2 events.

When the investigators compared the ART-40W and ART-96 arms – including 34 additional children included after ART-Def stopped enrollment ($n=143$ in each remaining arm) – there was no difference between the two in time to primary outcome, HR 0.84 (95% CI 0.51 – 1.4), $p=0.49$. The majority of deaths in both arms occurred early, during the initial period of ART.

At the end of the trial 30 (25%) children in ART-40W and 46 (33%) in ART-96W never started continuous ART and CD4 percent was a median of approximately 30% in both arms.

Dr Cotton concluded that treatment during early infancy protects against HIV-related high mortality and morbidity and ART interruption after infancy appeared to be safe. But further analyses of virologic suppression and resistance and immunological response to restarting and interrupting treatment are needed.

C O M M E N T

Stopping treatment in infants who receive ART during acute infection appeared to be safe in CHER. Although Andy Predegast questioned the value of the short duration off treatment before restarting (33 and 70 weeks after 48 and 96 weeks of early ART respectively), in his excellent overview exploring “controversies and consequences of early initiation” of ART in infants. [2]

Conflicting results to those from CHER were reported from The Optimising Paediatric HIV-1 Therapy 03 (OPH03) Study - a randomised trial of continued vs interrupted treatment in infants with CD4 >25%, following at least 24 months of ART and restarting if CD4 dropped to 25% - which was stopped by the DSMB due to the high proportion of children restarting by three months. [3] In this study, 42 children were randomised (21 in each arm) and 18/21 in the interruption arm (86%) restarted, the majority (14/21) before 3 months. The children in OPH03 differed from those in CHER in that they were initially treated with ART at a median of about 5 months of age with a lower pre-ART CD4 percentage. However although lower CD4 percentage at randomisation was predictive of starting treatment after <3 months ($p=0.04$ vs > 6 months) but neither age at ART or pre-ART CD4 were (both $p=0.7$).

Dr Predegast questioned whether one or two years early treatment was enough and noted that there was no comparison to early continuous ART.

Emphasising the controversies, a speaker from the floor declared he was “shocked” that treatment interruptions were even being considered in children and suggested such an approach belonged in the “middle ages”.

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CROI 2012: INFECTION & PREVENTION

PrEP: PK modeling of daily TDF/FTC (Truvada) provides close to 100% protection against HIV infection

Simon Collins, HIV i-Base

Introduction

New research at CROI suggested that protection against HIV could be close to 100% from daily TDF/FTC (Truvada) and this should change previous reservations about PrEP as an intervention. [1]

In some studies, daily Truvada dramatically reduced the incidence of HIV infection, especially in high-risk individuals, (by 42% in MSM in the iPrEX study) but produced conflicting results in other studies (notably the FEM-PrEP study in heterosexual African women).

All studies have proved complicated to interpret due to the high rates of self-reported adherence but the likely very low rates of actual adherence demonstrated in PK sub-studies finding low levels of tenofovir and FTC in both active and placebo arms. The projected efficacy of PrEP increased dramatically when PK results were taken into account (to 92% in iPrEX). [2]

This proven protection could potentially increase real-life adherence compared to that seen in historical studies. If someone knows they will be protected rather than being a participant in a placebo controlled trial, and that this protection is so effective it could eliminate the risk of HIV, this could change the pattern of low use, even in less adherent patients.

PrEP studies are further complicated by the differences in pharmacokinetic properties of individual drugs, by differences in absorption of each drug in the male and female genital tract as well as in rectal tissue, and by the intracellular concentration of the active metabolites at each sites. Differences between human and animal drug absorption may limit how closely efficacy against vaginal and rectal exposure can be interpreted from macaque studies.

At CROI new modeling data showed that the protection from PrEP may be even greater than previously thought. The report that protection approaches 100% argues for new considerations for how PrEP might be incorporated as a health intervention.

Other studies at the meeting addressed some of the concerns for why PrEP has not been universally protective in other some studies.

iPrEX: modeled prediction of 99% protection with daily adherence

Peter Anderson and colleagues presented a late breaker oral PK analysis of intracellular drug concentrations in the iPrEX study and correlated this with levels of adherence in the Strand Study. [1]

This group used regression model to estimate efficacy of PrEP based on intracellular levels of tenofovir diphosphate (TDF-DP) in viable PBMCs from 48 cases matched to 144 uninfected controls. The researchers then established TDF-DP levels achieved on observed therapy of 2, 4 and 7 day dosing in a separate PK study of 24 HIV negative volunteers (the Strand study). Finally, they used the iPrEX regression models from i-PrEX on the Strand study data to estimate PrEP efficacy based on 2, 4 and 7 day dosing.

In iPrEX, detectable tenofovir levels in either plasma or cells was seen to have steadily fallen from baseline to time of infection, to only 8% of cases (at infection) compared to approximately 40% of uninfected controls. In the month prior to infections these rates were 11% vs 50% respectively suggesting that infections occurred during periods of low drug exposure.

In the Strand study, dosing 2, 4 and 7 days a week produced median (IQR) levels (fmol/million cells) of TDF-DP of 11 (6-13), 32 (25-39) and 42 (31-47) respectively. This compared to levels of 11 fmol/M (4-11) in 8% of iPrEX cases with detectable TDF and 16 fmol/M (9-47) in the 44% of controls with detectable levels. Daily dosing could be imputed from drug levels for 18% of iPrEX controls (and that 82% controls were likely to be taking less than daily dosing).

Regression modelling produced and estimated EC90 of 16 fmol/M viable cells (95%CI 3-28) with sensitivity estimates of less than 23 fmol/M producing estimates for risk reduction of 76% (56-96%), 96% (90->99%) and 99% (96->99%) for 2, 4 and 7 day dosing (see Table 1).

Table 1: Estimates for risk reduction in iPrEX

Doses/week	TDF-DP fmol/M viable cells (95%CI)	Risk reduction (95%CI)
2 / week	9 (7 -13)	76% (56-96%)
4 / week	30 (23 - 37)	96% (90->99%)
7 / week	45 (32 - 59)	99% (96->99%)

C O M M E N T

This study involved 615 v-PBMC and 1146 plasma samples were tested from 1212 time points (302 cases, 910 controls) but limitations include that drug levels were only proximal to time of exposure and that the impact of FTC levels were not studied.

The confidence intervals for the target IC90 of ≥ 15.6 fmol/M viable cells (95%CI 3.0 to 28.2) appears wide and this should be confirmed in future studies.

Partners PrEP: protection in serodifferent heterosexual couples

Jared Beaten and colleagues presented updated results from the randomised Partners PrEP Study, a randomised placebo controlled study of both TDF/FTC and TDF only in 4758 negative partners of HIV positive people who were not yet eligible for ARV therapy. [3]

The study was conducted in nine urban and rural sites in Kenya and Uganda. HIV negative partners were seen monthly for HIV testing, adherence and prevention counselling and HIV positive partners were seen every three months and approximately 20% in each arm started ARV treatment when recommended by national guidelines.

The placebo arm was discontinued in July 2010 following a recommendation by the study DSMB and those preliminary results had already been presented. Placebo arm participants were then randomised to either of the active arms and follow up continues until December 2012.

Approximate baseline characteristics for the negative partner included: just over 60% male; median (IQR) age 33 years (28, 40; with 11% less than 25 years). Although the median (IQR) duration of partnership was 7 years (3, 14) the time they had know about their partners HIV status was only 4-5 months (0.1, 2.0 years). Median CD4 count of the positive partner was almost 500 cells/mm3 (IQR 375, 660).

Study retention was greater than 95% with median follow up of 23 months (IQR 16 - 28, range 1-36). This involved more than 7800 person years of follow up (PYFU) and >99,000 study visits, with >95% dispensing of study meds.

Of the 96 new HIV diagnoses in negative partners, 14 were found to be in acute infection at baseline by retrospective PCR testing after HIV seroconversion, leaving 82 acquisition events in the primary study. Of these, 17 occurred in the TDF arm vs 13 in the TDF/FTC arm vs 52 in the placebo arm giving incidence rates/100 PYFU of 0.65, 0.50 and 1.99 respectively. This produced highly significant protection rates of 67% (95%CI 44-81%) and 75% (95%CI 55-87%) compared to placebo, in the TDF and TDF/FTC arms respectively (both p<0.0001). There were no significant differences between the two active arms (p=0.23) and both ruled out the predefined lower efficacy of -30%.

Although 60% of the negative partners were men, 45/82 infections occurred in women (n= 8 vs 9 vs 28; incidence 2.81 in women vs n=9, 4 and 24; incidence 1.49 in men; in single vs dual vs placebo arms respectively. Protection was seen for both men and women with non statistically significant differences for the differences in the results observed in men vs women (p=0.65 for single and p=0.24 for dual PrEP (see Table 2.)

Table 2: Efficacy by gender

	Efficacy (95% CI)	p-value	Interaction
TDF			
women	71% (37-87)	p=0.002	p=0.65
Men	63% (20-83)	p=0.01	
TDF/FTC			
women	66% (24-84)	p=0.005	p=0.24
men	84% (54-94)	p,0.001	

There were no differences between serious adverse events between arms including placebo (7% each arm) or confirmed laboratory abnormalities (each arm had <1% grade 2 or higher creatinine increase, 9% phosphorus decrease). During the first month there was significantly more mild nausea or fatigue in the active arms but these became similar to placebo rates at later time points.

Although there was one person with K65R tenofovir mutation and one person with M184V FTC mutation in the people with confirmed acute infection at baseline, no mutations were detected in infections from the main study. Four cases of NNRTI resistance was seen indication transmission of resistant virus.

About one third of participants reported additional sexual partners (41% men, 9% women)

PK results for drug levels of tenofovir in each of the active arms in the Partners in PrEP study were presented in a second oral presentation by Deborah Donnell. [4]

This study used the 29 cases (n=17 single arm, n=12 dual arm) compared to drug levels in 100 uninfected controls from each arm, using multiple samples throughout the study (at months 1, 3, 6, 12, 18, 24, 30, and 36. Drug levels were tested using LCMS with lower limit of quantification of 0.3 ng/mL. Based on other studies tenofovir would be detected for nine days after a single dose and tenofovir levels at steady state from daily dosing would be >40 ng/mL.

Tenofovir was detected in >80% of samples in uninfected controls compared to 56% of samples of cases and in only 31% (6/17) of single arm and 25% (3/12) of dual arm samples at the seroconversion visit. This produced relative risk reduction associated with detectable drug of 86% (95%CI 57%, 95%; p<0.001) and 90% (95%CI 56%, 98%; p=0.002) in the single and dual arms respectively. Only 4/9 cases of infections with detectable drug had levels > 40 ng/mL consistent with high adherence.

Patterns of adherence in controls suggested than non- or poorly adherent patients did not change their adherence of the study. By contrast, about 50% of highly adherent patients maintained this through the study but 25% either dropped to lower adherence and 25% to non-adherence.

Several other analyses were presented from the Partners in PrEP study at CROI. These included:

- A report on nearly 300 pregnancies during the study, with similar rates in each of the three arms and no safety concerns, and suggesting a specific use for PrEP in serodifferent couples wanting to have a baby. [5]
- Details of ARV update in the 817 positive partners whose CD4 count declined during the study making them eligible to start treatment, with only 420 (55%) initiating treatment. Factors included reluctance to start, loss to follow up and unavailability of treatment. [6]
- High (>90%) positive acceptance to use PrEP amongst >negative partners with lower, but still high (60%) interest from positive partners in earlier treatment as prevention. [7]
- Implications from PrEP protection on the rate of false positive results from rapid tests. From over 99,000 tests, 266 were positive on dual rapid tests. Of these, 37% (99/266) were confirmed true positive by ELISA, 58% (155/266) were false positive by ELISA and 4.5% (12/266) were indeterminate. False positives were more common in the active arms 69% (110/159) vs 45% (45/107) in the placebo arm due to the lower incidence of HIV. [8]
- Modelling factors for a risk score to determine the population characteristics for most effective use of PrEP as an intervention. [9]

Why PrEP did not work in FEM-PrEP

Another late breaker oral presentation provided results from the FEM-PrEP study in which daily TDF/FTC (Truvada) used as PrEP was not effective. The FEM-PrEP study, which had enrolled just over 2000 of the planned 3900 participants was closed in April 2011 due to lack of efficacy between daily TDF/FTC compared to placebo in over 2000 African heterosexual women.

The DSMB recommended stopping the study when the study was only half way through enrollment when 28 infections had been seen in each arm. More pregnancies occurred and side effects were also higher in the active arm.

The final results from the study were presented at CROI by Lut Van Damme and colleagues. [10]

Baseline characteristics included approximately 60% younger than 25 years, 50% condom use, 13% had transactional sex with other than primary partners. However, 70% of participants thought they were at low risk for HIV, but 15% had Chlamydia and 6% had gonorrhoea at screening. Women had sex on average four times a week (mean 3.7, range 0-28).

Of 68 infections occurring during the main study, 33 infections occurred in the active arm (incidence rate, 4.7/100 person-years) and 35 in the placebo group (IR, 5.0/100 person-years), with an estimated hazard ratio (HR) for infection of 0.94 (95%CI 0.59 to 1.52, $p = 0.81$). Although seven infections were discounted due to lack of product at the study clinic, a sensitivity analysis censoring women at last date of product use did not change the main results (HR 0.82; 95%CI 0.49-1.36, $p=0.44$).

Tolerability generally good with no grade 3 events but included more nausea in the active group.

There were five cases of FTC-associated resistance (one in the placebo arm) but no cases of resistance to TDF.

As with other PrEP studies, adherence rates were very high by self-report (>95%) and pill count (~90%) but a pharmacokinetic analysis in a case-control sub study indicated that this was at best likely to be 20-30% in either arm, with detection lower in cases vs controls. Adherence levels below 50% in each arm also removed the power of this study to be able to detect a real impact of the active arm.

Of interest, an opinion piece by Anneke Grobler and colleagues in the 13 March edition of AIDS on the design challenges for future prevention studies includes a table that calculates projected effectiveness found with different levels of true efficacy of the comparator and new intervention in combination with different adherence levels. [11]

C O M M E N T

Although the lack of protection in this study was assigned to low adherence, this may be more complex as adherence was also low in iPrEX. This may also involve the baseline risk of participants and perception of risk, perhaps explaining the differences seen in other heterosexual studies such as TDF-2.

There may also be implications by gender related to pharmacokinetic and intermittent adherence highlighted in macaque studies, including the poster reported below.

Intermittent TDF/FTC (Truvada) in macaques: vaginal, cervical and rectal tissue and cell PK

Jessica Radzio and colleagues from the CDA in Atlanta presented results from a pharmacokinetic study in macaques. [12]

This study was important for studying both tenofovir and FTC in tissue site and intracellular levels. Both drugs peaked - at two hours in plasma and five hours in vaginal secretions - and then declined to low levels at 24 hours. In rectal secretions, levels increased more slowly and steadily, only peaking at 24 hours but then remaining high for at least 24 hours.

This aspect of the PK profile in macaques is comparable to that seen in women. The group then looked at active intracellular levels of the active metabolites of each drug, FTC-TP and TFV-DP.

FTC drug levels were very similar in vaginal, cervical, rectal and lymphoid tissue compared to cell biopsies with vaginal:rectal ratio of 1.04 in cells and 2.10 in tissue at 24 hours. This was similar for cervical:rectal ratios. However levels of tenofovir in vaginal, cervical and lymphoid tissue, both in tissue and cells was dramatically lower, while remaining high in rectal tissue and cells, with vaginal:rectal tissue concentrations ratios dropping to 0.04 for intracellular levels and 0.02 in tissue, with similar results for cervical:rectal ratios (0.04 and 0.03 respectively).

The group then looked at whether these levels would be sufficient for vaginal exposure in six macaques following oral dosing and repeat low dose exposure weekly for up to 18 weeks (through four menstrual cycles) to SIV to approximate to human sexual exposure, with six macaque controls. TDF/FTC or placebo was given 24 hours before or two hours after exposure. All control animals became infected quickly, mainly in the first menstrual cycle but none of the active macaques receiving intermittent TDF/FTC became infected over 18 weeks suggesting that the lower PK may be protective even with intermittent PrEP to prevent vaginal transmission.

This study reported a pattern of ratio (rather than absolute concentrations) suggesting this validates the macaque model for future studies. Although this study only looked at -24 plus +2 hour dosing for vaginal exposure, the rectal macaque studies emphasised the +2 hour dose to be essential and the protection from the pre-exposure dose extended from 1 to seven days. However dosing only 2 hours before exposure correlated with significantly reduced protection, though this was still higher than if no pre-exposure dose was given.

C O M M E N T

The potential for close to 100% protection against HIV infections with alternate or daily dosing should prompt pilot programmes that include access to this option in individuals who are at the highest risk for HIV.

For many people, higher risk behaviour and vulnerability to infection may be associated with a relatively short period of someone's life. Whether this is a period of weeks, months or several years, the option to use an oral prophylaxis when other prevention methods are unlikely to be used, can prevent the complications of life-long infection and treatment.

TDF/FTC (Truvada) has already been submitted to the FDA for an indication for use as PrEP with a decision expected later this year.

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Risk of HIV reinfection may be similar to risk of initial HIV infection

Simon Collins, HIV i-Base

The risk of HIV reinfection, sometimes called superinfection, has not been clearly established. Given the risk of initial sexual HIV infection from a single exposure in population studies is commonly calculated as generally low (although these estimates are dependent on the background prevalence) this is difficult to assess in small studies.

Genetic analysis is specialised and expensive and the biological evidence is strongly supported by the many viral sub-clades and recombinant forms that can only have occurred in vivo. The extensive global viral diversification provides the most practical evidence for reinfection.

Case studies have highlighted cases where reinfection with drug resistant HIV has clinical implications leading to either more rapid disease progression or treatment failure and reduced future treatment options. Although initial reports were in early or acute initial infection, cases have also included people in chronic infection, indicating that this may not be restricted by immune responses to the initial infection and in people on suppressed ART, indicating that the pressure from PrEP/PEP can also be overcome.

Three studies at CROI focused on issues of reinfection.

Andrew Redd and colleagues from the US NIH and Johns Hopkins University used high-throughput deep sequencing to retrospectively test for HIV superinfection in two regions of the viral genome (p24 and gp41) in 203 people from the Rakai Community Cohort Study (RCCS) in Uganda, who seroconverted from 1997-2002 with later samples for a total 15,000 person years of follow up (PYFU). This was compared to the primary HIV incidence rate for the HIV negative general heterosexual population in Rakai (n = 20,220; > 100,000 PY).

They identified reinfection in 7/149 people with identifiable sequences in the seroconverter cohort (1.44/100 PY (95%CI 0.37 to 2.51), all from significant changes in the gp41 region. These seven cases were initially infected with sub-type D. Four of the reinfections were with new sub-type D and three with sub-type A.

There were 1152 new infections in the general population over the same period giving an incidence rate of 1.15/100 PY (95%CI 1.08 to 1.21). This was not significantly different to from the primary HIV incidence rate (incidence rate ratio = 1.26, 95%CI 0.50 to 2.60; p = 0.26).

Differences between the risk factors for the people with reinfection (inherently at greater risk than the general population because they were clearly more susceptible to infection) were adjusted for using propensity score matching increased the background incidence rate to 3.28 /100 PYFU (95%CI 2.0-5.3) based on the baseline data but this reduced to 2.51 /100 PYFU (95%CI 1.5-4.3) using the follow up time point (when the difference between groups were more narrow).

The authors concluded: "Although other studies have examined superinfection in small groups of high-risk individuals, this is the first study to directly compare HIV superinfection rates to HIV incidence in a general heterosexual population. The finding that HIV superinfection occurs at approximately the same rate as primary HIV incidence has multiple public health ramifications, and could have significant implications for HIV vaccine research."

In a second oral presentation, Keshet Ronen from Fred Hutchinson Cancer Research Centre and colleagues looked at the incidence of reinfection in a high-risk cohort of female sex workers in Mombasa, Kenya who were enrolled within six months of initial infection and followed for two years. This is a cohort of almost 3000 HIV negative women who have been followed prospectively with monthly visits, 311 of whom have seroconverted since 1993, with median follow-up of five years.

This group amplified and analysed ~500 bp amplicons in gag, pol, and env from plasma RNA to identify cases of multiple infection. Between 100 and 2000 sequences were obtained per genomic region per time point for a total of ~380,000 sequences.

In earlier studies this group identified 12 cases of reinfection in 56 women. In this new analysis a further 94 women have been identified, with 7 cases of reinfection in the 63 women who have so far had data analysed. They presented combined result of 19 cases of superinfection among 117 women over 621 person-years of follow up (incidence of 3.06% PYFU for reinfection vs to 3.25 for initial infection) and ongoing screening and analysis continues to reach the 150 cases needed to be powered to compare these rates, adjusting for other risks. In this study, timing of reinfection was addressed and included cases plausibly occurring five or more years after initial infection.

However, some researchers suggest the possibility that cases attributed to reinfection could come from initial dual infections, with one infection outgrowing the other after several years. In the absence of being able to confirm a reinfection event by phylogenetic comparisons to the second donor an indirect way to rule out initial dual infection would be to look for closest ancestor for each dual strain to estimate whether one infection has been present for longer than the other.

A poster from the UCSF group that have previously presented this position included two cases where reinfection (superinfection) was initially described based on limited sample sequencing but that more sensitive analyses suggested were serially expressed dual infections (SEDI). [3]

C O M M E N T

The consensus after both studies seemed to be that initial HIV infection is not protective of subsequent infections. Researchers were divided over whether initial infection potentially increases the risk of second infection or whether longer duration of follow-up (>2 years) might uncover CTL responses.

Others suggested that cases of reinfection in these studies could easily have been underestimated by not looking early enough after initial infection and only reporting phylogenetically different infections. Further research is needed to determine risks for reinfection, currently assumed to generally be similar to those for initial infection (behaviour risk, viral load of the transmitting partner, STIs, genetics etc).

Ascribing reinfection to initial dual infection (SEDI), requires either one source partner (prompting the question of how this person became dually infected?) or exposures from multiple sources at a close time point, which becomes practically very close to dual infections as one infection must have predated the other, even if this involved a short window period.

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Case report: homozygous CCR5 delta-32 protection overcome by infection with X4 virus

Simon Collins, HIV i-Base

A sobering and important report documented the case study of a man who was homozygous for the CCR5 delta-32 mutation that generally provides effective protection against infection from HIV.

With most circulating (and infectious) virus using the CCR5 co-receptor, individuals with this deletion in both chromosomes who are exposed to HIV provide a dead-end for the infection, with the virus unable to infect CD4 cells without the use of the coreceptor.

This case of a 39 year-old man - who was diagnosed in 1996 - was indentified by Ester Ballana and colleagues after retrospectively testing DNA from stored peripheral blood mononuclear cells (PBMCs). The man had started treatment within 6 months of diagnosis, at a CD4 count of 520 and viral load of 3,500 copies/mL. Sequence analysis of the env gene idicated homogeneous X4 virus.

Fifteen years after seroconversion, total HIV-1 proviral DNA was 60 copies/million PBMCs. CD4 count had only increased to 600-700 over this time but HLA haplotype analysis showed multiple alleles associated with slower HIC progression including HLA-B*5701 and HLA-A*2402.

Ref: Ballana E et al. HIV-1 infection in a CCR5-D32/D32, HLA-B*5701, and HLA-A*2402 subject: a case report. Poster abstract 292.
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CROI: SIDE EFFECTS

No association between atazanavir and MI or stroke in D:A:D study

Simon Collins, HIV i-Base

An update from the D:A:D cohort on the risk of cardiovascular events was presented as a poster. The D:A:D is a large cohort that includes more than 49,000 HIV positive people from Europe, Australia and the US that in recent years has become sufficiently powered to be able to look at associations between safety outcomes and individual HIV drugs.

The cohort now includes 844 cases of myocardial infarction and 523 strokes, both from over 300,000 patient years of follow up (PYFU) and this year accrued sufficient data on atazanavir (>37,000 PYFU) to present this analysis. Previous associations had been reported for cumulative exposure to indinavir and lopinavir/r but not for saquinavir or fosamprenavir.

The rate of MI was 0.28 /100 PYFY (95%CI 0.26 to 2.30) in those with no exposure to atazanavir and 0.20 (0.12 to 0.32) in those with >3 years exposure. The rate of stroke was 0.17 (0.16 to 0.19) and 0.17 (0.10 to 0.27) in the same groups respectively.

The relative rates (RR) for MI and stroke were 0.95 (95%CI: 0.87, 1.05; p=0.30) and 0.90 (95%CI: 0.81, 1.01; p=0.07) after adjustment for clinical and demographic factors including ARV use. No association was seen with cumulative exposure (<1, 1-2, 2-3, >3 years) or after further adjustment for bilirubin. Rates were similar for atazanavir used with and without ritonavir.

Table 1: Rate (95%CI) of MI or stoke and exposure to atazanavir

	No ATV	>3 years
MI	0.28 (0.26 to 2.30)	0.20 (0.12 to 0.32)
Stroke	0.17 (0.16 to 0.19)	0.17 (0.10 to 0.27)

Reference

d'Arminio Monforte A et al. ATV-containing ART is not associated with an increased risk of cardio- or cerebro-vascular events in the D:A:D study. 19th Conference of Retroviruses and Opportunistic Infections, 5-8 March 2012, Seattle. Poster abstract 823.

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CROI: HCV COINFECTION

Hepatitis C coinfection studies

Simon Collins, HIV i-Base

The conference included very encouraging results from the first studies of telaprevir (tradename Incivek, Vertex) and boceprevir (tradename Victrelis, Merck) in people with HIV/HCV coinfection.

Both studies generally showed similar response rates in HIV/HCV coinfection to those seen in HCV mono-infection. Sustained virological response (SVR) results at 12 weeks are highly predictive of SVR at week 24.

Telaprevir: SVR-12 results in HIV/HCV coinfection

SVR results at 12 weeks after treatment, from a double-blind, placebo controlled Phase 2 study telaprevir in combination with pegylated interferon (peg-IFN) + ribavirin (RBV) in 60 patients with HIV and HCV genotype-1 coinfection were presented by Douglas Dieterich. [1]

Patients were randomised to either telaprevir (750 mg every 8 hours) or placebo, plus PEG-IFN alpha-2a (Pegsys) + RBV, (800 mg/day) for 12 weeks followed by 36 weeks of peg-IFN+RBV. This was a two-part study depending on whether patients were using ART (Part B, n=47) or not (Part A, n=13). In the ART arm atazanavir/ritonavir (n=23) or efavirenz (n=24) based regimens were allowed (with an increased telaprevir dose for efavirenz patients).

Baseline characteristics included: mean age of 46 years; 88% male; 27% African American; 68% with subtype 1a and 3% had cirrhosis. HCV RNA was >800,000 IU/mL in 92% and 81% of no-ART and ART groups respectively; median CD4 counts were approximately 500-600 cells/mm³ (range 300 - >1,100).

Undetectable HCV RNA in the combined active vs placebo groups were achieved by 68 vs 4.5%, 82% vs 32%, 63 vs 4.5% and 74% vs 55% at week 4, 12, weeks 4 and 12, and week 24 respectively, see Table1). ART use did not affect response rates. Outcomes by baseline HCV RNA were not presented.

Both safety and tolerability of telaprevir in combination with peg-IFN+RBV was comparable to that previously observed in HCV-mono-infected patients. No severe rashes were reported.

Table 1: Interim HCV RNA BLQ (%) response rates with telaprevir in HIV/HCV coinfection

N (%)	No ART		EFV/TDF/FTC		ATZ/r/TDF/FTC	
	T/PR	PR	T/PR	PR	T/PR	PR
N	7	6	16	8	15	8
Week 4 (RVR)	5 (71)	0	12 (75)	1 (12)	9 (60)	0
Week 12 (oRVR)	6 (66)	2 (33)	14 (80)	2 (25)	11 (73)	3 (38)
Week 4 and 12 (eRVR)	4 (57)	0	12 (75)	1 (12)	8 (53)	0
Week 24	6 (86)	2 (33)	12 (75)	4 (50)	10 (67)	6 (75)

T: telaprevir; P: peg-IFN; R: ribavirin. BLQ: undetectable; lower limit of quantification: 25 IU/mL; limit of detection 10-15 IU/mL.

Interactions between telaprevir and antiretrovirals

Interaction data between telaprevir and HIV drugs was also included in the same presentation. Telaprevir concentrations were similar with efavirenz and atazanavir to reference concentrations with mean (90%CI) C_{min}, C_{avg} and C_{max} of 93 ng/mL (56, 156), 97 ng/mL (64, 146) and 101 ng/mL (72, 143) with efavirenz and 131 ng/mL (77, 222), 107 ng/mL (70, 165) and 98 ng/mL (69, 140) with atazanavir, respectively.

The mean concentration ratios to reference levels were also close to 100% for levels of efavirenz and atazanavir, indicating the higher efavirenz dose is sufficient to overcome this interaction.

Telaprevir can only be used with boosted atazanavir, efavirenz (with a higher dose of telaprevir--1125 mg tid (vs. 750 mg tid) or raltegravir. Background nucleosides are tenofovir plus FTC or 3TC

Boceprevir: SVR-12 results in HIV/HCV coinfection

SVR results at 12 weeks after treatment from a randomised double-blind, placebo controlled study of Merck's boceprevir (BOC) with pegylated interferon (peg-IFN) + ribavirin (RBV) in 98 patients with HIV and HCV genotype-1 coinfection were presented by Mark Sulkowski. [2]

In this study, all patients were on stable antiretroviral treatment (not including NNRTIs, AZT or ddI) with suppressed viral load (<50 copies/mL). ART regimen included atazanavir/r (n=31), lopinavir/r (n=25), darunavir/r (n=17), other PI (n=7), raltegravir (n=10) and other (n=2).

Patients were randomised (2:1) ratio to receive boceprevir 800 mg every eight hours (n=64) or placebo (n=34) plus pegylated interferon-alfa-2b (Peg-Intron) and weight-based RBV (600 to 1400 mg/day). All patients also had a four-week lead-in phase with peg-IFN + RBV.

Baseline characteristics included: mean age of 45 years; 69% male; 82% white. 88% had HCV RNA >800,000 IU/mL and 65% were genotype 1a. Median CD4 counts were approximately 580 cells/mm³ (range 200 - >1,500). Only 4 patients had cirrhosis.

HCV RNA levels were undetectable in 59% vs 23% of patients at week 12 and 64% vs 29% at week 48 in the boceprevir vs control groups with SVR rates 12 weeks after the end of treatment of 61% vs 26% (see Table 2).

Table 2: Interim HCV RNA BLQ (%) response rates with boceprevir in HIV/HCV coinfection

	B/PR	PR
N	64	34
Discontinuation	24 (38%)	18 (53%)
week 4 (pegIFN/RBV lead-in)	3 (4.7%)	3 (8.8%)
week 8	27 (42%)	5 (15%)
week 12	38 (59%)	8 (23%)
week 24	47 (73%)	11 (32%)
week 48 (EOT)	42 (66%)	10 (29%)
SVR 12	37/61 (61%)	9/34 (26%)

B: boceprevir; P: peg-IFN; R: ribavirin.

Important drug interactions between HIV PIs and boceprevir

A late breaker poster was presented by researchers at Merck reporting significant interactions between boceprevir and HIV protease inhibitors (atazanavir, lopinavir and darunavir) in HIV negative volunteers. [3] This highlighted not just the complexity for future HCV treatment in people already on ART, but also the importance of conducting major drug-drug interaction studies prior to coadministration in new studies.

Boceprevir significantly decreased the exposure of the PIs by up to 41-75% for AUC_{0-last}, C_{max}, and C_{min} [GMR (90% CI)]. Coadministration with boceprevir also decreased the exposure of ritonavir AUC_t by 34%, 22%, and 27% in the atazanavir, lopinavir and darunavir groups, respectively. Co-administration with atazanavir/r did not alter boceprevir AUC_t, but co-administration with lopinavir/r and darunavir/r decreased boceprevir AUC_t 45% and 32%, respectively.

Table 3: Geometric mean ratio (90% CI) for interaction between boceprevir and HIV PIs

	AUC _{0-last}	C _{max}	C _{min}
ATZ	0.65 (0.55, 0.78)	0.75 (0.64, 0.88)	0.51 (0.44, 0.61)
LPV/r	0.66 (0.60, 0.72)	0.70 (0.65, 0.77)	0.57 (0.49, 0.65)
DRV	0.56 (0.51, 0.61)	0.64 (0.58, 0.71)	0.41 (0.38, 0.45)

C O M M E N T

These results are important for people with HCV genotype 1 who are in need of urgent treatment.

The interaction data between these HCV drugs and antiretrovirals in these studies was luckily not associated with high rates of treatment failure.

For further information on HCV drug interactions please see the excellent online resource produced by the pharmacology team at Liverpool University.

<http://www.hep-druginteractions.org/>

UK consensus guidelines for use of these new HCV drugs were recently published online with free access, and although are not HIV-specific, they include a reference to coinfection being a population where their use should be considered. [4]

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CROI: IMMUNISATION

Herpes Zoster vaccine safe and effective in HIV positive people

Simon Collins, HIV i-Base

Encouraging results were presented from the ACTG A5247 study on the use of two doses of a live varicella zoster virus (VZV) vaccine (Zostavax, Merck) in almost 400 HIV positive people who were VZV positive or who had herpes zoster (HZ)/shingles outbreak at least one year before study entry, and who were virally suppressed on stable ART. [1]

The incidence and severity of HZ and post herpetic neuralgia (PHN) is higher in HIV positive people and early use of early acyclovir treatment is not always effective. As susceptibility to HZ increases with reduced age-related immune function, a protective vaccine response already demonstrated in HIV negative people > 60 years [2] would be particularly important for HIV positive people.

Participants from over 40 US sites were randomised 3:1 to active or placebo arms and stratified by CD4 count at screening: >350 (high) vs 200-349 (low) cells/mm³. Vaccinations were given on day 0 and at week 6, with immune responses evaluated at weeks 2, 6, 8, 12, and 24.

Primary endpoints were safety (if ≤ 18 patients in the active arm had primary safety endpoints) and efficacy (change in VZV gpELISA titer at 6 weeks post each vaccination).

Baseline characteristics included: 84% male; 66% white, 31% black, 22% Hispanic; median age 49 years. Median CD4 count and CD4 nadir in the high ($n=203$) and low ($n=192$) groups was 602 (nadir 276) and 283 (nadir 106) cells/mm³ respectively. Almost all participant had a previous AIDS event ($>97\%$) with 75 having prior VZV and 33% HZ > 1 year prior to entry.

In the safety analysis, there were no significant differences between the active and placebo groups and none of the 15 primary endpoints in the active arm were vaccine related. Injection site reactions were seen more frequently in the active group (42% vs 12%, $p<0.001$). VZV-like rashes were seen in 3 active and 2 placebo patients with PCR showing negative or non-vaccine-strain results.

Geometric mean fold-rise in VZV antibody titre increased by 1.75 VZ vs 1.09 placebo from baseline to week 6 ($p<0.001$) and this remained similar at week 12 (indicating no change from the second dose). Patients with higher CD4 count at baseline had slightly higher antibody titer over time ($p=0.024$).

These responses were similar to those seen in HIV negative patients > 60 years. However this study was not powered to detect difference in HZ outcome and post-study follow up is not planned.

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<http://www.nejm.org/doi/full/10.1056/NEJMoa051016>

High dose flu vaccine improves antibody responses in HIV positive people

Simon Collins, HIV i-Base

Noah McKittrick and colleagues presented results from a randomised, double-blinded study comparing standard (15-ug/strain) to high dose (60 ug/strain) flu vaccine in 195 HIV positive adults. This study used the trivalent, inactivated, unadjuvanted, split-virus vaccine Fluzone (Sanofi Pasteur). Antibody titers to three strains (H1N1, H3N2 and B) were measured using the hemagglutination-inhibition (HAI) assay.

Baseline characteristics included: 71% male, 68% African American and median age 45 (range 20-78) years. The median CD4 and nadir CD4 count of 452 (IQR 293 - 629) and 180 (IQR 53 - 318) cells/mm³ respectively. In this group, 89% were on HAART and 89% of these 89% had viral load <200 copies/mL.

Approximately half the patients had protective titers at baseline. By week 3, geometric mean antibody titers and the proportion of individuals with protective HAI titers were higher in participants vaccinated with the HD. Greater responses were seen in the high vs low dose groups but this was only significant for H1N1 +9% (0.9 to 17.8%, $p=0.04$), and B +12% (1.5 to 22.6%, $p=0.03$) with a non-significant difference H3N2 + 4% (-3.6 to 12.1%, $p=0.39$).

Both vaccines were well tolerated with no differences between groups and no serious adverse events.

The high dose group achieved protection rates of 80-90% (similar to standard dose in HIV negative studies) increased from 50-70% previously reported for standard dose use in HIV positive people.

Ref: McKittrick N et al. Improved immunogenicity with high-dose seasonal influenza vaccine in HIV+ individuals: a double-blinded, randomized trial. 19th CROI, 5–8 March 2012, Seattle. Oral abstract 97.

<http://www.retroconference.org/2012b/Abstracts/44150.htm>

ANTIRETROVIRALS

Dolutegravir Expanded Access Programme

An Expanded Access Programme (EAPs) for dolutegravir, an integrase inhibitor in Phase 3 studies has been announced by ViiV Healthcare. [1]

This will provided open-label access to adults living with HIV who have documented raltegravir or elvitegravir resistance, who have limited treatment options, and who require dolutegravir to construct a viable antiretroviral regimen for therapy. [2]

As with all EAPs, this is based on the understanding that the safety and efficacy of dolutegravir has not been fully established or thoroughly evaluated by regulatory agencies, but that results from phase 2b studies usggest this may be an important life-saving option for people unable to enroll in clinical studies.

The dolutegravir EAP is now open and accepting participants in the USA and Canada.

For Europe and the International region, it's expected that the EAP will start to open in March/April 2012 as local regulatory and ethics approvals are obtained.

Further details are available online.

<http://www.dolutegravir-eap.org>

C O M M E N T

The importance of understanding the importance of using dolutegravir in combination with other active drugs was highlighted by US community treatment activists. [3]

As with earlier EAP access, the benefits from using a single active drug will be limited. This may still be a life-saving option for someone at serious clinical risk of progression, but people who are able to defer use until other active drugs are available, are likely to gain the most durable response.

References

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<http://www.acria.org/content/activists-advise-caution-about-access-program>

FDA approves etravirine for treatment-experienced children 6 to 18 years of age and new scored 25 mg tablet for paediatric dosing

On 26 March 2012, the United States Food and Drug Administration (FDA) approved dosing recommendations for etravirine (Intence) for treatment-experienced paediatric patients 6 to 18 years of age and weighing at least 16 kg.

In addition a new scored 25 mg tablet was approved for use in paediatric patients. Listed below are a summary of major changes to the product labelling.

2.2 Paediatric patients (6 years to <18 years)

The recommended dose of etravirine for paediatric patients 6 years to less than 18 years of age and weighing at least 16 kg is based on body weight not exceeding the recommended adult dose. Etravirine tablet(s) should be taken orally, following a meal. The type of food does not affect the exposure to etravirine. The safety and efficacy of etravirine have not been established in children less than 6 years of age.

Healthcare professionals should pay special attention to the accurate dose selection of etravirine, the transcription of the medication order, the dispensing information and the dosing instructions to minimise the risk of medication errors, overdosing, and underdosing.

2.3 Method of administration

Patients should be instructed to swallow the etravirine tablet(s) whole with a liquid such as water. Patients who are unable to swallow the etravirine tablet(s) whole may disperse the tablet(s) in a glass of water. The patient should be instructed to do the following:

- Place the tablet(s) in 5 ml (1 teaspoon) of water, or at least enough liquid to cover the medication.
- Stir well until the water looks milky, if desired, add more water or alternatively orange juice or milk (patients should not place the tablets in orange juice or milk without first adding water). The use of grapefruit juice or warm (greater than 40°C) or carbonated beverages should be avoided.
- Drink it immediately.
- Rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the patient takes the entire dose.

6 ADVERSE REACTIONS

The safety assessment in children and adolescents is based on the Week 24 analysis of the single-arm, Phase 2 trial TMC125-C213 in 101 participants. The frequency, type and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adult subjects, except for rash, which was observed more frequently in pediatric subjects.

8.4 Paediatric use

Treatment with etravirine is not recommended in children less than 6 years of age.

For full details see the complete labeling posted on the FDA web site.

Source: FDA list serve. (26 March 2012).

TREATMENT ACCESS

Global action over the challenge to India's patent laws

Rebecca McDowall, HIV i-Base

From 6-10 February 2012, activists from Delhi to New York, Johannesburg to London took to the streets to appeal to the Indian government and European Commission (EC) to act to ensure that the developing world continues to have access to affordable medicines.

Currently, the EU is pushing for India to adopt measures that would choke generic production in the country, and by restricting generic exports, threaten access to medicines for millions of people worldwide. Negotiations on the proposed India-EU Free Trade Agreement (FTA) were expected to culminate at the EU-India Summit, which took place in New Delhi on 10 February 2012.

The Summit was expected to be the climax of a five-year-long negotiation process over an EU-India Free Trade Agreement (FTA). The agreement seeks to strengthen trade relations between the two economies and holds promise of huge development for many Indian industries. It also, however, is a source of concern for the global health because India is the world's largest producer of generic medicines making it the "pharmacy of the developing world".

India currently produces 80% of ARVs used in the developing world and 90% of paediatric HIV medicines. Despite curtailment of generic production following India's inclusion into the World Trade Organisation in 2005, the country has successfully utilised TRIPS flexibilities to ensure that it still produces affordable medicines for the world's poorest countries.

The FTA, however, threatens to over rule India's national patent laws and increase restrictions on generic pharmaceutical production from within the country.

One of the most harmful provisions within the agreement – that of data exclusivity - was the focus of activist pressure throughout 2011. The provision (known as data monopolies in the US) requires manufacturers of all generic formulations to conduct new clinical trials rather than simply demonstrating equivalence to the innovator drug, even though the FDA recognises the scientific safety and rigour of bioequivalence studies. If these trials are not conducted the generic company would be required to wait 10 years to gain access to the original trial data.

Following widespread pressure from global health advocates and activists and resistance from the Indian government the EC announced that this provision has been removed from the agreement. Despite this assurance the newer drafts of the agreement indicate that similar provisions, albeit in subtler wordings, are being pushed to be included in the final agreement.

Further harmful inclusions into the agreement include:

- Border measures - restricting the exportation of generic drugs out of the country.
- Intellectual Property enforcement measures - putting third parties such as treatment providers at risk of court cases and police action.
- The 'Investment Chapter' that would remove the Indian government's right to place public health before private profits by allowing companies to directly sue the government in disputes over IP rights.

In the end, no agreement was reached on 10th February and the negotiations between the EC and India are ongoing. As pressure grows to come to an agreement in the near future there is increasing concern that provisions harmful to access to medicines may be slipped into the FTA. The consultation process is being conducted with little sign of accountability or transparency, leaving activists largely in the dark about these worrying provisions. Ongoing pressure is essential to protect India's generic industry and ensure that the developing world retains access to the affordable medicines it needs.

For more information, and to become involved in the campaign please see:

<https://action.msf.org>

<http://www.healthpovertyaction.org/campaigns/trading-with-lives/>

<http://www.stopaidscampaign.org.uk/>

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

<http://donttradeourlivesaway.wordpress.com/>

<http://students.stopaidscampaign.org/>

Pictures of the Global Week of Action are online:

<http://www.msfaccess.org/our-work/hiv-aids/article/1755>

The Stop AIDS Campaign is an initiative of the UK Consortium on AIDS and International Development.

What can you do

Sign on to MSF initiated letter to Commissioner De Gucht, DG Trade:

https://action.msf.org/en_CH

Video demonstrations

London

<http://www.flickr.com/photos/stopaidscampaignactivism/sets/72157629201133095/>

India

<http://www.facebook.com/media/set/?set=a.329076807136539.88526.144687138908841&type=1>

Nepal

<http://www.facebook.com/media/set/?set=a.329076807136539.88526.144687138908841&type=1>

France

<http://www.actupparis.org/spip.php?article4754>

South Africa

<http://www.msf.org.za/event/picket-against-fta-threats-indian-generics-johannesburg>

Malaysia

<http://www.facebook.com/notes/stop-the-eu-india-free-trade-agreement/malaysian-groups-will-protest-tomorrow-at-eu-office-in-kuala-lumpur/381058168586572>

Report shown on Sky News

<http://news.sky.com/home/world-news/article/16169181>

Why global health activists are fired up about Novartis

Brook K. Baker, Health GAP

On 22 February 2012, the eve of the Swiss pharmaceutical company's annual shareholders meeting in Berne, Switzerland, 50 AIDS activists, students, and community group members protested at Novartis's Institute for BioMedical Research in Cambridge, Massachusetts.

The protest was part of a global day of action drawing attention to the pharma giant's pending lawsuit against cancer patients and the government of India, aiming to reinterpret India's strict patent standards.

Novartis is seeking to establish a binding court precedent that will make it much easier to obtain overlapping and successive patents on minor variations to existing medicines – a precedent that will increase the number of patents on medicines and extend the length of patent monopolies, thereby limiting and delaying generic competition. In the absence of generic competition, Novartis and other “Big Pharma” companies will be able to set prices affordable to elites, but unaffordable to the broad mass of poor people in India. Because India is the “pharmacy of the developing world,” Novartis's case threatens affordable global access to all categories of life-saving and health-enhancing medicines.

Indian generic companies manufacture 80 percent of the antiretrovirals used to treat people living with HIV/AIDS around the world. Although the manufacturing of existing AIDS and other medicines is not threatened specifically by this court case, the threat with respect to newer and future medicines is very real. With more frequent and longer patent monopolies, poor people and poor governments will be priced out of access for many, many years.

Background of the case

This court case is part of a long series of legal actions by Novartis designed to eviscerate India's lawful efforts to restrict the widespread practice of “ever-greening” by pharmaceutical companies. In these instances, pharmaceutical companies seek new or additional 20-year patent monopolies for minor changes to existing medicines and chemical entities based on those minor changes.

In the present case, scientists had invented a basic compound imatinib, which is used to treat certain cancers. It was first patented globally in 1993, but not in India. Thereafter, researchers at Novartis tweaked the basic compound, resulting in a 30 percent improvement in the drug's absorption into the body. This revised active pharmaceutical ingredient became the basis of a powerful anti-cancer medicine called Gleevec in the U.S. and Glivec in India. In 1998, Novartis filed a patent application on the revised drug in the India Patents Office and in many other countries.

Although the Gleevec/Glivec patent was granted in 40-plus countries that had relatively weak patent standards, the patent was denied in India for three simple reasons:

1. Prior to 2005, India (like many countries before it) did not grant patents on medicines at all. Although the 1994 World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) forced India to start granting patents on medicines in 2005, TRIPS did not require India to retroactively grant patents on medicines invented before 1995.
2. India enacted Section 3(d) of its patent law, a so-called exclusion that does not ordinarily allow patenting of variations, new uses, new combinations, and new formulations of preexisting chemical entities.
3. India incorporated a narrow exception to the no-patent-for-variations rule if, but only if, a patent applicant could demonstrate that changes to an existing substance actually showed significantly increased efficacy – which the Indian courts decided does not include changes in absorption, among other things.

Novartis continues to take action to reverse the patent office's denial of its patent application, and allow section 3(d) to be reinterpreted to allow routine “ever-greening” of minor modifications to existing medicines based on a minimal showing of any positive effect.

Global protests

Demonstrators in Cambridge tried to deliver a Silver Urn (for the ashes of people who would die if Novartis's court challenge is successful) to Novartis officials, but they were barred from the building and ordered off the premises by Cambridge police. Demonstrators in Washington, DC, delivered an "indictment" against Novartis's CEO, and protesters in New York City "occupied" Novartis offices. Organised by Health GAP, Student Global AIDS Campaign, Occupy Boston Health Justice Group, these protesters and others were joined by a larger group of protesters at the Novartis annual general meeting in Basel. There, activists from Act Up Paris, Act Up Basel, Médicines Sans Frontières, Oxfam, the Berne Declaration and others showed videos and interacted with shareholders, many of whom were sympathetic to the campaigners' protests against Novartis's lawsuit.

Novartis's reaction

In response to the protests, Novartis issued a statement to Pharmalot: "We believe that working through the judicial system is the legitimate and appropriate approach to gaining clarity on the unique aspects of India's patent law We disagree with assertions ... that access to medicines is threatened by our case. The basis of this argument is false and very misleading. Currently available generic drugs launched in India before 2005 – including HIV/AIDS medicines and generic versions of Glivec – will continue to be available under a grandfather clause in the Indian patent law regardless of the legal outcome of our case. All pharmaceutical products, including HIV/AIDS medications, have been patentable in India under the existing patent law since 2005, and some have been patented."

This defense is patently evasive – the part truth that tells a lie. Yes, there is some degree of grandfathering, even for Glivec; yes, since 2005, India has patented some medicines. However, India has tried to limit patent monopolies, to address public health needs, and to ensure access to medicines within the bounds of the TRIPS Agreement. Novartis's statement ignores that is trying to erase those legislative efforts, hiding behind the fig leaf of seeking "clarity."

Source: Baker BK. Why global health activists are fired up about Novartis. Web blog 27 February 2012).

<http://sciencespeaksblog.org/2012/02/27/why-global-health-activists-are-fired-up-about-novartis/>

Obama's global, domestic & HIV research budget backslides on existing commitments

TAG press release

On 14 February, the US activist organisation TAG issued a press release, summarised below, that criticised President Obama's recent budget and policy announcements.

Treatment Action Group (TAG) is deeply disappointed by President Obama's proposed cuts to PEPFAR (President's Emergency Plan for AIDS Relief) and bilateral TB funds, freezing of NIH (National Institutes of Health) research as well as the insufficient attention to the worsening domestic AIDS crisis in the administration's fiscal year 2013 budget plan. "Why does President Obama want to turn his back on the most effective, life-saving global health and development program in history?" said Mark Harrington, Executive Director of TAG,

Since 2003, PEPFAR has been the most efficient and effective U.S. global health initiative ever. [...] Now, in a stunning reversal, President Barack Obama has proposed an incomprehensible cut of over a half billion dollars — nearly 13% decrease of \$543 million — in what can only be interpreted as a clear signal that the President may allow PEPFAR to expire when its current authorisation ends next year.

While Administration officials may argue that these cuts will be partly offset by program efficiencies, lower drug prices, and the proposed increase in U.S. support to the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) — which TAG supports — the reality is that U.S. support alone cannot reverse the deep effects of the broken promises of the G-20 and the other Global Fund donors. By cutting the PEPFAR budget, over half a million people will be denied life saving HIV treatment, and countless new HIV and TB/HIV infections will occur that could have been averted.

"For the first time since he entered office, President Obama also proposed a flat budget for the National Institutes of Health (NIH) — undermining our ability to translate scientific advances into cures, and jeopardising [the US] long term status as the global leader in health research. President Obama would have turned back the clock on the search for an AIDS cure, and better treatments for Hepatitis C and TB." said TAG's Director of Communication and Advocacy, Lei Chou.

Furthermore, the Administration's 2013 proposal continued an unbroken string of insufficient support for U.S. Centers for Disease Control and Prevention's (CDC) work to fight the two leading killers of people with HIV — tuberculosis and viral hepatitis. [...] The \$67 million increase for ADAP (AIDS Drug Assistance Programme) will not come close to meeting the increasing demand [...] for the most marginalised amongst us.

Source: TAG press release, (16 February 2012).

<http://www.treatmentactiongroup.org/press>

See also: Cohen J. Global health advocates aren't impressed with budget plan. Science (14 February 2012).

<http://news.sciencemag.org/scienceinsider/2012/02/global-health-advocates-arent.html>

President's budget request reflects strong commitment on global AIDS

<http://blog.aids.gov/2012/02/presidents-budget-request-reflects-strong-commitment-on-global-aids.html>

SIDE EFFECTS

FDA reject capsaicin patch for HIV-related neuropathy

Simon Collins, HIV i-Base

On 9 February the Advisory Committee to the US FDA rejected by a vote of 12-0 an application for a capsaicin skin patch (NGX-4010, Qutenza) for an indication of HIV-related pain based on proven efficacy. They also voted 11-0 that data the benefits did not outweigh the risks, with the community representative abstaining. [1]

The patch was approved by the FDA in November 2009 for post herpetic neuralgia (PHN) [2] and by the European Medicines Agency (EMA) in May 2009 for treatment of peripheral neuropathic pain in non-diabetic adults, either alone or in combination with other medicinal products for pain [3].

The active ingredient in the patch comes from hot chili peppers and it has been previously approved to relieve pain from shingles. The mechanism for reducing pain comes from a prolonged desensitisation to any local pain following this acute attack on the nerve in the damage area. Lidocaine cream is required to the affected area prior to the application to reduce pain from capsaicin.

The decision was based on 12-week results from two randomised, double-blinded, controlled phase III studies, in people with moderate to severe symptomatic HIV-related PN (total n~800), one of which has been published in JAIDS. [4]

Patients were randomised to either an 8% capsaicin patch, or a low-dose (0.04%) capsaicin control patch. The patches were applied for either 30, 60, or 90 minutes in one trial and either 30 or 60 minutes in the other trial.

The primary endpoint in both was a change in average pain for 24 hours.

The studies showed no relationship between dose or duration of exposure and impact on reducing pain. This may have been related to the study design where the control patch was designed to mimic the burning sensation of the active patch and use of other pain medication by participants.

There were no new safety concerns.

C O M M E N T

Because Qutenza has EU approval this decision by the FDA was reported to highlight the different interpretation of similar data.

A recent systematic review of randomised, controlled studies concluded that evidence of efficacy in the treatment of neuropathic pain associated with HIV-PN exists only for the Capsaicin 8% Patch, smoked cannabis, and subcutaneous recombinant human nerve growth factor (rhNGF). [5]

Up to four patches may be applied at one time, but this can only be repeated after 3 months.

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TREATMENT GUIDELINES

US HHS adult treatment guidelines updated (March 2012)

Updated US guidelines from the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents are available online.

Key additions and revisions to the guidelines include:

- New section on HIV and the older patient

Effective antiretroviral therapy (ART) has led to greater longevity in HIV-infected individuals resulting in an increasing number of older individuals living with HIV infection. Compared with younger HIV-infected patients, older patients may have more comorbidities, which can complicate treatments of HIV and other diseases. This section focuses on HIV diagnosis and treatment considerations in the older HIV-infected patient.

- New table on cost of antiretroviral drugs

This new table lists the monthly average wholesale price (AWP) for U.S. Food and Drug Administration (FDA)-approved brand and generic antiretroviral (ARV) drugs, including fixed-dose combination products. (The AWP listed for an ARV may not represent the pharmacy acquisition price or the price paid by consumers for that drug.)

- Updated recommendations on initiation of antiretroviral therapy (ART) in treatment-naïve individuals

The changes are primarily based on increasing evidence showing the harmful impact of ongoing HIV replication on AIDS and non-AIDS disease progression. In addition, the updated recommendations reflect emerging data showing the benefit of effective ART in preventing secondary transmission of HIV. The updated section includes more in-depth discussion on the rationale for these recommendations and on the risks and benefits of long-term ART.

ART is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count: CD4 count <350 cells/mm³ (AI); CD4 count 350 to 500 cells/mm³ (AII); CD4 count >500 cells/mm³ (AIII).

Regardless of CD4 count, initiation of ART is strongly recommended for individuals with the following conditions: Pregnancy (AI), AIDS-defining illness (AI), HIV-associated nephropathy (HIVAN) (AII) and HIV/hepatitis B virus (HBV) coinfection (AII).

- Effective ART also has been shown to prevent transmission of HIV from an infected individual to a sexual partner. Therefore, ART should be offered to patients who are at risk of transmitting HIV to sexual partners (AI [heterosexuals] or AIII [other transmission risk groups]).
- Patients starting ART should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.
- Expanded discussion of use of hormonal contraceptives in HIV-infected women
This revised section includes an expanded discussion on the use of hormonal contraception in HIV-infected women. The discussion focuses on drug-drug interactions between combined oral contraceptives and ARV drugs as well as on recent data showing a possible association between hormonal contraceptive use and acquisition or transmission of HIV.
- Preliminary recommendations on coadministration of the newly approved hepatitis C virus (HCV) NS3/4A protease inhibitors (PIs) boceprevir and telaprevir
- Recommendations on “when to start” ART in HIV-infected individuals diagnosed with tuberculosis but not receiving ART
- Discussion of the role of effective ART in preventing HIV transmission

Ref: Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (March 2012)

http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/?utm_source=At-a-Glance&utm_medium=e-mail&utm_campaign=Adult%2BGuidelines%2B1

C O M M E N T

It is always particularly helpful that these guidelines clearly highlight all changes in the text from the previous edition.

There are several notable differences compared to the UK BHIVA guidelines (March 2012 draft).

This includes the new US section on HIV and ageing, with age >50 years being an independent factor for starting treatment. Although UK guidelines included this recommendation in 2008 it has been dropped from the 2012 draft.

Also, for starting treatment at higher CD4 counts (at 500 compared to 350) with the US also having a stronger indication for starting at higher than 500, with no CD4 exclusion criteria. This last difference is not based on new evidence about the short-term risk of disease progression, AIDS events or mortality from randomised studies - this will come from the ongoing START study - but from accumulating concerns about uncontrolled viraemia and its impact on immune inflammation, and also on the benefit of ARV treatment to reduce further transmission.

The latest BHIVA guideline were released in draft format last month for comment and are still online while the final version is in press.

<http://www.bhiva.org>

DRUG INTERACTIONS

FDA warning of drug interactions between boceprevir and some HIV protease inhibitors

The US FDA have notified health care professional and patients that drug interactions between boceprevir and certain ritonavir-boosted HIV protease inhibitors (atazanavir, lopinavir and darunavir) can significantly reduce the effectiveness of these drugs when used together. [1]

Merck, the manufacturer's of boceprevir also issued a drug warning giving the pharmacokinetic data and the recommendation that "coadministering boceprevir and ritonavir-boosted PIs is not recommended". [2]

Source: FDA list serve

References:

1. FDA warning. Victrelis (boceprevir) and ritonavir-boosted Human Immunodeficiency Virus (HIV) protease inhibitor drugs: drug safety communication - drug interactions, (9 February 2012).
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm291144.htm>
2. Merck. Dear Healthcare Professional letter. Results of pharmacokinetic study in healthy volunteers given VICTRELIS (boceprevir) and ritonavir-boosted HIV protease inhibitors may indicate clinically significant drug interactions for patients coinfecting with chronic hepatitis C and HIV. (6 February 2012).
http://www.merck.com/newsroom/pdf/FINAL_DHCP_2_6_2012.pdf

BOOK OFFER

Free comic book for HIV positive children about CD4, viral load and ARV treatment

A booklet by designed specifically to explain HIV and HIV treatment to children.

The booklet is produced by Medikidz and HIV is one of many health issues in a series.

A low resolution copy can be viewed online.

<https://www.yousendit.com/download/M3BuYkJoZEt6RTIBSXRvag>

i-Base have a limited number free copies of this booklet for HIV positive children. If you would like us to send you one please contact Rebecca McDowall at i-Base:

subscriptions@i-Base.org.uk

ON THE WEB

Free full text online articles:

PLoS Medicine

The following HIV related papers were published in PLoS Medicine, Volume 9(3) March 2012

CD4 Cell Count and the Risk of AIDS or Death in HIV-Infected Adults on Combination Antiretroviral Therapy with a Suppressed Viral Load: A Longitudinal Cohort Study from COHERE. Young J et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001194>

The European COHERE cohort shows that in successfully treated patients the risk of a new AIDS event or death follows a CD4 cell count gradient in patients with viral suppression.

No Treatment versus 24 or 60 Weeks of antiretroviral treatment during primary HIV infection: The randomized Primo-SHM Trial.

Grijzen ML et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001196>

This study of approximately 170 people diagnosed in primary HIV infection randomised participants to immediate treatment for either 24 or 60 weeks or to now treatment, finding that both treatment arms resulted in significantly longer time until treatment was started or restarted.

The Evolving Landscape of the Economics of HIV Treatment and Prevention. Nosyk B et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001174>

The cost-effectiveness of HAART roll out has been significantly underestimated because economic analyses do not account for the beneficial impact of HAART on HIV transmission.

FUTURE MEETINGS

Conference listing 2012

The following listing covers some of the most important upcoming HIV-related meetings and workshops.

Registration details, including for community and community press are included on the relevant websites.

13th Intl Workshop on Clinical Pharmacology of HIV Therapy

16–18 April 2012, Barcelona

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

47th European Liver Conference (EASL)

16–18 April 2012, Barcelona

<http://www.easl.eu>

18th Annual BHIVA Conference

17–20 April 2012, Birmingham

<http://www.bhiva.org>

20th Intl HIV Drug Resistance Workshop

9–13 June 2012, venue tbc

<http://www.informedhorizons.com/resistance2012>

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

19–21 July 2012, Washington

<http://www.intmedpress.com/comorbidities>

7th Intl Workshop on HIV Transmission

19–20 July 2012, Washington

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

4th Intl Workshop on HIV Paediatrics

20–21 July 2012, Washington

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

Towards a Cure: IAS pre-conference symposium

20–21 July 2012, Washington

<http://www.iasociety.org/Default.aspx?pageld=606>

19th IAS World AIDS Conference

22–25 July 2012, Washington

<http://www.aids2012.org>

3rd Intl Workshop on HIV and Ageing

5–6 November 2012, Baltimore, USA.

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

11th Intl Congress on Drug Therapy in HIV

11–15 November 2012, Glasgow

<http://www.hiv11.com>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

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

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

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

Publications and regular subscriptions can be ordered online.

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

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

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

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

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

Non-technical treatment guides

i-Base treatment guides

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

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

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

Publications and reports

HIV Treatment Bulletin (HTB)

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

HTB South

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

HTB Turkey

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

ARV4IDUs

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

Why we must provide HIV treatment information

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

Translations of i-Base publications

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 35 languages. Information to support this is available on the i-Base website.

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

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

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

Languages include:

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

Advocacy resources

Online treatment training for advocates

<http://i-base.info/tffa>

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

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

UK CAB: reports and presentations

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

<http://www.ukcab.net>

Phoneline and information services

Treatment information request service - 0808 800 6013

i-Base runs a specialised treatment information service.

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

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

Online Q&A service

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

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

Recent questions include:

- Can I buy my HIV medication online?
- Does taking steroids cause drug interactions with my meds?,
- My CD4 is 9, on Kaletra with diarrhea, wasting and sleeplessness
- I have HIV and Hep B. I'm very tired, should I be worried?
- What is an undetectable viral load?
- Somebody at work had TB - am I at risk?
- Can I try to conceive on efavirenz and Truvada?
- I'm HIV+, can I still drink beer?
- Are there any updates on cure research?
- Will diet and exercise increase my CD4 count?
- Will my CD4 count drop after I give birth?
- My baby is quite small, should I be worried?
- Should I start taking statins?

- I started treatment at a high CD4 - will I live longer?
- Can I take Venteze (salbutamol) with my ARVs?
- How bad is it to have diabetes and HIV together?
- Can I feel better at work from Atripla side effects?
- Should I start treatment in seroconversion?
- Is a fast heartbeat on Atripla normal?

Other resources

Treatment 'Passports'

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

Generic clinic forms

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

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

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

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

Order publications and subscribe by post, fax or online

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

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

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

htb(e)

HIV TREATMENT BULLETIN (e)

HTB(e) is the electronic version of HTB, which is published six times a year by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered by fax or post using the form on the back page or directly from the i-Base website:

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

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

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

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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.

**However you chose to donate to i-Base,
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- Introduction to Combination Therapy (April 2012)
1 5 10 25 50 Other _____
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- HIV and your Quality of Life: Side Effects and other Complications (December 2010)
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- Guide To HIV and hepatitis C coinfection (March 2009)
1 5 10 25 50 Other _____
- Clinical Trials: a community guide to HIV research (March 2009)
1 5 10 25 50 Other _____

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

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