ISSN 1472-4863

hiv treatment bulletin (e)

htb(e): volume 2 number 3/4

march–april 2013

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Published by HIV i-Base

EDITORIAL

At with every year, CROI 2013 had so much to report that this will be spread over two issues of HTB.

This year's big story in mainstream media – picked up by reporters worldwide (and provoking some sensationalist journalism) - was the news of a functional cure in an HIV infected infant. We include Richard Jeffreys' elegant analysis of this case report. We hope that the attention this child has been given will lead to further steps in cure research as well as improvements in the implementation of maternal/ infant programmes where transmission is a risk.

Developments in pipeline drugs were presented at the conference, including for dolutegravir and tenofovir alafenamide (TAF, GS-7340), which might offer improved antiretroviral options in the not to distant future. With low milligram doses both also have the potential for low cost. MK-1439 and cenicriviroc are covered, as well as long-acting formulations of rilpivirine, GSK-744 and novel nanoformulations. Important data for GSK-744 showed two intramuscular doses, a month apart, protected rhesus macaques after repeat HIV exposure compared to placebo. Monthly injections have the potential to overcome the adherence obstacles associated with oral PrEP, seen in the VOICE trial, also reported in this issue.

Functionally cured infant aside, there was an abundance of other paediatric data. The completed ARROW trial, conducted in Uganda and Zimbabwe, in collaboration with the UK MRC has produced a rich set of data to help guide children's treatment, particularly in resource limited settings. The development of lopinavir/ritonavir for infants and young children continues and other presentations add to what we know about new and older antiretrovirals for children.

The conference had a generous focus on TB. Nathan Geffen covers the much-anticipated RIFAQUIN trial of moxifloxacin and rifapentine. This regimen is notably taken only once a week in the continuation phase compared to the daily dosing required for standard of care. Also for TB was a study showing that combining two tests improves diagnostic sensibility.

And a study on cryptococcal meningitis showed deferring ART by six weeks reduces mortality compared to immediate treatment – in contrast to TB and most other opportunistic infections.

Other non-CROI news includes a positive EU opinion for Stribild (an FDC formerly known as Quad), a detailed look at the question "When to start?", the updated US guidelines (starting earlier) and an increase in the sample size of the START trial (that will finally answer this critical question).

HTB supplements

Two of the i-Base treatment guide have been updated and are included as supplements to this issue of HTB.

- HIV, Pregnancy and Women's Health (March 2013)
- Introduction to Combination Therapy (April 2013)

Both are already online and are available free, including in bulk to UK clinics. Please order online in the regular way.

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

CONFERENCE REPORTS

20th Conference on Retroviruses and Opportunistic Infections (CROI)

3-6 March 2013, Atlanta

Introduction

The annual CROI continues to be the most important HIV scientific meeting covering the diversity of basic and clinical science.

Also, both the main conference and a pre-meeting programme of lectures for new investigators are promptly posted online as open access webcasts.

http://www.retroconference.org

This year the meeting resulted in wide press coverage of the case of a baby who appears functionally cured following 18 months treatment initiated within two days of birth. But the conference included a wealth of other studies covering HIV treatment and prevention. This included studies reporting new drugs, new strategies (especially treatment during early infection), paediatrics, TB and other OIs - principally in resource limited settings - and exciting results for hepatitis C coinfection.

Reports in this issue of HTB include:

- ARV pipeline: dolutegravir, TAF (GS-7340), MK-1439 and cenicriviroc
- ARV pipeline: long-acting formulations - rilpivirine, GSK-744 and nanoformulations

- Five-year results from the AntiRetroviral Research for Watoto (ARROW) Trial
- Comparison of ritonavir-boosted lopinavir or NNRTI ART and PK with antimalarials in Ugandan children
- Pharmacokinetics and acceptability of lopinavir/ritonavir sprinkles in children aged 1 to 4 years
- Pharmacokinetics of currently available antiretroviral options for young children
- Safety of transplacental raltegravir in neonates and washout pharmacokinetics
- Tenofovir use in children
- ddI resistance in South African children failing an abacavir or d4T based first-line regimens
- Statin use in HIV positive people
- RIFAQUIN study demonstrates once-weekly dosing during continuation phase of TB treatment
- Combining Xpert and LAM urine testing improves TB diagnostic sensitivity
- Deferring ART by four weeks reduces mortality in patients diagnosed with cryptococcal meningitis
- Tenofovir DF ring protects macaques from vaginal exposure
- Monthly injection protects macaques from rectal exposure: results should fast-track human studies for advanced PrEP options
- VOICE study reports low adherence as reason for lack of efficacy for PrEP: anal sex common in African heterosexuals
- Further studies on how male circumcision may reduce HIV transmission
- Report of a functional cure in an HIV infected infant

Further reports will be continue in the next issue of HTB, with pre-press articles available earlier online.

Unless stated otherwise, references are to the Programme and Abstracts of the 20th Conference on Retroviruses and Opportunistic Infections (CROI), 3-6 March 2013, Atlanta.

http://www.retroconference.org

CROI 2013: ANTIRETROVIRALS

ARV pipeline: dolutegravir, TAF (GS-7340), MK-1439 and cenicriviroc

Simon Collins, HIV i-Base

Promising compounds for new treatments that were discussed at CROI 2013 included the integrase inhibitor dolutegravir, a new version of tenofovir, a new NNRTI, a new CCR5 inhibitor and several long-acting formulations.

Dolutegravir

With two phase 3 studies completed, dolutegravir has already been submitted for regulatory assessment in both Europe and the US. As a once-daily drug with a low milligram dose and no requirement for boosting, dolutegravir may have advantages over other integrase inhibitors (INSTIs) including raltegravir and the recently approved elvitegravir (as a component of Quad/Stribild).

Interim 24 weeks results were presented from the ongoing international phase 3 SAILING study in 715 treatment-experienced (integrase-naive) patients randomised to either 50 mg dolutegravir once-daily or 400 mg raltegravir twice-daily, each plus matching placebo. Patients could use an additional two investigator-selected ARVs, at least one of which had to be fully sensitive. The background combinations were generally robust (PI/r plus tenofovir 40%, lopinavir/r only 10%, darunavir/r plus etravrine 10%).

At baseline, median CD4 count and viral load were approximately 200 cells/mm3 and 15,000 copies/mL, respectively, with approximately half of participants having resistance to three or more classes and a median six years prior ART. Approximately 30% were women, 50% white and 40% African American and 15% had HIV/HCV coinfection.

At week 24, the dolutegravir arm had greater viral suppression compared to raltegravir (79% vs 70% with VL <50 copies/mL; difference 9.7% [95%CI: +3.4, +15.9], p=0.003). However, this was in an analysis that adjusted for baseline viral load, phenotype sensitivity and use of darunavir without PI mutations. The differences were based on fewer discontinuations in the dolutegravir arm (14% vs 17%) and lower rates of virological failure (4% vs 7%). Side effects were broadly similar with few treatment discontinuations in each arm.

In patients with hepatitis B or C coinfection, IRIS-related liver complications were reported more frequently in the patients using dolutegravir (6 vs 3 patients).

The primary endpoint for the study will be results at week 48.

A second late-breaker poster reported that CSF levels of dolutegravir were similar to the unbound fraction in plasma and that this was above the IC50 for wild-type virus (0.2 ng/mL) indicating likely therapeutic levels. This was an open label, single arm intensive PK study in 13 men receiving doultegravir with abacavir/3TC. [2]

Baseline viral load in CSF and plasma were 3.64 and 4.73 log copies/mL, with 12/13 men achieving undetectable levels at week 16 (using <2 c/mL and <50 c/mL cut-off tests for CSF and plasma respectively). Levels the patients with detectable levels were 5 c/mL and 77 c/mL respectively.

A lack of interaction between dolutegravir and either methadone or combined oral contraceptives (ethinyl estradiol 0.035 mg and norgestimate 0.25 mg) was also reported in a poster showing two drug interaction studies in HIV negative volunteers. [3]

Tenofovir alafenamide (TAF, GS-7340)

Several studies were presented on a new prodrug of tenofovir that was previously in development as GS-7340 and now has the generic compound name tenofovir alafenamide (abbreviated to TAF). At a 25 mg dose, TAF results in 7-fold greater intracellular levels of tenofovir with 90% lower plasma levels, compared to 300 mg formulation of tenofovir disoproxil fumerate (TDF).

Early clinical data on TAF compared to TDF in treatment-naive patients was shown in a late breaker oral presentation. Both formulations were included in single tablet, four-drug combinations with elvitegravir, cobicistat and FTC. [4]

This is an ongoing, double-blind phase 2 study in 170 patients randomised 2:1 to TAF or TDF formulations respectively. The 4-drug combination uses a 10 mg TAF dose as cobicistat boosts TAF by 2.4-fold.

This was a largely male (97%), white (67%) group in early infection. Baseline CD4 and viral load were approximately 400 cells/mm3 (15% were <200) and 40,000 copies/mL (17-28% were >100,000 copies/mL), respectively. Entry criteria included eGFR >70 mL/min, with median baseline levels at 115 mL/min, as with previous studies using cobicistat and tenofovir.

For the primary endpoint of virological suppression at 24 weeks, 87% vs 90% in the TAF vs TDF arms had viral load <50 copies/mL (weighted difference: -4.9%, 95%CI -15.7, +5.9, p=0.36). CD4 increases were similar (+163 vs +177 cells/mm3).

With efficacy expected to be high, the focus on side effects showed similar short-term results. The five side effects occurring in ≥10% of patients were: nausea (18% vs 12%), diarrhea (12% vs 12%), fatigue (12% vs 9%), headache (10% vs 10%), and upper respiratory tract infection (7% vs12%); any grade, TAF vs TDF.

Both arms had an increase in serum creatinine and reduction in eGFR related to use of cobicistat. These occurred by week 2 but then stablised to week 24, and were greater with TDF (–4.9 mL/min vs –11.8 mL/min, p = 0.032).

Mean (+/-SD) bone mineral density (BMD) was reduced less in the TAF arm for both spine [–0.8 (+/-3.4) vs –2.5 (2.5], p = 0.002 and hip [–0.3 (+/-1.8) vs –2.0 (+/-2.7)], p <0.001.

There were no cases of proximal renal tubulopathy or discontinuations for renal events.

MK-1439 – a new NNRTI

First efficacy and safety data in HIV positive people were presented for a new NNRTI with the development name MK-1439 (from Merck) that has in vitro activity against common NNRTI drug resistant mutations (K103N, Y181C and G190A). [5]

This was a double-blind, placebo controlled, single-site, phase Ib study in 18 treatment-naive men randomised (1:1:1) to 25 mg (n=6), 200 mg (n=6) or placebo (n=3 for each placebo), taken once-daily for seven days as monotherapy. All participants started standard ART from day eight for 10 days to minimise risk of drug resistance during the washout phase.

Mean viral load reductions (90%CI) compared to placebo of –1.37 (–1.60, –1.14) and –1.26 (–1.51, –1.02) log copies/mL in the 25 and 200 mg arms, respectively, with non-significant differences between active doses at all time points.

A total of 21 non-serious side effects were reported in 13/18 participants, including headache (n=5), nausea (n=2), common cold (n=2) and sore throat (n=2). Night sweats, headache (at 200 mg) and loss of appetite (at 25 mg) were considered possibly related to MK-1439. The single serious event was a increase in LFT in one patient on day 7, judged related to acute HCV infection between screening and study entry.

Pharmacokinetic results were similar to those seen in HIV negative studies, with mean concentrations at 24 hours post dose that were 14-fold (25 mg dose) and 87-fold (200 mg dose) higher than the adjusted IC95 for wild-type virus (19 nM, in 50% serum).

Results from a phase 1a safety study in HIV negative people including multiple doses up to 750 mg for ten days were presented as a separate poster, reported a lack of significant interactions with or without food, and that at steady-state, a 12 mg dose produced 24-hour post dose drug levels that remained above the adjusted IC95 for wild-type virus. [6] Other phase 1 studies in 140 HIV negative individuals included 14 young women and 12 elderly women, without reports of clinically relevant side effects, including rash or CNS events.

Phase 2b studies continue using 25, 50, 100 and 200 mg doses.

Cenicriviroc

A late-breaker oral presentation of 24-week primary endpoint results from a randomised, double-blind, double placebo, phase 2b of the CCR5/CCR2 inhibitor cenicriviroc in 143 treatment-naive patients, was presented by Joseph Gathe. [7]

This compound has been in development in various formulations by Tobira for several years (previously as TBR-652). The current study used a 50 mg formulation and randomised patients 2:2:1 to either 100 mg or 200 mg cenicriviroc compared to efavirenz 600 mg, all with matching placebo and plus open label tenofovir/FTC. This was a twice-daily combination with a requirement for cenicriviroc/placebo to be taken as a morning dose following breakfast and efavirenz/placebo to be taken at night.

Baseline characteristics included approximate baseline CD4 and viral load of 400 cells/mm3 (range 77-1090) and 25-40,000 copies/mL (14-25% >100,000), respectively. The study was 94% male; 62% Caucasian, 32% African American; 24% Hispanic. Mean age was 36 (range 19-63)

At week 24, viral suppression to <50 copies/mL (ITT analysis, snapshot algorithm) was achieved by 76% and 73% vs 71% of patients in the 100 mg and 200 mg vs efavrienz arms respectively. Virologic non-response was higher in the cenicrivoc arms (12% and 14% vs 4% efavirenz). Cenicriviroc arms appeared less effective compared to efavirenz in the small percentage of patients with baseline viral load >100,000 copies/mL (50% and 60% vs 75%) although discontinuations due to non-response were similar (20% and 29% vs 25%). In the results stratified by baseline viral load, a range of non-responders due to lack of virologic data at week 24 related to early discontinuation (from 0% with efavirenz at >100,000 to 29% with efavirenz at <100,000), complicated the interpretations of these results.

Better viral responses were reported with highest quartile (141-400 ng/mL) of modeled Cmin trough concentrations of cenicriviroc (100%) with 12%, 9%, and 17% non responders in Q3 (70-141 ng/mL), Q2 40-71 ng/mL) and Q1 13-40 ng/mL), respectively, showing a wide range of interpatient variability.

CD4 changes from baseline were similar (+147 and +170 vs +135 cells/mm3).

Discontinuation related to side effects was significantly more frequent with efavirenz (0% and 2% vs 18%) as were grade 3 events (2% and 4% vs 11%). There were no grade 4 events, serious events or deaths in the study.

Laboratory abnormalities were higher in the 200 mg arm, principally increased creatinine phosphokinase, but these generally resolved without treatment discontinuation.

Resistance mutations in patients with viral load rebounding to >400 copies/mL were predominantly M814V/I in 5 patients taking cenicriviroc (vs 0% in the efavirenz arm).

The impact of CCR2 blocking on the monocyte activation pathways was seen by dose related increases in the CCR2 ligand MCP-1 of approximately 450 ng/L in the 100 mg arm and 750 ng/L in the 200 mg arm. Both cenicriviroc arms also reported a reduction in levels of the monocyte activation marker of soluble CD14 of -0.2 vs +1.3 x 10(6) pg/mL in the efavirenz group. Soluble CD14 has been associated with an increased risk of all-cause mortality independent of CD4 and viral load and this potential was highlighted in the conclusion as a property of cenicriviroc that warranted additional research.

A new formulation of cenicriviroc will be used for phase 3 studies although the dose for fuuture research has still to be decided. The company intends to coformulate cenicriviroc with other ARVs although this is currently only at a preliminary planning stage.

Other studies.... news on maturation inhibitors

Studies on long acting parental and nanoformulations are reported below in a separate article, [8] but an oral presentation included in vitro data on maturation inhibitor showing that this potential drug class remains a focus for ongoing research. [9]

Maturation inhibitors target the final stage of HIV gag processing that inhibit release of fully formed capsid, with early studies focused on the compound beviramat (as PA-457). This was of most interest for drug-resistant HIV, with viral load reductions of approximately –1.2 log in treatment responders, but that common polymorphisms at baseline, principally V370A, present in 50% of patients, correlated with non-response. Although early phase 1/2 studies raised no safety concerns, the development of beviramat was discontinued in June 2010 (by Myriad who had bought the compound from Panacos).

The study at CROI provided in vitro data on second-generation maturation inhibitor molecules developed to overcome V370A. Results were presented by Carl Wild from DFH Pharma (who was previously involved with the Panacos team) and the group collaborated with researchers at the US National Cancer Institute.

The IC50 for DFH-055 had similar activity at (0.032 uM) to wild type and V370A (compared to <0.08 and >32.0 uM for wild-type and V370 respectively for beviramat). Current best compounds (DFH-068 and DFH-070) further improved on activity against V370A with 5-fold greater sensitivity compared to DFH-055 at 30.1 and 38.3 nM, respectively. Although these results are encouraging the presenter was cautious in not announcing whether either molecule had been selected as a lead compound for further development.

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ARV pipeline: long-acting ARVs - rilpivirine, GSK-744 and nanoformulations

Simon Collins, HIV i-Base

A useful poster discussion focused on long-acting (LA) formulations that are in early stages of development, some of which appear to be prioritised for use for prevention rather than treatment. [1]

This session included an introduction by Marta Boffito from the Chelsea and Westminster Hospital in London. [2]

Current ARVs with long acting formulations include a monthly intramuscular (IM) injection of rilpivirine LA and injectable formulations of the integrase inhibitor GSK744 (both IM and sub-cutaneous) where therapeutic drug levels are sustained for well over a month. The monoclonal antibody ibalizumab that has been in development for many years as a potential entry inhibitor to overcome drug resistant HIV is based on intravenous delivery every 2-4 weeks.

Understanding the pharmacokinetics of these formulations in plasma and tissue and interpatient variability are essential when they are being developed for PrEP. When used as treatment, potential advantages include improved adherence (from dramatically fewer doses linked to long half-lives), reduced potential for drug interactions related to first-pass metabolism, reduced GI toxicity, reduced renal, hepatic and other toxicity due to lower doses. Many nanoformulations also require lower formulation doses, resulting in higher target cell concentrations and the potential to reduce costs in resource limited settings where the active pharmaceutical compound accounts for a significantly greater proportion of the total production costs. [3]

Pharmacokinetic profiles of long acting compared to oral formulations often include a longer time to maximum concentration (Tmax can be several days rather than hours) and a longer time with concentrations close to the Tmax (days or weeks rather than hours). This may raise different toxicity concerns to oral dosing but also suggests efficacy targets may relate to Cmax rather than Cmin levels. Drug levels are steadier, with fewer fluctuating peaks and troughs associated with most oral drugs and this may also alter drug target levels, and whether these will be in plasma or tissue.

Unless an antidote is available to enable rapid clearance, oral lead in periods and strategies for treatment discontinuation are likely to important. As long as ART remains dependent on combination therapy, long acting individual drugs have the greatest potential as part of a long-acting combination, ideally co-formulated in a single injection.

In the first poster in this session, Pavan Puliguji form University of Nebraska presented results on an nanoformulation of atazanavir/ritonavir that in a mouse study resulted in ten-fold higher concentrations in plasma and tissue (ling, liver, kidney, spleen, lymph nodes and brain) and sustained for two weeks following a single intramuscular injection. [4]

A second poster from the same research group reported on properties of more advanced “small magnetite” (super-SMART) nanoformulation of atazanavir/ritonavir developed to target monocyte and macrophage cells. [5]

Early in vitro and rat results using a solid drug nanoformulation of efavirenz developed using a freeze-dry technique at Liverpool University was presented by Neill Liptrott. [6] This formulation produced a four-fold higher absorption, with a lower Cmax and similar Cmin, but using a two-fold lower dose compared to the standard oral formulation. The Liverpool group also has nanoformulations of lopinavir/ritonavir and both molecules have the potential for parenteral formulations. Production costs for this freeze-dry technique is minimal at $4-16 per kilo and pharmacokinetic and safety studies in HIV negative human volunteers are expected to start later in 2013.

Matching the PK exposures for long-acting ARVs are more complex than bioequivilence studies that are normally used for new formulations and the session was concluded by Kimberly Strumble from the US FDA with a summary of regulatory issues related to new nanoformulations of currently licensed ARVs.

Additional data on a very long acting formulation of an analogue of the integrase inhibitor dolutegravir (compound name GSK744) was presented in an oral late breaker. [7] Although this was in the setting of PrEP the compound is also in development for use in treatment. Viral load reductions of 2.0-2.5 log copies/mL were seen following ten days monotherapy using 5 mg and 30 mg doses of the oral formulation. Parenteral formulations are nanoparticle suspensions (both subcutaneous and intramuscular injections) that support monthly or possibly quarterly injections.

Importantly, for PrEP, two intramuscular doses one month apart protected all 8/8 rhesus macaques from multiple rectal exposure to SHIV compared 0/8 animals receiving placebo injections. These early results should drive fast-track research into whether this offers a similar protection in human studies, with the potential to overcome many of the practical difficulties associated with daily oral PrEP. See the later report in this issue of HTB for details of the PrEP study. [8]

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CROI 2013: PAEDIATRICS

Five-year results from the AntiRetroviral Research for Watoto (ARROW) Trial

Polly Clayden, HIV i-Base

Results from the ARROW Trial comparing routine and clinically driven monitoring in children were presented at CROI 2013. [1]

This trial also investigated stopping vs continuing cotrimoxazole in children on ART; a four-drug induction strategy for starting treatment; as well as and once- vs twice-daily 3TC and abacavir. [2, 3, 4] Results from these evaluations were also presented at the conference.

ARROW was an open-label parallel-group trial conducted in Ugandan and Zimbabwean children, aged 3 months to 17 years and eligible for ART.

Small difference between routine and clinical monitoring

Adeodata Kekitiinwa presented findings from the monitoring comparison in an oral presentation. These results were also published in the Lancet on 7 March 2013. [5] Overall, long-term survival on ART was high in ARROW at 95%. Routine CD4 monitoring provided clinical benefit after the first year of treatment but event rates were very low, with small absolute differences between monitoring strategies and no difference in adverse events.

The trial enrolled 1206 children who were randomised to either clinically driven monitoring or routine laboratory and clinical monitoring for toxicity (haematology and biochemistry).

Clinicians were given12-week results for children assigned to routine laboratory monitoring (n=600) but in the clinically driven monitoring arm (n=606), only had toxicity results returned if requested for clinical reasons or grade 4 toxicities. Children switched to second-line ART if they had new WHO stage 3 or 4 events or (routine laboratory monitoring only) age-dependent CD4 criteria. Primary endpoints were new WHO 4 events or death and grade 3/4 adverse events, with the intention to show non-inferiority for efficacy margin +1.6/100 patient years.

At baseline, children were a median age of 6 years (range 0.4-17). Approximately one third overall were 3 years or younger and half were girls. Their median CD4 percent was 12% and weight for age -2.2; the majority (56%) was WHO stage 3. Sixty-two percent of children received nevirapine as their NNRTI and the remainder received efavirenz.

Only 33 (0.3%) children were lost to follow up over median of 4 years (IQR 3.7-4.4) from 2007 to 2012 (total 4685 child years). Few clinical participants had external CD4 tests done privately (4/571 at trial exit) and clinicians remained blinded.

At the end of the trial 94% and 95% of children in the laboratory and clinical arms respectively were still on their first line regimens with low rates of substitutions (7.5% overall) – where this occurred it was usually to accommodate TB treatment or for toxicity.

Thirty-five (6%) and 28 (5%) children in the laboratory and clinical arms switched to second line treatment. This was due to CD4 in 28 children in the laboratory monitoring arm, and for clinical reasons in 7 vs 28 children in the laboratory and clinical arms respectively. A further, 3 and 16 children in the laboratory and clinical arms switched due to unexplained failure to thrive.

The rates of switching to second line was low overall: 1.2 with laboratory and with 1.5 clinical monitoring per 100 child years, p=0.22. At switch the median CD4 percent was similar, 7% and 8% in the laboratory and clinical arms respectively. Dr Kekitiinwa noted that monitoring weight gain appeared to avoid an excess of very low CD4 switches.

There were 39 (1.7 per 100 child years) vs 47 (2 per 100 child years) new WHO stage 4 events or deaths in the laboratory and clinical monitoring arms, HR (clinical: laboratory) 1.13 (95% CI 0.73-1.53), p=0.59. This gave an absolute difference of +0.3 per 100 child years (95% CI -0.5 to +1.1), which fell within the specified non-inferiority margin.

Most of these events occurred in the first year of ART: 33/39 and 24/47 in the laboratory and clinical monitoring arms respectively. In years 2-5 of ART the difference was significant, with respectively 6 (0.4 per 100 child years) vs 23 (1.3 per 100 child years) events. This gave an absolute difference of +1.0 per 100 child years (95% CI +0.4 to +1.6), p=0.002, which remained within the non-inferiority margin.

Survival was high overall with 96% and 95% in the laboratory and clinical monitoring arms alive at 4 years. After the first year there was an absolute difference of +0.6 per 100 child years (95% CI =0.2 to +1.0), p=0.009. Of the 14 children that died during this period 12 were > 8 years old at time of death.

There was no difference in change of absolute CD4 counts or percent between the two arms. Viral load suppression rates were tested retrospectively and were also similar across both arms. Suppression rates were higher among children receiving NNRTI containing regimens and did not differ by strategy.

Dr Kekitiinwa concluded that it is possible to deliver ART safely to children with good quality clinical care without the need for routine monitoring. She noted that monitoring weight gain could be an important indicator of first line failure. However she added that there might be a role for targeted CD4 monitoring from the second year of ART.

“Resources should be focused on getting as many children onto treatment as possible rather than providing routine laboratory monitoring to fewer on ART”, she said.

She also noted that ARROW analyses did not find routine laboratory monitoring cost effective. These data were shown in a separate poster authored by Paul Revill and colleagues from the trial group.[6]

Analyses restricted to 12-228 weeks from starting ART revealed mean total costs per child of $2068 (laboratory) and $1532 (clinical), driven by higher costs with laboratory monitoring ($679 vs $25), although these were slightly offset by lower hospitalisation costs ($105 vs $145). There was an incremental cost-effectiveness ratio per life-year gained of $595,870. In weeks 52-228, mean total costs and life-years were $1536 and 3.37 (laboratory) compared to $1131 and 3.34 (clinical), leading to an incremental cost-effectiveness ratio per life-year gained of $14,560.

Removing the toxicity monitoring tests from the evaluation gave incremental cost-effectiveness ratio per life-year gained of $356,500 and $3,121 in weeks 12-228 and 52-228 respectively. In weeks 52-228, in <3-, 3- to 6-, 7- to 11-, and >11-year-olds these values were $56,784, $19,242, $11,235, and $3,144 respectively.

Continuing cotrimoxazole with ART beneficial

An important sub-study of ARROW looked at continuing daily cotrimoxazole prophylaxis in children on ART. This study found benefit to continuing cotrimoxazole in children on ART for 96 weeks or more, with persisting reductions in hospitalisations for malaria and other infections across all ages and CD4 levels. [2]

Mutsa Bwakura-Dangarembizi showed these data in an oral presentation following the main trial results. She explained that DART showed the benefit of continuing with cotrimoxazole in adults in the first 18 months of ART but there are no data on discontinuation in children. Based on expert opinion the WHO recommends that children >5 years who are stable on ART for at least 6 months with CD4 >350 cells/mm3, may stop.

For this analysis, 758 children were randomised to stop (n=382) or continue (n=376) daily cotrimoxazole after median 2.1 years (IQR 1.8 to 2.2) years on ART. Eligible children were aged >3 years, on ART >96 weeks, currently on receiving cotrimoxazole, using insecticide-treated bed-nets if living in malaria endemic areas and had no previous pneumocystis pneumonia (PCP). Primary endpoints were hospitalisation or death and grade 3 or 4 adverse events. Secondary endpoints were malaria, pneumonia, and gains in weight, height, BMI and CD4.

At baseline children were a median age of approximately 8 years old with a median CD4 percent of 33%. Dr Bwakura-Dangarembizi noted that this was a substantial improvement compared to 12% when the children entered the trial pre-ART.

The study found children stopping contrimoxazole had higher rates of hospitalisation or death, HR 1.57 (95% CI 1.09 to 2.26), p=0.007. This effect did not vary by age, sex, centre, country or monitoring strategy. Benefits in continuing were greatest in children with the highest CD4 (≥ 30%), HR 2.15 (95% CI 1.30 to 3.54).

Mortality was low and similar in the two groups, 2/382 and 3/376 in the group that stopped and continued respectively. Increased hospitalisations in the stop group were for malaria (49 vs 2l), HR (stop:continue) 2.10 (95% CI 1.43 to 3.09), as well as non-malarial infections (53 vs 25), particularly pneumonia, sepsis, and meningitis.

Overall, grade 3/4 adverse events were similar HR 1.17 (95% CI 0.82 to 1.68), p = 0.39, but there were more grade 4 events in children stopping contrimoxazole, HR 2.03 (95% CI 0.98 to 4.18), p=0.05. This was mostly driven by differences in anaemia (12 stop vs 2 continue).

Changes in height-for-age and CD4 were similar between groups; there was a trend towards greater weight gain in the children that continued contrimoxazole.

Dr Bwakura-Dangarembizi concluded that continuing cotrimoxazole in children on ART for >96 weeks is beneficial, with persisting reductions in hospitalisations for malaria and other infections across all ages and CD4 levels. Based on these results the ARROW investigators recommend that the guidelines for cotrimoxazole should be updated. She stressed that healthcare systems and supply-chains will have to be strengthened to avoid stockouts.

Short-term benefits of induction strategy do not persist

A late breaker poster authored by Patricia Nahirya-Ntege and colleagues showed results from the induction strategy, which found short-term benefits of four-drug first-line ART do not persist with three-drug maintenance. [3]

This randomisation was simultaneous with that by monitoring strategy and was to a standard three-drug or four-drug induction first-line ART. All children received an NNRTI, abacavir and 3TC (Arm A received this regimen alone). The children receiving four-drug induction regimens also received AZT. At 36 weeks those on the four-drug regimen reduced treatment to either NNRTI, abacavir and 3TC (Arm B) or abacavir, 3TC and AZT (Arm C).

At the trial end, 371 (93%) Arm A vs 387 (96%) Arm B vs 385 (95%) were still on first-line treatment with the majority on their original regimen. Only 5% switched to second-line ART and this was in similar proportions across the treatment groups.

Thirty children in Arm A, 20 in Arm B and 9 in Arm C stopped first-line nevirapine for TB treatment. In Arm A, nevirapine was mainly substituted with AZT in children less than 3 years old or efavirenz in older children. In the four-drug arms about a third just dropped the nevirapine to continue with three NRTIs.

There was no difference in CD4 percent change to 72 weeks across arms when all children were on three-drugs, p=0.33 or 144 weeks, p=0.69. At week 36 the four-drug (B and C) arms were superior to Arm A; +14.3% versus 12.4%, p <0.001.

At week 24, viral load suppression was significantly greater in induction four-drug arms (B and C) with 88% <400 copies/mL vs 77% arm A, p=0.002, but was similar across all arms by week 48, p= 0.76. At latest retrospective test at a median 3.7 years on ART, 83% A vs 84% B vs 65% C had viral load <400 copies/mL, p< 0.001.

One hundred and fifty seven (40%) A vs 190 (47%) B vs 218 (54%) C children had grade 3/4 events, p<0.001. Increases in arms B and C were driven by increased asymptomatic neutropenia in AZT-containing arms there were only 6 associated drug substitutions. Grade 3/4 anaemia occurred in similar proportions across arms.

The investigators noted that it is unknown whether continuing with four drugs would provide ongoing benefit and they suggested that triple NRTI ART might be useful during relatively short-term TB co-treatment.

Once- vs twice-daily abacavir and 3TC similar

The final presentation from ARROW was a poster showing findings from a further sub-study, a randomised comparison of once- vs twice-daily abacavir and 3TC in 669 children, authored by Victor Musiime and colleagues

The ARROW investigators previously demonstrated bioequivalence of plasma concentrations between abacavir and 3TC taken once- or twice-daily in 41 Ugandan children aged 3- 12 years.

In this comparison, children in ARROW receiving abacavir and 3TC-containing regimens twice-daily for at least 36 weeks, were randomised to remain on twice-daily or change to once-daily dosing (open-label). The children received single or co-formulated (Kivexa) antiretrovirals.

Primary outcomes were viral load at 48 weeks - measured retrospectively with a 12% non-inferiority margin for suppression - and study drug related grade 3/4 adverse events.

This study was conducted in a subgroup of 669 children who were a median age of 5.5 years (range 1.8-16.9), had a median CD4 percent of 33% and about half were girls. They were randomised to twice- daily (n = 333) vs once-daily (n=336) strategies after a median 1.8 years (range 0.9-3.0) on twice-daily abacavir and 3TC-containing first-line ART.

At the time of the twice-/once-daily randomisation, 51% vs 44%, 15% vs 22% and 34% vs 34% of children were receiving nevirapine, efavirenz and AZT respectively as their third drug. The majority (approximately 80%) took tablet formulations and the remainder syrups.

Over median 2.2 years follow-up, 98% vs 97% child-time was spent on twice- vs once-daily abacavir and 3TC in the two groups respectively. Self reported adherence was similar in the two groups.

There was no difference between groups in grade 3/4 or serious adverse events, WHO 3/4 events or weight- or height-for-age.

Proportions with viral load <80 copies/mL were similar in the twice- vs once-daily groups: at 48-weeks (n=661) there was a difference of -1.6% (95% CI, –8.4% to +5.2%), p = 0.65; at 96 weeks (n=539, assays ongoing) this was +0.7% (95%CI +6.9% to +8.3%), p=0.86.

Increases in CD4 percent in twice- vs once-daily were respectively +1.3% vs +0.8% at 48 weeks, p=0.25, and +2.5% vs +1.5% at 96 weeks, p = 0.06.

The investigators concluded that once daily dosing of abacavir and 3TC can be used to simplify treatment in children. Using efavirenz, this has the potential for a once-daily regimen.

C O M M E N T

ARROW gives us a very rich data set to further inform children's treatment, particularly in resource-limited settings.

The most recent US guidelines include discussion on switching from twice-daily to once-daily dosing of 3TC at 8 to 10 mg/kg, based on review of data from the ARROW and PENTA 13 and 15 trials. [7, 8]

Triple NRTIs are expected to be the preferred regimen for children receiving ART and TB treatment in the next WHO guidelines, according to the discussion at the WHO hosted satellite just before the opening of CROI 2013. These revised guidelines will be released at the International AIDS Society conference in Malaysia—June 30 to July 3 2013.

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Comparison of ritonavir-boosted lopinavir or NNRTI ART and PK with antimalarials in Ugandan children

Polly Clayden, HIV i-Base

Ugandan children in the PROMOTE (Prevention of Malaria and HIV disease in Tororo) paediatrics trial were randomised to receive ritonavir-boosted lopinavir (LPV/r)-based ART vs NNRTI-based.

Recently published data (also presented last year at CROI 2012) showed children receiving LPV/r experienced a lower incidence of malaria compared to those receiving NNRTI-based ART. [1, 2, 3]

At CROI 2013, Theodore Ruel showed results from a planned non-inferiority analysis of virologic efficacy and a comparison of immunologic outcomes between the two ART regimens in a late breaker oral presentation. [4]

ART-naïve and eligible, or virologically suppressed (<400 copies/mL) children ages 2 months to <6 years were enrolled in this open-label randomised trial from October 2009 to October 2011.They received either LPV/r- or NNRTI-based ART with nevirapine (<3 years) or efavirenz (>3 years) with 2 NRTI (3TC/AZT, or d4T if the child was anaemic). Children who had been exposed to nevirapine perinatally and were less than 2 years old were excluded form the trial.

The primary endpoint was viral load <400 copies/mL at 48 weeks. A pre-specified non-inferiority margin of -11% for LPV/r in per-protocol analysis was used. The mean change in CD4 count and CD4 percentage since enrollment, and the proportion of children experiencing grade 3/4 adverse events were also compared by arm.

The trial randomised 185 children to LPV/r-based (n = 92) or NNRTI-based (n = 93) ART. Children were a median age at enrollment of 3.1 years, about half were girls and 70% were ART naïve. Children who were ART naïve at baseline had CD4 counts of about 570 cells/mm3, CD4 percentage of 16% and viral load 5.4 log copies/mL. In children who were already receiving ART, these values were, approximately 1100 cells/mm3, 30% and all had undetectable viral loads. Characteristics were similar across both arms.

A total of 163 children had available viral load results at 48 weeks; (67/84) 80% in the LPV/r-arm were suppressed vs (60/79) 76% in the NNRTI-arm, a difference of 4% (95% CI 17 to -9). This excluded the pre-specified non-inferiority margin of -11%.

Differences in the proportion of children with viral suppression between the treatment groups were not significant when they were stratified by ART naïve or experienced. Time to suppression between the groups was also similar, as was increase in CD4 count and percentage.

Similar numbers of children experienced grade 3/4 adverse events in the LPV/r (n=91) and NNRTI (n=92) arms. The majority of events were neutropenia: 23% vs 16% in the LPV/r and NNRTI arms respectively. Small proportions of children also experienced anaemia, thrombocytopenia, elevated ATT and Stevens Johnson syndrome – the later occurred in a child receiving nevirapine and led to the only antiretroviral substitution in the study. There were 4 deaths (1 LPV/r vs 3 NNRTI), none considered to be associated with the study medication.

Dr Ruel remarked that as there was also a reduction in malaria incidence associated with LPV/r use in this cohort, the results suggest that wider use of LPV/r to treat HIV positive African children in similar settings could be considered.

ART regimen and antimalarial pharmacokinetics

In a related oral presentation, Norah Mwebaza showed results from a study in PROMOTE children (with negative controls) to evaluate the pharmacokinetics/pharmacodynamics (PK/PD) of artemether-lumefantrine (AL) - the most widely used first-line regimen for malaria – co-administered with different ART regimens. [5]

Children treated for uncomplicated malaria with a 3-day regimen of AL were enrolled. The children were HIV negative children receiving AL alone or HIV positive children receiving AL plus stable LPV/r, nevirapine or efavirenz containing ART.

This study used extensive PK sampling: exposure was estimated to 21 days (AUC) with 42 days follow-up. Artemether (AR), its active metabolite dihydroartemisinin (DHA), and the long-acting partner drug, lumefantrine (LR) were assessed by LC/MS/MS.

As in the main study, children receiving efavirenz were slightly older than those receiving the other two antiretrovirals (and negative controls).

PK data for 85 children (27 receiving AL alone, 29 LPV/r, 13 efavirenz and 16 nevirapine) showed reduced exposure of artemether and DHA with efavirenz compared to negative controls: AUC 0-8hr (hr*ng/mL) ratio 0.36, p=0.002 and Cmax (ng/mL) ratio 0.35, p=0.004. Artemether but not DHA exposure was reduced with nevirapine, AUC0-8hr ratio 0.28, p=0.0004 and Cmax ratio 0.22, p=0.0002. Co-administration with LPV/r did not result in significant differences to exposure from the controls.

Furthermore, LPV/r increased lumefantine concentrations by 2-3 fold whereas efavirenz reduced this by half; nevirapine had no significant effect.

When the investigators compared the risk of re-infection at 28-days between the three ART regimens, preliminary findings revealed LPV/r to be associated with a 90% reduction in risk of recurrent parasitaemia compared to efavirenz as reference, HR 0.1 (95% CI, 0.01-0.82), p=0.03. Low lumefantrine exposure was also associated with parasitological failure.

C O M M E N T

These data are compelling, for settings with high malaria risk and add to the evidence in favour of starting treatment with a boosted PI, particularly for infants and young children.

Nevertheless, the logistical problems and cost of the current formulation of LPV/r remain. As well as the question of what to do for second line, which was raised after the presentation by Charles Gilks, who described an NNRTI plus two NRTI second line after PI-based regimen failure as "brittle".

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Pharmacokinetics and acceptability of lopinavir/ritonavir sprinkles in children aged 1 to 4 years

Polly Clayden, HIV i-Base

Last year the Children with HIV in Africa—Pharmacokinetics and Adherence of Simple ARV Regimens (CHAPAS)-2 trial found similar pharmacokinetics (PK) of a novel sprinkle formulation of lopinavir/ritonavir (LPV/r 40/10 mg per capsule from Cipla Pharmaceuticals) in Ugandan infants, compared to innovator syrup.

Acceptability data were also collected, showing most caregivers preferred the sprinkle formulation to the syrup for this age group [1, 2] A poster at CROI 2013 authored by Sabrina Kitaka and colleagues from CHAPAS-2 showed findings from the same comparison in children aged 1-4 years. [3]

This was an open label, crossover, PK trial in which children were dosed according to 2010 WHO weight bands guidelines. Four weeks after randomisation to syrup or sprinkles, samples were taken at 0, 1, 2, 4, 6, 8 and 12 hours after observed intake of LPV/r plus two NRTIs with food. After switching formulation, PK was repeated at week 8. Caregivers then chose which formulation to continue through 48 weeks of follow up and acceptability data were collected at each clinic visit.

LPV/r plasma concentrations were determined using high performance liquid chromatography. Comparisons in PK parameters were made between the two formulations.

A total of 26 children were enrolled with 46 evaluable PK profiles. All were already receiving LPV/r syrup for a median of 1.1 years (range 0.07-2.7). Twenty children had two evaluable PK profiles for within child sprinkle vs syrup comparisons. The children were a median age 2.0 years (IQR 1.8-2.8) and weight 10.7 kg (IQR 9.4-12.6) kg. Just over half (54%) were boys.

The evaluation revealed geometric mean (GM) of PK parameters of LPV sprinkles vs syrup:

	Sprinkes (95%CI)	Syrup (95%CI)	GMR (90%CI)
AUC0-12h (h.mg/L)	135.4 (115.5-158.8)	109.6 (93.3-128.6)	1.24 (1.08-1.42)
Cmax (mg/L)	14.9 (13.1-16.9)	12.6 (11.0-14.4)	1.18 (1.07-1.31)
C12h (mg/L)	6.22 (4.6-8.4)	4.42 (3.3-5.9)	1.41 (1.07-1.85)

The investigators noted that LPV exposure with sprinkles was higher than with syrup and historical data for children aged 6 months -12 years. There was moderately high variability (CV% 26 – 55%) in with both formulations but neither gave subtherapeutic levels (defined as <1.0 mg/L). Ritonavir PK was similar.

Most caregivers (58%) gave the sprinkles with porridge. Poor taste was reported most frequently as a problem with both formulations (38% sprinkles and syrup), followed by swallowing difficulty (27% sprinkles vs 19% syrup). At entry, 12% caregivers expected to prefer sprinkles, but at 12 weeks 67% preferred this formulation. At week 8, 73% caregivers chose to continue with sprinkles. Although 69% of caregivers rated both formulations unpleasant, they reported easier storage and transportation with sprinkles (0% problems) compared to syrup (54%). Independent scoring of administration showed no significant differences between the two formulations. Child refusal within the last week was reported by 19% with sprinkles and 12% with syrup.

Further PK and acceptability investigations are planned with an improved granule formulation with better taste masking.

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Pharmacokinetics of currently available antiretroviral options for young children

Polly Clayden, HIV i-Base

While we wait for the lopinavir/ritonavir (LPV/r) sprinkles for young children, two posters at CROI 2013 reported results from pharmacokinetic (PK) evaluations of currently available and recommended antiretroviral options.

Quirine Fillekes and colleagues from the Children with HIV in Africa—Pharmacokinetics and Adherence of Simple ARV Regimens (CHAPAS)-1 trial showed findings from a sub-study to evaluate whether dose escalation of nevirapine (NVP) is appropriate in young children.

Young children metabolise NVP faster than older children or adults, increasing the potential for inadequate NVP plasma levels with dose escalation. This could lead to slow viral load suppression and possible treatment failure.

In this study, 211 HIV positive Zambian children, aged 3 months to 14 years, were randomised to start ART in accordance with WHO 2006 weight-band dosing, using full dose twice-daily NVP, or with two week NVP dose escalation. Children received either a NVP-containing fixed dose combination (FDC) generic tablet immediately or started with the FDC in the morning with a two nucleoside dual combination tablet in the evening, for the dose escalation period.

Samples were obtained 2 weeks after starting NVP, 3-4 hours post morning dose for single sample PK. NVP plasma levels were measured using high-performance liquid chromatography (HPLC), with a lower limit of quantification of <0.05 mg/L. Plasma levels were defined as subtherapeutic at <3.0 mg/L. Viral load was measured, where stored samples were available, at weeks 4 (n=62) and 48 (n=121).

A total of 162 (77%) children had week 2 samples available; 45 and 117 children were aged <2 and >2 years (with similar proportions in each randomisation group). At baseline, the children were a median age, weight and CD4% of 5.2 years (IQR 1.5-8.7) years, 13.0 kg (8.1-19.0) and 13% (8-18) respectively.

In children <2 years old the median NVP levels at week 2 were 5.3 mg/L (IQR 4.2-9.0) for the group receiving full dose vs 4.8 mg/L (IQR 2.9-6.4) for those in the dose escalated group, p <0.41. In children > 2 years, the difference in these levels was more pronounced, respectively 10 mg/L (IQR 7.9-12.2) vs 5.0 mg/L (IQR 3.9-6.6), p=0.001.

The investigators noted that statistical power to detect interactions between the dosing strategy and subtherapeutic concentrations was limited. But results suggested that the younger children in the dose escalated group had the largest proportion with subtherapeutic concentrations, p=0.05 versus older children in the dose escalated group.

There was no difference between week 2 NVP plasma concentrations in those with viral load >250 copies/mL vs <250 copies/mL at either week 4, p = 0.97; or week 48, p = 0.40. At week 4, 43% in the full dose vs 32% in the dose escalated group had viral load <250 copies/mL, p = 0.43; at week 48, 72% versus 75% did so, p=0.84.

All11/162 children with grade 1/2 rash were aged >2 years, p = 0.04, and 10 were in the full dose group, p=0.009. In children >2 years, the median NVP plasma concentration was 15.1 mg/L (10.4-19.6) in those with rash (n=11) vs 6.8 (9.7-4.5) mg/L in those without rash (n=106), p <0.001.

The investigators concluded that although children >2 years should continue to receive an escalated dose of NVP, full dose at ART initiation should be considered for younger children.

In the second study, Jorge Pinto and colleagues from the IMPAACT P1083 group looked at the WHO recommended paediatric weight band dosing schedule of lopinavir/ritonavir (LPV/r). Although WHO weight band dosing is now standard in many resource-limited settings, there are no data describing drug exposure or safety profiles in infants and children dosed in accordance with this guidance.

IMPAACT P1083 is a phase 1/2 trial to evaluate short-term PK, safety, efficacy and tolerability of LPV/r in HIV-positive infants and children weighing ≥3 to<25 kg. The heat-stable paediatric LPV/r 100/25 mg tablet or the liquid 80/20 mg/mL formulations were used, dosed according to the WHO weight band dosing schedule. LPV/r was given in regimens with two NRTIs as background therapy.

After 4 weeks of receiving LPV/r intensive 12-hour PK samples were collected at 0, 2, 4, 6, 8, and 12 hours post observed dose. LPV/r plasma concentrations were measured by HPLC. The target geometric mean (GM) for LPV AUC0-12 was 80 (range 40-160) mcg.h/mL.

The study plans to enrol 94 subjects to have a target of 85 evaluable infants and children from Brazil, Thailand and USA.

At the time of this interim analysis, 48 subjects, with a median age 4.24 (range 0.4- 12.9) years CD4 percent of approximately 25% and viral load 5.0 log10 copies/mL, had intensive PK results. Thirty subjects received the liquid formulation. The median dose was 316 mg/m2.

The geometric mean of LPV parameters were: AUC 119.8 mcg*hr/mL (range 29.3-261); Cmin 5.5 mcg/mL (range 0.03- 13.83); Cmax 13.42 mcg/mL (range 3.84, 29.17) and CL/F 3.36 L/hr/m2 (range0.14-11.62).

The investigators reported no ≥ grade 3 adverse events considered to be associated with the study drug, but two grade 3 events that were possibly associated. For the 42 children with week 24 results available, the mean change from baseline to week 24 in log10 copies/mL viral load was –2.1 (SD 1.6), and in CD4 percent was 5.3% (SD 6.2).

They concluded that LPV/r, prescribed according to the WHO weight band dosing regimen in children, achieved adequate plasma exposure. Exposure was higher than seen in adults with soft gel capsules but the treatment was well tolerated and the preliminary efficacy data were favourable.References

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Safety of transplacental raltegravir in neonates and washout pharmacokinetics

Polly Clayden, HIV i-Base

Use of raltegavir (RAL) in pregnant women is on the increase, not only due to its widening use generally, but because of its good transplacental transfer and rapid first and second phase viral decay.

BHIVA guidelines recommend women who are untreated in pregnancy or do not initiate treatment until after 28 weeks receive it as part of their regimen. These guidelines also recommend it as an option for pregnant women requiring intensification.

IMPAACT P1097 is a US multicentre, washout pharmacokinetic (PK) trial in neonates born to HIV positive women receiving RAL. Promising early data from 12 mother/infant pairs, presented last year at the PK workshop, showed cord blood to maternal plasma concentration ratio of approximately 1.5 and no safety issues in the first 20 weeks of life. [1,2] Data presented at CROI 2013 in a poster, authored by Diana Clarke and colleagues from the study team, showed similar findings for 22 mother/infant pairs.

RAL is approved in children two years old and above. The drug is metabolised primarily by UGT1A1 – which is immature in infants and has much reduced activity, so there might be competition with biliruben (that uses the same metabolic pathway) for albumin binding sites.

Full term infants of normal birth weight, born to mothers who had received at least two weeks of RAL 400 mg twice daily, as part of their ART regimen, were eligible for PK sampling. Cord blood and a single maternal blood sample were collected at delivery. Infant blood samples were collected 1-5, 8-14, 18-24, and 30-36 hours after birth. RAL concentrations were measured using a validated HPLC-MS-MS method. Infant t1/2 was estimated using terminal 2 or 3 concentration-time points. Infant safety was evaluated up to 6 months.

Over half (59%) of the mothers were African American and 55% overall delivered by Caesarean section. The infants were a mean gestational age of 38 weeks at birth. Evaluable PK samples were obtained from 19 mother/infant pairs.

Median RAL plasma concentration values were: cord blood, 957 ng/mL (range 24-3974); maternal at delivery, 540 ng/mL (range 12-5809) and ratio of cord/maternal blood, 1.48 (range 0.32-4.33). Median infant plasma concentrations were 671 ng/mL (range 13 -2672) at 1-5 hours, decreasing stepwise over the time points to 291 (range BLQ – 1402) at 30-36 hours.

RAL concentrations were above the IC95 (16ng/mL) up to the last time point in all but one infant. RAL concentrations increased after birth before decreasing in 50% of infants. The median infant terminal t1/2 was 26.6 hours (range 9.3-184). No clinical or laboratory abnormalities associated with RAL were observed during this evaluation and there were no HIV transmissions.

Neonatal RAL elimination was highly variable. The investigators noted this suggested potential roles for developmental aspects of neonatal UGT1A1 enzyme activity, redistribution, and/or enterohepatic recirculation of RAL.

The next step for this programme is to investigate potential neonatal dosing regimens (IMPAACT P1110).

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Tenofovir use in children

Polly Clayden, HIV i-Base

Last year both the FDA and the EMA approved tenofovir (TDF) for children two years and above, albeit with rather sparse data. The recommended dose is 8 mg/kg (up to a maximum of 300 mg), once daily using either an oral powder formulation or reduced strength tablets.

For adults, with FTC or 3TC, TDF is the currently preferred backbone for antiretroviral regimens worldwide.

One of the goals of treatment optimisation in low- and middle-income countries is to harmonise paediatric antiretroviral regimens with those for adults. Using TDF for children could offer this possibility – although with current options, very young children and infants still need to be considered differently.

That these approvals, for children aged 2 to 12 (FDA approval for the 12-18 age group was in 2010 but EMA only gave this last year), took eleven years since adult approval in 2001 speaks volumes both of problems developing the formulations and lack of safety data in children.

Following the FDA approval, WHO published a review of the current literature and unpublished data on the safety and efficacy of TDF in this population. [1]

Overall, the review found that, based on the available data, TDF is efficacious in children and adolescents at current FDA-approved doses, but further studies are needed to confirm the dose and investigate the side-effects of TDF in combination with efavirenz in this population.

At CROI 2013, the lead author of the WHO review, Peter Havens, provided a brisk summary of what is known (and not known) about TDF use in children as part of a themed discussion. [2] This session is worth watching and was followed by findings from two Thai paediatric cohorts; all were presented as posters [3,4,5]. There was a great deal of discussion about what and how to monitor TDF in resource limited settings.

Jintanat Ananworanich showed pharmacokinetic (PK) data from 20 Thai adolescents aged 12-18 receiving TDF and boosted PI based second line regimens. Dr Ananworanich explained that they performed this investigation because TDF levels tend to be higher in Thai adults than those reported from high income countries, which can lead to higher rates of toxicity.

In this study, adherent adolescents had pre-dose and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, and 24 hours samples taken after TDF dose. TDF was measured by HPLC. TDF dose was 210 mg/m2 once daily (maximum 300 mg). Geometric mean regression models evaluated predictors of higher TDF levels. The investigators also assessed renal toxicity.

Participants were a mean age of 15 years, weighed was 46 kg, had CD4 percent of 30%, and 75% were girls. Eighteen received lopinavir/ritonavir and the remaining 2 atazanavir/ritonavir. Nineteen participants took 300 mg TDF once daily and 1 took 300 mg on alternate days. The median duration of receiving TDF was 1.1 years.

Dr Ananworanich reported that concentrations matched those reported in published studies of adolescents from high-income counties receiving similar TDF doses. In multivariate analysis, lower GFR predicted higher AUC0–24, coefficient 0.995 (95% CI, 0.991 – 0.999), p = 0.02; and Clast 0.993 (95% CI 0.988-0.997), p=0.005. Higher ritonavir concentrations per body surface area also predicted higher Clast, 1.006 (95% CI 1.001-1.012), p=0.02.

No participants had abnormal serum creatinine, low glomerular filtration rate, glucosuria or tubular phosphate reabsorbtion levels. Four patients had evidence of proximal tubular injury: 3 proteinuria and 1 hyperuricosuria.

She concluded that although published studies have shown higher levels of several antiretrovirals in Thai patients, this one did not reveal elevated levels of TDF in adolescents and resulted in adequate PK and good short tem renal toxicity profile.

The second presentation by Virat Sirisathana was from a 48-week prospective study of TDF in children also receiving efavirenz.

This was an open label study enrolling 40 virologically suppressed (<50 copies/mL) children aged 3-18 years, weighing ≥15 kg and receiving a first-line regimen of 2 NRTI (neither TDF) and an NNRTI.

Following enrollment, their ART was changed to a once-daily regimen of TDF/3TC/efavirenz. TDF was prescribed according to weight band dosing: 150 mg for 15 - <22 kg, 225 mg for 22 - <33 kg, and 300 mg for >33 kg.

The study also enrolled a control group of 40 children matched for age, gender, and CD4 receiving regimens without TDF. The investigators looked at renal function (glomerular, creatinine clearance [eGFR], tubular, calcium and phosphate excretion), as well as bone mineral density (BMD). BMD z-score (BMDZ) was calculated using age-matched healthy Thai children references: ≤2.5 was defined as low.

Dr Sirisathana that all participants except for 4(2 in each group) remained virologically suppressed. She reported a downward trend of estimated glomerular filtration rate (eGFR) for participants in both groups over 48 weeks. This change was significant in the group receiving TDF (179±48 vs 166±52 mL/min/1.73 m2), p = 0.02.

The fraction excretion of calcium and phosphate were slightly increased with time, but this was not significant. The investigators did not observe hypophosphatemia, proteinuria, or glucosuria.

Mean BMDZ decreased significantly in children receiving TDF from baseline to week 24 (0.01±SD 1.31 vs –0.43±1.12), p <0.01, but not between weeks 24 and 48. The change in mean BMDZ was significantly higher in the TDF than the control group at both time points.

Among participants with normal baseline, incidence of low BMDZ after starting TDF was 10.68 per 1000 patient-months in the study group vs 6.41 in the control group, p = 0.75.

C O M M E N T S

Although there is still much that is unclear about the safety and efficacy of tenofovir in children, from an operational standpoint, harmonising treatment with that of adults, in children three years and above, is likely to hugely benefit scale up in resource limited settings and to be an option for this age group in the upcoming WHO guidelines.

The WHO Paediatric ARV Working Group has developed guidance on appropriate future TDF-containing paediatric fixed dose combinations (FDCs) and a simplified weight band-based dosing schedule. [1]

FDCs with 3TC are priority, these include:

- **Dual TDF/3TC FDC – either scored adult tablet if feasible or a child-specific tablet containing TDF 75 mg and 3TC 75 mg (a 1/4 scale down of the adult tablet)**
- **Triple TDF/3TC/EFV FDC – either scored adult tablet or a child-specific tablet containing TDF 75 mg, 3TC 75 mg and EFV 150 mg (a 1/4 scale down of the adult tablet)**
- **Dual TDF/FTC FDC child-specific tablet containing TDF 75 mg and FTC 60 mg**
- **Triple TDF/FTC/EFV child-specific tablet containing TDF 75 mg, FTC 60 mg and EFV 150 mg.**

The feasibility of scoring adult FDC tablets once on one side and twice on the other has been discussed but there is concern that in practice it may be difficult to manufacture, score and split large, multilayered FDC tablets in this way.

More data in children, particularly naïve children, on TDF given with 3TC and EFV as well as appropriate formulations are urgently needed.

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ddI resistance in South African children failing an abacavir or d4T based first-line regimen

Polly Clayden, HIV i-Base

In 2010 the preferred first-line regimen for South African children changed from d4T/3TC to abacavir (ABC)/3TC-based regimens. The second-line regimen is based on AZT/ddI.

Kim Steegen and colleagues from Johannesburg showed data at CROI 2013 from a retrospective study of drug resistance after first-line virologic failure conducted to investigate the implications for a ddI-based second line regimen.

This analysis was performed using a retrospective dataset of 370 antiretroviral drug resistant genotypes from children ≤15 years who had failed on either ABC (n=91) or d4T (n=279) based regimens between 2009 and 2012. Data were retrieved from the HIV genotyping laboratory at Charlotte Maxeke Johannesburg Academic Hospital. The investigators submitted the obtained pol sequences to the Stanford HIV database for genotypic predictions.

The children were a mean age of 8 years with viral load of 4.6 log10 copies/mL. The mean viral load was significantly higher in the ABC compared to the d4T group, p=0.03. The d4T group had been receiving ART longer than the ABC group, respectively 37 and 21 months, p<0.0001.

As the investigators noted, it was predictable that the majority of children (n=290) developed the M184V/I mutation conferring resistance to 3TC/FTC. At time of failure, 61.7% of children exposed to ABC demonstrated high-level resistance to ABC compared to 7.3% exposed to d4T, p<0.0001. But development of intermediate resistance to ABC was more common in children exposed to d4T, occurring in 87.2% compared to 23.5% in the ABC group, p<0.0001. A surprisingly large proportion of children remained susceptible to d4T regardless of exposure to ABC (77.8%) or d4T (74.7%).

Predicted reduced susceptibility to ddI occurred frequently in the ABC-exposed group: 49 (60.5%) and 7 (8.6%) children developed high and intermediate levels of resistance respectively. The investigators explained that this was most commonly attributed to L74V/I (n = 39) and to a lesser extent K65R (n = 8) mutations.

Despite the lower occurrence of high-level ddI resistance after d4T-exposure (n=25, 9.2%), a considerable proportion of children in this exposure group still developed intermediate resistance to ddI (n=93, 34.1%)

The investigators concluded that the currently recommended 2nd-line regimen for children in South Africa is far from ideal, given the high frequency of cross-resistance to ddI seen at 1st-line failure; especially after ABC exposure.

They suggest that a combination of AZT and recycled 3TC might provide a better 2nd-line backbone for children failing both ABC and d4T based regimens. In older children, they propose a combination of AZT and tenofovir for those exposed to d4T. They also write that these data provide evidence for the need to revise the current paediatric ART guidelines in South Africa.

Ref: Kim Steegen K et al. High-level Resistance to didanosine observed in South African children failing an abacavir- or stavudine-based 1st-line regimen. 20th CROI, 3-6 March 2013, Atlanta, GA, USA. Poster abstract 952a.

CROI 2013: SIDE EFFECTS AND COMPLICATIONS

Statin use in HIV positive people

Simon Collins, HIV i-Base

At CROI 2013, statins use in HIV management was the focus of a poster discussion and two late breaker oral presentations.

Most usefully, this poster session included an overview by Steven Grinspoon from Massachusetts General Hospital prior to the main discussion and a summary afterwards by Priscilla Hsue from University of California, San Francisco.

The introduction covered both general population and HIV positive issues. Data on statins comes largely from non-HIV populations where they are widely used to reduce cardiovascular risk by inducing plaque regression and reducing LDL cholesterol. However, the Jupiter study looked at primary prevention in the general population (with normal LDL: men were over 50 and women over 60) and reported clinical benefits based on their anti-inflammatory properties, that were independent of the lipid effect.

In a recent meta analysis of 76 studies in the general population, including >170,000 patients with 14,878 deaths, statin use significantly reduced cardiovascular-related mortality by about 20% and all cause mortality by 10%. Side effects included increased liver enzymes and CPK and were generally mild, but 17 randomised clinical trials reported a 9% increased risk of development of incident diabetes (OR 1.09; 95% CI 1.02-1.17, p=0.001). [2]

In the Jupiter study, patients had no prior cardiovascular disease and normal LDL (<130 mg/dL) but increased CRP (>2 mg/mL). CVD deaths were reduced by 50% using rosasuvastatin, with a slight reduction in deaths from cancer (0.4% vs 0.7%), but statistically significantly higher rates of new diabetes (3% vs 2.4%) were also reported, with the mechanism for this unknown. [3]

However, how and when HIV may have an impact on statin use and optimal use of statins in HIV positive people is unclear. While statins are widely recommended for lipid-lowering in HIV management, data in HIV positive people, especially long term safety data, is limited.

A review of the efficacy of lowering LDL in HIV positive people reported broadly similar results to HIV negative studies, even though this was slightly lower in some HIV studies (by approximately 2% less, but statistically significant). Also, although tolerability was good, rate ratios for some of the complications were also slightly (and significantly) higher compared to HIV negative studies. [4]

Some statins are commonly contraindicated (simvastatin and lovastatin) due to drug-drug interactions with some antiretrovirals and dose adjustment is often required with others. [5] While rosuvastatin (10 mg) is more effective than pravastatin (40 mg) at lowering LDL and triglyrcerides in patients on protease inhibitors, drug levels were increased in HIV negative studies using atazanavir/ritoanvir.

Similarly, interesting preliminary data from patients on ART reported survival benefits from comorbidities (relative Hazard Ratio 0.33 (0.14, 0.76), p=0.009) in the 15% of patients on statins. [6] Statins may have potential antiretroviral activity and may disrupt CCR5 and RANTES and decrease CCR2 expression in monocytes.

Four posters were also selected for discussion but although these are summarised below, all had methodological issues that highlighted the need for further research.

Line Rasmussen from Odense University Hospital presented results from a Danish observational study of HIV positive people starting ART from 1998 with undetectable viral load within 6 months, and statin use before and after a cormorbidity diagnosis (CVD, renal disease or diabetes mellitus), compared to the general population. [7] A reduction in all cause mortality was only reported in patients with diagnosed comorbidities, and only in a censored model when VL >400 copies/mL (adj mortality RR 0.32, 95%CI 0.10-0.99; without censoring aMMR was 0.57, 95%CI 0.28-1.15).

No difference was seen without a comorbidity diagnosis. However, this was a retrospective study and statin prescription is likely to have been for a clinical indication (suggesting confounding factors), suggesting that the beneficial impact in this analysis may have been underestimated.

Henning Drechsler from the University of Texas Southwestern Medical Centre reported on the impact of statins on mortality and non-AIDS complications in >25,000 patients on ART in the Veteran's Association (VA) cohort, stratifying by virological suppression and choice of statin. [8]

Approximately 35% of patients used statins. There were 6435 deaths during a median follow up of 6.3 years (>25,000 PY). There were also 2199 cardiovascular events (acute myocardial infarction and cerebrovascular accident), 5011 malignancies, 3196 cases of chronic kidney disease (CKD), and 610 fragility fractures.

Adjusted multivariate analysis showed significant reductions in deaths with statin use, irrespective of viral suppression but with a greater benefit in patients using atorvastatin or rosuvastatin but no effect was seen on CVD (which was inexplicably increased), malignancy or fracture outcomes. As with the Danish study, confounding by clinical indication was suggested for the lack of effect seen in these results. The lack of mortality data in the VA cohort limited further understanding of the cause of death.

Vincenzo Spagnuolo from the San Raffaele Hospital, Milan, presented a retrospective longitudinal data on the incidence of Type-2 diabetes mellitus (DM) in 5380 HIV positive patients on ART (n=726 using statins) followed for 9.8 (IQR 4.4-14.9) years. [9]

Significant differences at baseline included median age of the statin users was slightly older (50.7 vs 45.7 years), with longer use of ART (14.1 vs 9.6 years) and significantly worse lipid profiles.

The overall crude incidence rate (IR) for new DM was 2.82 per 1000 PYFU (95%CI 2.74-2.91). Approximately 14% patients used statins (81% rosuvastain, 18% pravastatin) for a median of 24.4 months (IQR 10.2-42.4). However DM occurred significantly less in 12/726 (1.7%) statin users (IR 1.32; 95%CI 0.68-2.18) compared to 150/4654 (3.2%) not statin users (IR 3.40; 95%CI 2.86-3.95); p = 0.020.

In multivariate analysis, older age, higher BMI, basline triglycerides and glucose and prior use of d4T or ddI were all significantly associated with increased risk of DM, with higher CD4 nadir and statin use being protective. Data on choice of statin and dose were not available.

This study reported very low rates of DM, below general population incidence, but only 5% of participants had BMI >30 kg/m2. This was raised in the question session, including how DM was diagnosed.

In contrast to this study, the final poster presented by Kenneth Lichtenstein reported an increased risk of DM with statin use in 4962 patients at 9 US clinic sites in the HIV Out Patients Study (the HOPS cohort) who were prospectively followed from 2002-2011. [10]

Of these patients, 590 received statins during follow-up of a mean 49.4 months (IQR 21.7-78.1). New DM was diagnosed in 355 patients (crude incidence of 3.06 per 100 person-year while prescribed statins vs. 1.16 otherwise). In multivariate analysis, per year of statin use was associated with a 10% increased risk of incident DM (HR 1.10; 95%CI 1.01, 1.30), p=0.038. Other significant factors included older age, Hispanic race, BMI > 30 kg/m2 but not with individual ARVs or protease inhibitor use.

The conclusion from this study was that this showed the importance of routinely monitoring glucose in HIV positive patients and that these findings would be unlikely to reduce appropriate statin use for hyperlipidaemia and statin use should not be avoided when clinically warranted.

Questions relating to the methodology of this study included whether patients on statins would routinely be monitored more frequently for glucose tests, that higher diagnosis might relate to use of single elevated glucose results and that the US background population risks, including BMI might be higher compared to Italians.

The full panel discussion emphasised the importance of separating use when clinically indicated from use when not clinically indicated (in the belief there are other benefits). While there are no data to support not using statins when indicated, the data are currently unknown for non-indicated use and this was not answered by any of the retrospective studies discussed in the session. It also included a comment that the assumption that inflammation is on the causal pathway for cardiovascular disease may be incorrect as there is little data supporting this in the general population.

In summary, Priscilla Hsue emphasised the strong associated between even modest LDL reductions in the general populations reducing major coronary events and mortality, with the impact on risk correlating to the degree of LDL reductions. [11, 12]

HIV studies are largely small and observational compared to large randomised studies in the general population. In general population studies, statins are largely beneficial even in patients with diabetes, with similar benefits irrespective of DM status. [13] However, the 9% increase risk of incident diabetes reported has a low absolute risk: requiring 255 patients (95%CI 150-852) to be treated for four years to produce on new case of DM. [14]

Finally, there were two late breaker oral presentations to the main conference.

In the first, Grace McComsey from Case Western Reserve University and colleagues reported early 24-week results on impact of rosuvastatin on cellular activation markers in treatment experienced patient on ART (~ median 6 years; IQR 3-10), but with normal LDL cholesterol (<130 mg/dL). [15]

This is a 96-week study looking at the impact of rosuvastatin on cardiovascular and bone health in 147 adults randomised to rosuvastatin 10 mg or matching placebo. Entry criteria included evidence of immune activation and/or inflammation (defined as CD8+CD38+HLA-DR+ >19% and/or hsCRP >2 mg/L, respectively).

At 24-weeks, rosuvastatin only significantly reduced one out of five inflammation markers (Lp-PLA2, with no impact on IL-6 or hsCRP) and two out of six markers of monocyte activation (sCD14 and CD14dimCD16+TF+ monocytes). Rosuvastatin had no impact on a panel of markers of lymphocyte activation or coagulation.

Further results from this study are needed in this mixed population. Although LDL was normal, median BMI was 26 and >30 kg/m^2 in 25% of participants, >60% are current smokers, ART experience is extensive with 50% of current PI-based treatment.

The second late-breaker presented results from a randomised phase 4 study, designed to show superiority of the more recently approved pitavastatin (approved 2010 in the UK) compared to pravastatin (available as generic for at least five years) based on the primary endpoint of greater reductions in LDL cholesterol at 12 weeks. [16]

Although pitavastatin has reduced potential for CYP-mediated drug-drug interactions, metabolism is glucuronidation via UGT1A3 and UGT2B7. Pitavastatin is only marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8

The study was sponsored by Kowa Pharmaceuticals, manufacturers of pitavastatin, and enrollment criteria included dyslipidaemia defined as LDL-C between 130–220 mg/dL and triglycerides ≤400 mg/dL.

Mean (SD) percentage changes in LDL at week 12 were -31.5 mg/dL (15.3) vs -20.9 mg/dL (15.2), mean difference -9%, p<0.001. Similarly significant differences were seen in reductions in Apo B and total cholesterol, but no difference were seen for HDL or triglyceride levels. No results were given in terms of the percentages of patients achieving target lipid levels. Tolerability results were similar for both drugs.

C O M M E N T

Taken together, the posters in this session did not add to what is already a confusing field, due to problems in the study designs.

The first study (Rasmussen) found no effect for primary prevention, but did find an effect in those with a prior co-morbidity. This would be slightly at odds with the general population where there is a (albeit relatively small) benefit of statin use in the general population.

The second study (Drechsler) didn't find any association with CVD - but did adjust for LDL as a time-updated covariate. This is on the causal pathway between statin use and MI development, so adjusting for this as a time-updated covariate is likely to remove the very effect you're looking for (like adjusting for time-updated CD4 count when assessing the effect of ART on mortality). This makes interpretation difficult. For example, they report that statins were protective of mortality in the univariate analysis which would not normally be expected as people who receive statins generally have multiple risk factors for CVD, many of which are also risk factors for mortality (high BMI, smoking, family history of CVD, older age, male gender). A study that doesn't find a negative association of mortality with statins in unadjusted analysis is unusual.

Most studies also have too limited data to be able to remove confounding in multivariate analyses. The same issue is relevant for the Spagnuolo study (as well as the issues about under-ascertainment).

The final study (Lichtenstein) is most convincing, although whether statins had causal relationship to the increased DM risk, or were just a consequence of unmeasured confounding), remains unclear.

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CROI 2013: TUBERCULOSIS & OIs

RIFAQUIN study demonstrates once-weekly dosing during continuation phase of TB treatment

Nathan Geffen, CSSR

The results of the much-anticipated RIFAQUIN trial were announced at CROI 2013 by Amina Jindani of St Georges Hospital, University of London. Jindani has been involved in TB trials since the 1960s and her work has informed WHO guidelines.

The RIFAQUIN trial found that a regimen using moxifloxacin and rifapentine was non-inferior to using isoniazid and rifampicin. Moreover, in the continuation phase, moxifloxacin and rifapentine were taken once-weekly compared to the daily dosing required for the standard regimen. [1]

In mice, a rifapentine, moxifloxacin and pyrazinamide regimen sterilised TB at two months. However, Jindani explained that in clinical studies of rifapentine at 600mg, relapse rates have been unacceptably high and patients with HIV developed resistance to the rifamycin group (rifampicin, rifabutin and rifapentine). The RIFAQUIN trial sought regimens to address this by randomising patients to one of three arms.

- Control regimen (standard WHO): Two months of daily ethambutol, isoniazid, rifampicin and pyrazinamide followed by four months of daily isoniazid and rifampicin.
- Four-month study regimen: Two months of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by two months of twice weekly moxifloxacin (500mg) and rifapentine (900mg)
- Six-month study regimen: Two months of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by four months of once weekly moxifloxacin (500mg) and rifapentine (1200mg)

This trial was designed to detect non-inferiority within a six percent margin. Patients were followed up for 18 months after randomisation. The primary endpoint was the absolute difference in the proportion of unfavourable outcomes, calculated using modified intention-to-treat and per-protocol analyses. The planned sample size was 1,100.

Recruitment began in August 2008 and was completed in August 2011 at which point 827 patients had been enrolled from Johannesburg (n=255), Cape Town (209), Macha (15), Harare (203), Marondera (89) and Botswana (56). After exclusions, withdrawals, loss-to-follow-up and after accounting for missing or contaminated cultures, there were 592 patients included in the modified intention-to-treat (ITT) analysis, of whom 188 were on the control arm, 191 on the four-month regimen and 213 in the six-month regimen.

Baseline characteristics were similar across the three groups. Men comprised 64% of participants. Median (range) age and weight were 32 years (18 - 75) and 53 kg (35 - 82), respectively. Only 28% of the participants were HIV positive, with a median CD4 count of 312 cells/mm3 (IQR: 253-441).

The primary outcomes in the per-protocol analysis of the control and six-month arms were almost identical. In the control arm, of whom 163 patients were assessable, there were two culture-confirmed treatment failures, one death during treatment, four culture-confirmed relapses and one clinical relapse for a total of eight unfavourable outcomes (5%). In the six-month regimen, of whom 187 patients were assessable, there was one death during treatment, five culture-confirmed relapses and one clinical relapse for a total of seven unfavourable outcomes (4%).

Likewise, in the modified ITT analysis, outcomes were almost identical between these two arms. In the control arm, in addition to the unfavourable outcomes listed above, eleven patients changed their regimens, five were lost to follow-up and two were inadequately treated. There was also one further clinical relapse not included in the per-protocol analysis, for a total of 27 unfavourable outcomes out of 188 patients (14%). For the six-month regimen, there were also eleven regimen changes, ten lost to follow-up and one inadequately treated patient for a total of 30 unfavourable outcomes out of 213 patients (14%).

The four-month regimen had significantly worse outcomes on both analyses. In the per-protocol analysis of 163 patients there were 28 unfavourable outcomes (17%) including two culture-confirmed failures, 18 culture-confirmed relapses, six clinically assessed relapses and two patients who were culture-positive when last seen. In the modified intention-to-treat analysis there were 50 unfavourable outcomes (26%). A Kaplan-Meier graph showed that most of the unfavourable outcomes in the four-month regimen were due to relapses in months five to nine.

After the two-month intensive phase, 90% of the six-month intervention arm were culture-negative versus 85% of the control arm. This was on the border of significance (p=0.058).

There were 39 grade three and four adverse events, 13 in the control arm, 11 in the four-month study regimen and 15 in the six-month study regimen.

Adherence was high on all regimens. There were no differences across arms according to HIV status. No rifamycin mono-resistance occurred in any of the arms.

Jindani concluded that the six-month study regimen was non-inferior, safe and well-tolerated. The four-month study regimen was safe and well-tolerated but its efficacy was inferior to the control.

C O M M E N T

This trial has exciting implications for TB treatment. The 6-month study regimen appears more convenient than the current standard of care. In settings were treatment is directly observed it will require less health worker time to administer, at least from the third month of treatment, and patients will have lower transport to clinic costs and interruptions to their normal schedule.

The cost of these drugs is a barrier to wider use. In the South African private sector, 10 x 400 mg moxifloxacin pills costs over R250 per month. [2] Rifapentine is not available in South Africa, but according to TB Online the price of 100 x 150 mg pills is $363 (as of 2011). [3] By comparison, a 4-in-1 fixed dose combination of the standard regimen costs R38. [2] Unless the cost of rifapentine is dramatically reduced, there is no prospect of this regimen being used at scale in poor countries and this should be an activist priority.

Perhaps the four-month study regimen should not be discarded if a patient-profile can be developed that predicts risk of relapse, though at twice-weekly dosing the four-month regimen is not necessarily more convenient to patients and health-workers than the six-month study regimen.

This trial was funded 5.4 million Euros (5.1m Euros from the European & Developing Countries Clinical Trials Partnership and 270,000 Euros from the Wellcome Trust), excluding drug costs which were donated by Sanofi, Genus and Sandoz. This had considerably lower per patient costs compared to industry-run phase 3 studies. [4]

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Combining Xpert and LAM urine testing improves TB diagnostic sensitivity

Nathan Geffen, CSSR

Despite recent advances in TB diagnostics, current technologies suffer serious disadvantages.

- Mycobacterial culture tests, like the MGIT, are the closest to a gold standard. But results often take weeks, they require reference laboratories and are expensive.
- The Gene Xpert (Xpert) is also expensive and has good but not excellent sensitivity, especially in sputum-negative patients. Its place in the clinic, as opposed to laboratories, is not established. Also, with a two-hour turn-around time, it is still not a point-of-care test.
- Microscopy is affordable, but despite advances in microscope technology, its sensitivity is still poor and it has long turn-around times.
- Lipoarabinomannan (LAM) assays, which use urine to diagnose TB, are quick and reasonably affordable but have poor sensitivity, especially at higher CD4 counts. Additionally, detecting patients with extra-pulmonary TB, especially in cases where they do not have pulmonary TB, brings its own challenges.

Maunank Shah from Johns Hopkins, presented an important Ugandan study at CROI 2013 that considered whether TB diagnosis could be improved in HIV positive people using combination testing, particularly LAM assays and Xpert, and whether this has advantages in specific patient groups.

Shah pointed out that the Xpert's advantages are that it detects smear-positive TB 95 to 98% of the time, that its specificity is 94 to 99% and that it detects rifampicin resistance with 97 to 100% sensitivity and 98 to 100% specificity. However, it detects smear-negative TB in only 55-77% of cases. Even with subsided pricing, the cheapest four-cartridge machine costs about $17,000 and each cartridge costs just under $10.

LAM is a component of mycobacterial cells walls. It is detectable in the urine of some HIV positive patients with active disease. The urine ELISA LAM has a sensitivity of 50 to 80% in HIV positive patients and is more sensitive at lower CD4 counts, especially in patients with disseminated

disease, but its sensitivity is poor in most other patients. However, LAM is a point-of-care test and results are available in 20 minutes. LAM costs about 3 to 4 dollars per test.

This was a substudy of the "Feasibility of LF-LAM in HIV-infected individuals" study that included 208 patients, of whom 103 had culture-confirmed or clinically diagnosed active TB and 105 did not have active TB. Using two specimens, MGIT (the most sensitive single diagnostic test) detected 92% of cases compared to 80% for Löwenstein-Jensen. Mycobacterial blood culture detected TB in 48% of active-TB patients.

At baseline 60% of the active TB group were women versus 68% of the no-TB group. The median age was between 32 and 34 across the two groups. The CD4 median was 63 (IQR: 19-152) in the TB group and 280 (IQR: 97-486) in the TB-negative group. Most of the TB group (84%) was hospitalised versus 34% of the group without TB.

In the TB group, 54 (52%) had pulmonary TB alone. A further 43 (42%) had pulmonary TB and mycobacteremia. Six patients had mycobacteremia alone and would not be detectable using sputum, which, as Shah said, shows the value of doing blood cultures for TB in patients with HIV.

The accuracy of smear microscopy, Xpert and LAM were compared on this group of patients. Microscopy performed the worst. Using two specimens for each method, Ziehl-Neelson stains were 30% sensitive and fluorescence microscopy (FM) 42%. The lateral flow urine LAM test was 49% sensitive and was significantly better than smear microscopy. Xpert detected 76% of cases.

Specificity was 100% with microscopy, 97% with LAM and the 98% with Xpert 98%.

The urine LAM assay has graded bands on it: the higher the grade the more strongly positive the result. Reducing the grade increases sensitivity but worsens specificity. The study used grade 2 as the cut-off, which Shah said also avoided incorrectly detecting a few non-MTB mycobacterial infections. During questions, Shah said that it was worth exploring whether two LAM tests improved sensitivity.

Xpert detected 98% of the smear-positive FM cases but only 60% of smear-negative FM cases. LAM detected 56% of smear-positive FM and 45% of smear-negative FM cases.

Table 1 shows the LAM and Xpert sensitivities by CD4 count and that, as in other studies, LAM sensitivity is dramatically higher in patients with lower CD4 counts.

Table 1: Sensitivity of LAM and Xpert by CD4 count

CD4 count (cells/mm^3)	LAM sensitivity	Xpert sensitivity
< 50	65%	74%
51 to 100	71%	76%
101 to 200	21%	84%
> 200	19%	81%

In patients with pulmonary TB alone the LAM and Xpert sensitivities were 22% and 74% respectively. For patients with pulmonary TB and mycobacteremia, these were 79% and 86% respectively. And for patients with mycobacteremia alone, the LAM actually performed better than Xpert, finding TB in four of the six patients versus the one found by Xpert.

The main purpose of the study was to compare combinations of tests. FM combined with MGIT and blood culture yielded close to perfect sensitivity, but obviously this is not a practical combination in the vast majority of settings or even for most patients in very well resourced settings.

By combining LAM with smear microscopy, sensitivity rose to 67% (95%CI: 57-76), significantly better than either test alone ($p<0.001$ in both cases) and non-significantly different from Xpert alone ($p=0.15$). Specificity was 97% (95%CI: 92-99).

Using the LAM with Xpert produced even better results. This combination was 85% sensitive (95%CI: 77-92), significantly better than either alone and the combination of LAM and microscopy. It was non-significantly different from MGIT ($p=0.167$). Specificity was 95% (95%CI: 89-98). Also, combining LAM and Xpert yielded a sensitivity to smear-negative TB of about 80%. Shah explained that the difference in sensitivity by CD4 count seen with LAM alone disappeared using both tests in combination, that there is incremental gain using them together.

Shah also presented a slide summarising cost-effectiveness analyses of diagnostic algorithms, although it was beyond the scope of his talk to present how these estimates were derived (all monetary amounts rounded to nearest dollar):

- Smear alone costs $4 per person. The total cost of treating a TB patient using smear is $48.
- Smear plus LAM costs $8 per person. The total cost of treating a TB patient using smear plus LAM is $63. Per 10,000 people who might have TB, this adds an additional 4,046 disability adjusted life years (DALYs) over smear alone and costs $37 per DALY averted.
- Xpert alone costs $18 per person (presumably this incorporates the cost of the machine). The total cost of treating a TB patient using Xpert is $75. Per 10,000 people who might have TB, this adds an additional 4,706 disability adjusted life years (DALYs) over smear alone and costs $57 per DALY averted.
- Xpert plus LAM costs $22 per person. The total cost of treating a TB patient using Xpert plus LAM is $80. Per 10,000 people who might have TB, this adds an additional 6,284 disability adjusted life years (DALYs) over smear alone and costs $50 per DALY averted.

Shah concluded that all the incremental benefit that can be obtained from combining tests gains sufficient DALYs to be cost-effective.

C O M M E N T

This excellent study provides guidance to TB clinicians that can help improve diagnosis cost-effectively.

However, clinicians need to consider the data carefully in relation to the profile of patients at their site before implementing combinations of diagnostics. In this setting, patients with TB had very low CD4 counts and this benefited the relative sensitivity of the LAM. In sites with a different patient profile, the advantages of combining LAM and Xpert might not be as clear.

We still do not have anything close to an acceptable point-of-care TB diagnostic. While Xpert is an important advance, results still take too long and it requires greater expertise than many health facilities have available. LAM has important applications as a point-of-care test, but it is not good enough to be used alone.

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Deferring ART by four weeks reduces mortality in patients diagnosed with cryptococcal meningitis

Nathan Geffen, CSSR

David Boulware from University of Minnesota, reported improved 26-week survival rates in patients diagnosed with cryptococcal meningitis (CM), by deferring ART for five weeks compared to initiating ART within a week. [1]

These results, from the Cryptococcal Optimal ART Timing (COAT) trial run counter to what has been found for trials that have examined immediate versus deferred strategies for other opportunistic infections.

Based on cohort studies, CM is estimated to be responsible for up to a quarter of AIDS deaths in sub-Saharan Africa. The disease has a high mortality rate, so optimisation of treatment has substantial benefit. CM is the highest cause of meningitis-related deaths in adults in Africa.

The study was designed to evaluate the risks of early or deferred ART including IRIS, tolerability of ART during CM illness and unknown drug-drug interactions between antiretrovirals and amphotericin B and fluconazole compared to benefits of reduced time with low CD4 count and high viral load.

As background, the ACTG A5164 trial published in 2009 compared disease progression and death in patients who initiated ART within 14 days of opportunistic infection diagnosis versus those who deferred until the end of acute treatment. Its primary endpoint had a non-significant trend favouring earlier ART, but its secondary endpoints provided compelling evidence for earlier ART: early treatment had less AIDS progression and death (OR = 0.51; 95%CI: 0.27–0.94). Interestingly, the trial also showed significantly less progression to AIDS or death for patients with CD4 counts <50 cells/mm3 who had fungal diseases (cryptococcal infections and histoplasmosis) and a trend to less disease progression and death when cryptococcal was considered alone. [2]

However, a Zimbabwe study by Azure Makadzange and colleagues found that patients with CM had greater mortality at three years when treated immediately with ART (54% vs 88%; p < 0.006), although CM treatment was fluconazole monotherapy. [3]

In a third small trial of only 27 patients with CM in Botswana by Gregory Bisson and colleagues, those initiated on ART within seven days had no difference in outcomes. Two of 13 (15%) and five of 14 (36%) patients died in the intervention and control arms, respectively (**p** = 0.39), but seven of 13 (54%) people in the intervention arm versus none in the control arm experienced CM-IRIS (p = 0.002). Amphotericin B was used with fluconazole in this trial. [4]

The COAT trial planned to randomise 500 ART-naive patients with CM who had been on anti-fungal treatment for 7 to 11 days to start ART within 48 hours or defer ART for more than four weeks. Randomisation was stratified by site and altered mental status. The primary endpoint was 26-week survival. Secondary endpoints included survival at 46 weeks. The trial was stopped early by the DSMB the trial before these numbers were reached. It was started in November 2010 and halted in April 2012.

The CM treatment regimen was amphotericin B and fluconazole 800 mg for the first two weeks, with fluconazole at this dose continuing until cerebrospinal fluid (CSF) was clear, with subsequent dose reductions of fluconazole.

A total of 389 patients were screened, of whom 237 had confirmed CM. A further 60 were not randomised, mostly because of death (n=33). In all, 177 patients were randomised, 115 in Kampala, 35 in Mbarara and 27 in Cape Town, of whom 88 were assigned to early ART and 89 to the deferred arm. The median time to starting ART on the immediate arm was eight days versus 35 on the deferred arm.

Baseline characteristics included median age 35, just over 50% male, 65% with no prior AIDS or TB and 23% had prior or current TB. About 14% had altered mental status. Median CD4 count was 19 (IQR: 9 to 69) in the immediate arm versus 28 on the deferred arm (IQR: 11-76). CSF opening pressure was similarly elevated in both arms. Number of colony forming units were a median of 5.2 and 4.8 log/mL in the immediate and deferred arms respectively. Slightly more patients in the immediate arm had white blood cell counts in CSF below 5 cells/mm3 (45% vs 32%).

The primary outcome of survival at six months was 55% in the immediate versus 70% in the deferred arm (p=0.03), with 68 deaths (40 versus 28). This was 20% lower than is usually seen in CM studies. A Kaplan-Meier graph showed that the excess mortality occurred in the treatment induction period of the immediate arm. After this period, the mortality graphs of the two arms were nearly identical.

Two groups drove mortality. Patients with altered mental status (less than 15 on the Glasgow Coma Scale – see Wikipedia for an excellent explanation of this scale) had a hazard ratio of 3.0 in the early ART group. Patients with low white blood cell counts in their CSF (<5 cells/mm3) were at even greater risk in the immediate arm, being 3.3 times more likely to die (p=0.01). By contrast the 60% of patients with more than 5 cells/mm3 had a hazard ratio of death of 0.8 on the immediate arm (i.e. non-significantly less likely to die than in the deferred arm, p=0.73).

Several other pre-defined sub-group analyses did not show significant differences between the two arms. There were more CM-related IRIS events in the early ART group but this was not statistically significant (16% vs 10%; OR: 1.7; 95%CI: p=0.35). A Kaplan-Meier graph showed time to IRIS was quicker in the immediate group.

Cause of death data was presented for 51 cases. CM was the cause of 21 and 10 deaths and septicemia was responsible for eight and five in the immediate and deferred arms respectively. There were two TB deaths on each arm as well as one IRIS death on the immediate arm and two on the deferred. Excess mortality was therefore primarily CM-related. Perhaps relevant is that a poster at CROI by the same team showed that early ART was associated with an increase in CSF cellular markers for macrophage activation among the Ugandan patients. At day 14, patients on the immediate ART (in both countries) were more likely to have an elevated CSF white blood cell count (58% vs 40%, p = 0.047). [5]

A Kaplan-Meier graph showed that more than 50% of patients had grade 4 or 5 serious adverse events, which Boulware explained was primarily due to amphotericin B toxicity. There were more adverse events in the immediate arm, but this was not statistically significant.

This trial showed that there is no benefit to starting ART during CM induction therapy. Deferred ART resulted in significantly fewer deaths and a trend for less IRIS events.

The conclusion proposed several recommendations:

- Treat CM first and optimally.
- Counsel patients for HIV and ART while they are in hospital.
- Verify that CSF culture is sterile at two weeks before starting ART or dropping fluconazole to 400mg.
- Aim to start ART at about four weeks, perhaps delaying ART initiation to five or six weeks in patients with low CSF white blood cell counts or altered mental status.

Boulware noted several limitations of the study including the early DSMB stop and the difficulty of discerning causes of death. For example, some of the deaths attributed to CM might have been IRIS-related. Also, the high level of care in the study cannot be easily generalised to operational settings: there was no loss to follow-up, 99% linkage to care, HIV counselling for patients while they were hospitalised and the full gamut of treatment as per the WHO guidelines.

During questions, Boulware explained that patients that are treated using fluconazole monotherapy clear cryptococcal from CSF about 30% slower than if amphotericin B is also used. He therefore suggested that patients in these settings should probably be initiated after five or six weeks.

C O M M E N T

WHO recommends that ART only be initiated when there is evidence of a sustained clinical response to anti-fungal therapy. It recommends against immediate treatment. These guidelines can now be changed from low- to high-quality evidence recommendations. [6]

This excellent study, with its relatively low mortality compared to other CM studies, once more shows the importance of using amphotericin B for the treatment of CM. Barriers to its wider adoption in many poor settings are price and the complexity of administering it.

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CROI 2013: PREVENTION

Monthly injection protects macaques from rectal exposure: results should fast-track human studies for advanced PrEP options

Simon Collins, HIV i-Base

Probably, the most important prevention study at CROI 2013 came from a study in 16 macaque monkeys.

Half these animals were given a long-acting formulation of an integrase inhibitor and all were protected from SHIV infection, following multiple rectal exposures, compared to none of the control animals.

This was an oral late breaker abstract presented by Chastity Andrews and colleagues at the Aaron Diamond Institute, in association with GSK, with the research funded by a public grant from the US NIAID. [1]

The compound, called GSK744, is similar to dolutegravir, and at 5 mg and 30 mg doses of the oral formulation produced viral load reductions of –2.0-2.5 log copies/mL after ten days of monotherapy. In a poster presented at the AIDS 2012 conference in Washington last year, five long acting parenteral (LAP) formulations (IM and SC) with a plasma half-life of 21-50 days in HIV negative volunteers, maintained therapeutic drugs levels (above the adjusted IC90 with 200, 400 and 800 mg/mL doses) from a single injection out to six months. At the highest dose, therapeutic levels were maintained at 4 times the IC90 levels for greater than three months, with a half-life ranging from 3-7 weeks. [2]

The macaque study at CROI included 16 animals, randomised half the animals to two cycles of intramuscular injections of 50 mg/kg GSK 744 LAP, dosed on weeks -1 and 3 (with the monthly dose based on a shorter half-life compared to human PK). Each cycle involved two injections into each quadrecept. Animals were challenged rectally with SHIV162P3 at week 0 and then weekly for up to eight weeks, or until infection was confirmed by real time PCR.

All 8 animals receiving active drug were protected throughout the 8 weeks and during subsequent 10 weeks follow-up in contrast to control animals who became infected following 1-7 challenges (median 2 challenges), $p<0.0001$. Proviral DNA in PBMCs and virus specific antibodies were only detected in the infected animals.

Plasma concentrations of GSK-744LAP were variable but remained more than four-fold above the IC90 level for all animals for 6/8 weeks but dropped to below the IC90 level in two animals for the last two weeks. These data were comparable to human results using an 800 mg injection.

C O M M E N T

These first efficacy results in macaques are similar to those seen with tenofovir/FTC more than 12 years ago, which had a similarly high level of protection from rectal exposure. Crucially, the compound has the potential for monthly or perhaps quarterly injections – overcoming the considerably reduced effectiveness of daily oral PrEP due to intermittent adherence. Similarly, the low active dose and more effective and targeted drug delivery has the potential to dramatically reduce concerns about toxicity, treatment cost and perhaps drug resistance.

Given the experience learned from studies using oral PrEP, the timeline for development should be shorter than was required for tenofovir/FTC and could offer a safer setting for non-inferiority prevention studies, enabling all participants to receive potentially active interventions.

Public funding for this research should be matched by an affordable access price to the final compound if it is proved to be effective.

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Tenofovir DF ring protects macaques from vaginal exposure

Simon Collins, HIV i-Base

Efficacy data for a reservoir intervaginal ring (IVR) using slow release tenofovir disoproxil fumerate (TDF), developed to deliver a daily dose of 2.4 mg/day over 28 days, was presented at CROI 2013 by James Smith from the CDC Atlanta, in an oral presentation and a poster. [1, 2]

This ring delivered sufficient intracellular drug levels in upper and lower vaginal tissue and cervical tissue samples expected to provide protection (based on >1000 ng/mL required for efficacy in the Caprisa 004 study gel study), with some penetration but at lower levels in inguinal lymph nodes and rectal tissue.

The efficacy study included 12 female macaques, half of which used the active ring, half as controls, plus an additional six historical controls. Rings were inserted at baseline and changed monthly for four months, with vaginal exposure to SHIV given weekly for 16 weeks.

All macaques using the active ring were protected throughout the four months, remaining RNA and antibody negative, compared to 11/12 control animals who became infected after a median of 4 exposures, p<0.0004.

No safety concerns were raised during the study, including a lack of changes in microflora or menstrual cycle. Human phase I studies are expected to start in 3Q 2103.

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VOICE study reports low adherence as reason for lack of efficacy for PrEP: anal sex common in African heterosexuals

Simon Collins, HIV i-Base

The five-arm placebo controlled VOICE HIV prevention study randomised over 5000 HIV negative women in South Africa (n= 4077), Zimbabwe (n=630) and Uganda (n=322) to one of three active (oral TDF, oral TDF/FTC and TDF gel) or two placebo arms (oral and gel).

Interventions by the study DSMB stopped both the tenofovir oral and gel arms in late 2011 due to lack of efficacy, but the data analysis from the full study, including the efficacy data for the discontinued arms, was presented for the first time as an oral presentation at CROI 2013. As previously suggested, low adherence drove the lack of efficacy.

The mean age at baseline was approximately 25 years, with 20% married, >90% using oral (>20%) or injectable (70%) contraceptives. More than 20% or participants reported having more than two male partners in the previous three months but condom use was high (85% on last occasion).

Perhaps most notably, with information collected using computer assisted self-reported questionnaires (A-CASI), rather that by interview, 18% of women had anal sex in the previous three months. This has rarely been listed as a risk factor in previous prevention studies.

Approximately 10% of participants were lost to follow up, but >95% of the projected person years of follow up (PYFU) were available. Adherence by self-report and returned medication bottles was close to 90% in all arms.

Overall, 344 women became HIV positive during the study, 22 of whom were excluded due to likely seroconversion at study enrollment leading to an incidence of 5.7%.

Primary efficacy results in terms of new infections were not statistically different between arms and are detailed in Table 1. There were also no safety differences between arms. The overall pregnancy rate was 7.8%.

The PK substudy, essential to explain both positive and negative findings in PrEP studies, included over 3,200 samples from 773 participants (median 4 samples, range 1-12 per participant), including all seroconvertors. Less than 40% of women in any of the active arms had detectable tenofovir (test sensitive to >0.3 ng/mL) during the first three months of the study and this fell steadily to 20% by the sixth quarterly visit. More than 50% of the women had no detectable tenofovir at any point during the study.

Although there was insufficient PK data to determine efficacy rates for active arms, women older than 25 and married women were both more likely to have detectable tenofovir, and these factors correlated to lower risk of catching HIV. In South African sites, the incidence of HIV acquisition per 100 PY was 8.7 (7.6, 10.0) vs 4.7 (3.8, 5.8) in women younger vs older than 25 and 0.9 (0.2, 2.7) vs 7.5 (6.6, 8.4) in married vs unmarried women.

Table 1: Primary efficacy results in VOICE study

	PYFU	No. infect-ions	Incidence /100 PY (95%CI)	HR (95%CI) (vs placebo)	p-value
Oral TDF	823	52	6.3 (4.7, 8.3)	1.49 (0.97, 2.3)	0.07
Oral TDF placebo	837	35	4.2 (2.9, 5.8)		
Oral TDF/FTC	1285	61	4.7 (3.6, 6.1)	1.04 (0.7, 1.5)	> 0.2
Oral TDF/FTC placebo	837	60	4.6 (3.5, 5.9)		
TDF gel	1026	61	5.9 (4.5, 7.6)	0.85 (0.6, 1.2)	> 0.2
Gel placebo	1030	70	6.8 (5.3, 8.6)		

C O M M E N T

This major prevention study failed to show benefit from potentially effective interventions due to minimal adherence, with rates that were especially low in the people at the highest risk of infection, even when incidence rates were higher than expected.

This highlights the urgency of more acceptable and effective interventions, including long-acting parenteral formulations.

Although minimal data are collected on partners in the study, this will be one of the many factors that will try to explain why participants were not actively retained in the study.

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Further studies on how male circumcision may reduce HIV transmission

Simon Collins, HIV i-Base

Two posters at CROI 2013 reported different potential mechanism for why circumcision reduces the risk of HIV heterosexual acquisition compared to uncircumcised men.

An understanding of the mechanism may allow alternatives to circumcision that mimic the active circumstances and offer a similar protection.

Minh Dinh and colleagues from Northwestern University, Chicago have presented research in this area for several years. Initial studies suggested this was related to a combination of greater numbers of target immune cells and a thinner keratin layer in the inner foreskin, however this was superseded last year with new data reporting that the penis glans (rather than inner foreskin) of uncircumcised men had higher concentrations of CD4 cells that were also closer to the surface membrane.

This year, the same group, presented a new study looking at whether moisture-related differences to the skin following circumcision by measuring cell capacitance (relating to moisture content) and trans epithelial water loss (TEWL) which correlates with decreased skin barrier function.

The study included non-invasive measures to compare ten men who had been circumcised in childhood, ten who had recent elected circumcision and ten uncircumcised men. In a related animal study, tissue biopsies were taken from ten male rhesus macaques were circumcised and followed for 12 months.

The group reported that skin barrier function was significantly reduced in the uncircumcised glans and inner foreskin as compared to the circumcised glans or shaft tissue (mean uncircumcised vs circumcised glans was 100.34 vs 43.60 g/m2h, $p < 0.001$, inner foreskin = 97.05, shaft = 43.05).

In explanted foreskin tissues, the inner foreskin was more permeable to tritiated water than the outer foreskin. In the macaques, TEWL decreased and skin capacitance increased over time after circumcision. This correlated to qualitative changes in the expression of filaggrin and E-cadherin from serial biopsies.

A second poster presented by Cindy Lui and colleagues looked at different microbes on the penis head by circumcision status. [2]

This was a prospective study that randomised 156 men in Rakai, Uganda to early (immediate) circumcision or deferred (for 24 months) circumcision.

Swabs taken from the coronal sulcus (the underside ridge where the penis head joins the shaft) at baseline and at 12 months measured bacterial activity using 16S rRNA gene-based quantitative real-time PCR and pyrosequencing analysis.

At baseline, men in each group had comparable total bacterial load and microbiota composition but this was significantly different 12 months after circumcision, with no changes seen in the deferred control group.

Circumcision significantly decreased the prevalence of 15 bacteria at the coronal sulcus, 12 of which are anaerobic bacteria and increased the prevalence of aerobic and facultative anaerobic bacteria. Circumcision also reduced the biodiversity, producing a microbiota that also had fewer dominant bacterial groups. The decreases in anaerobic bacterial load (–1157 to –25,327 16S rRNA gene copies) were greater than the corresponding increases in aerobic and facultative anaerobic bacteria (+8 to +2857 16S rRNA gene copies).

Although both anaerobic bacteria are not well studied in the male urogenital tract they are known to have pro-inflammatory capabilities and this may warrant further assessment. However, although these changes were significant they were not universal, indicating that environmental or host factors may play a role on the microbial effects of male circumcision.

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CROI 2013: CURE RESEARCH

Report of a functional cure in an HIV infected infant

Richard Jefferys, TAG

On Monday 4 March at the Conference on Retroviruses and Opportunistic Infections 2013 (CROI) in Atlanta, details were presented on a case of a potential "functional cure" of HIV infection in an infant.

The story has already broken widely in the media due to a CROI press conference held on Sunday afternoon, during which the researcher describing the case, Deborah Persaud, gave a preview of the data. The webcast of Persaud's talk is now available for viewing online. [1]

The context of the case report is unusual because the mother was not diagnosed with HIV infection until in labor, and there was no opportunity to give her antiretroviral therapy (ART) to reduce the risk of mother-to-child transmission. The infant was therefore considered at high risk of acquiring infection, and HIV DNA and RNA tests were performed at 30 and 31 hours after birth, respectively. The HIV DNA test was positive, and the RNA test showed a viral load of 19,812 copies. Although current U.S. guidelines recommend initiating a prophylactic regimen of AZT and nevirapine pending the results of virological testing, the treating pediatrician, Hannah Gay, chose to initiate combination ART including AZT, 3TC, and nevirapine (the latter at the therapeutic rather than prophylactic dose). Nevirapine was switched in favor of Kaletra after seven days. Subsequent sequential viral-load testing showed the typical decline in response to treatment, with measurements of 2,617 copies, 516 copies, 265 copies and then less than 48 copies (beneath the limit of detection).

ART was maintained for around 18 months until the mother and infant were lost to follow-up. When the infant was returned to care around five months later, Gay learned that treatment had been stopped. The reasons for the disengagement from care and cessation of treatment have not been made clear, with Gay stating in one article only that the mother was battling "some life changes." [2]

Testing of the infant after the return to care revealed a highly unusual outcome: viral load remained undetectable despite the five-month period off ART (there have been many studies of paediatric ART interruptions, all demonstrating that viral-load rebound occurs rapidly, typically to very high levels, almost without exception [3]). This prompted Gay to consult with external experts in pediatric HIV infection Deborah Persaud at Johns Hopkins University and Katherine Luzuriaga at Massachussetts General Hospital. The results of further investigations led to the findings presented by Persaud at CROI: several independent laboratories with expertise in searching for trace amounts of HIV evaluated samples from the infant but could only rarely detect extremely low levels of viral genetic material (there was no detectable replication-competent HIV).

These results echo those from follow-up studies of the single adult considered cured of HIV infection, Timothy Brown. Methods employed included digital droplet PCR, single-copy assays for HIV RNA, and a test for viral outgrowth from 22 million resting CD4 T cells. Immune responses to HIV, including antibody and CD4 and CD8 T-cell responses, were not detectable. Genetic studies showed that neither mother nor infant possessed the CCR5-Delta32 mutation or any HLA genes known to be associated with control of HIV replication. The totality of the findings has led the researchers to conclude that the infant represents a case of a functional cure of HIV infection (essentially an infant equivalent of Timothy Brown); the virus may not have been completely cleared, but at the current time—after over 10 months off ART—no viral activity is detectable.

Not too surprisingly, the media interest in the story has been intense. Several stories, including a piece in the New York Times, have included quotes from scientists suggesting the possibility that the infant was not infected in the first place. [4]

This scenario is difficult to reconcile with the stepwise decline in HIV RNA levels after ART initiation (this would have to involve not only four sequential false positive RNA results, but false positive results that also coincidentally mirrored the expected viral-load decline in response to ART—a possibility that seems vanishingly unlikely). Another sceptical viewpoint cited by some articles is that HIV might have been cleared even in the absence of ART. This suggestion is based on occasional reports in the scientific literature of apparent transient HIV infection in exposed infants [5]; however, a study published in 1998 that analysed many of these cases in detail showed that most were explained by PCR testing contamination or sample mislabeling. [6] Even the few reports that could not be fully explained by these problems were considered to be lacking the evidence necessary to formally prove that transient infection had occurred.

Some other aspects of the case deserve comment: although the baseline viral load of 19,812 copies might seem relatively low in the context of adult values, it should be noted that data on early viral loads among infected infants indicate this level is not atypical. A study published in 1998 reported that "all 18 infants defined as in utero infected by DNA PCR or co-culture (or both) were also positive with a wide range of plasma HIV-1 RNA values within 48 hours of birth and a median level of 26,940 HIV-1 RNA copies/mL (25th and 75th percentiles, 1,556 and 468,390)." [7]

In terms of other cases of pediatric ART interruptions in which viral-load rebound did not occur, a search of the literature did not turn up many examples. In 2006, researchers from Massachusetts General Hospital published a case report regarding a perinatally infected child who stopped ART as a teenager and maintained undetectable viral-load levels for five years of follow-up; the individual was heterozygous for the CCR5-delta32 mutation and, unlike the infant described by Persaud, displayed strong HIV-specific T-cell responses. [8]

A 2008 survey of outcomes among children and adolescents undergoing unstructured ART interruptions notes the following: "In only 1 patient (6% [1 of 17]) did HIV-1 RNA remain undetectable after 12 months off therapy." However, no additional information is provided, and the cut-off for the viral-load assay used was <400 copies. [9]

Based on the data presented, the Persaud case report appears unique, and the evidence that HIV infection occurred and has subsequently been controlled or even cleared after short-term ART is more compelling than some of the skeptical comments in the press have suggested. However, there is a lack of stored samples that might be able to bolster the evidence by confirming the genetic relationships between the separate virus samples from the infant and the linkage to the virus in the mother. It also remains possible that viral load could rebound at some point in the future.

The implications for paediatric HIV care and cure research are now the subject of ongoing discussions:

- Most basically, the case raises questions about the accessibility and quality of the health care system in Mississippi and the U.S. generally (as eloquently described in a posting by Jim Merrell of the Prevention Justice Alliance). [10]
- Deborah Persaud has cited the possibility of studying triple-combination ART instead of the normally recommended dual-prophylactic regimen of AZT and nevirapine in infants with HIV positive mothers who have not received prophylaxis, in order to assess whether similar outcomes can be obtained (the British HIV Association guidelines already recommend triple-drug therapy as postexposure prophlylaxis for infants whose mothers have detectable viral loads at delivery [11]).
- For other perinatally infected children treated very early with ART, it has been suggested that there is now reason to carefully study whether control of HIV might be maintained after ART interruption (the reason that many ART interruption studies have already been conducted in the pediatric population is the recognition that they face the greatest burden of lifelong treatment). A related proposal is that perinatally infected children on ART should be candidates for studies of approaches that might increase the possibility of HIV control after ART withdrawal (such as therapeutic vaccines). A poster presentation at CROI by Katherine Luzuriaga describes five early-treated children in whom no replication-competent HIV can be detected, and makes the point that these individuals are "prime candidates for interventions to achieve functional cure or eradication." [1]
- More broadly for the cure research field, the case suggests that early ART may have prevented the establishment of a long-lived latent reservoir of HIV-infected memory CD4 T cells. This suggestion fits with current efforts to deplete the latent HIV reservoir as a means to a cure.
- The question whether very early ART could lead to a similar outcome in adults might potentially be addressed by another ongoing study presented at CROI by Jintanat Ananworanich from Thailand, which involves a sizable population of individuals initiating ART at the very earliest stage of acute HIV infection (Feibig I). Ananworanich reported that the majority of individuals treated at this stage showed undetectable levels of integrated HIV DNA in both the blood and colon after 24 weeks of ART; future plans include analytical treatment interruptions to assess whether HIV viral load returns. [12]

On 11 March 11th in the Wall Street Journal, Dr Mark J. Seidner from Massachussetts General Hospital and Harvard Medical School published an opinion piece arguing that the case represents an example of successful infant post-exposure prophylaxis (PEP) against HIV infection, rather than a cure of HIV infection that had occurred in utero as Persaud and colleagues have suggested. [13]

There is a published case report of an adult recipient of an HIV infected blood transfusion who showed a single viral load value of 3 copies/mL (the lower limit of detection of the assay) but proved to be uninfected after receipt of PEP. However, there are also published studies that include assessments of viral load values in infants receiving PEP to prevent mother-to-child transmission and none appear to offer examples consistent with the idea that viral load values are detectable in this situation e.g. a large French study from 2012, [14] and a US analysis from 2003 [15]; the latter reports two examples of low values in infants receiving AZT prophylaxis, but they are considered false positives because DNA PCR tests taken the same day were negative (unlike the case reported at CROI).

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ANTIRETROVIRALS

Dietary requirements changed in Europe for fixed dose combination rilpivirine/ tenofovir/FTC (Eviplera)

On 20 March 2013, Gilead isseud a letter noting that the European Medicines Agency (EMA) had modified the Summary of Product Characteristics (SPC) for the fixed dose combination rilpivirine/tenofovir/FTC (Eviplera). [1]

The new recommendation is to take Eviplera "with food". Previously the indication was "take with a meal" (See Section 4.2 in the SPC). [2]

This was based on a review of results from a pharmacokinetic study that was presented at the Glasgow conference, reporting a slightly different impact of food on rilpivirine absorption when part of the fixed dose combination Eviplera compared to when taken as a separate medication. [3]

This study reported that rilpivirine and tenofovir exposure are increased after intake of a standard (533 kcal, 21 g fat) or light meal (390 kcal, 12 g fat) relative to fasting conditions. Compared to fasting conditions, rilpivirine AUC was 9% and 16% higher with a light meal or standard meal, respectively. Compared to standard meal, RPV AUC was 14% and 6% lower with fasted or light meal administration, respectively. These details have not been added to Section 5.2 of the SPC on pharmacokinetic proterties.

These changes only relate to the prescribing information with regard to food intake for the FDC formulation. The SPC for single agent rilpivirine still retains the requirement to take with a standard (533 kcal) meal.

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EU adopts positive opinion for decision on regulatory approval of Quad

On 22 March 2013, Gilead announced in a press release that the EU has adopted a positive opinion for the once-daily, single tablet regimen Stribild (previously developed as Quad).

This indication is for use in treatment-naive and treatment-experienced patients.

Quad contains elvitegravir, an integrase inhibitor, and cobicistat, a PK booster, with tenofovir and FTC and was approved in the US in August 2012.

The decision came from the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA) and such recommendations are usually followed. Full approval is therefore expected within three months.

Reference

Gilead PR. European CHMP adopts positive opinion for Stribild, a once-daily, integrase inhibitor-based, single tablet regimen for the theatment of HIV-1 infection. (22 March 2013).

Gilead Sciences announces fourth quarter and full year 2012 financial results

On 4 February 2013, Gilead announced details of its antiviral product sales which increased 17 percent to $2.17 billion for the fourth quarter of 2012, up from $1.86 billion for the fourth quarter of 2011.

This reflects sales growth of 20 percent in the U.S. and 9 percent in Europe.

For 2012, antiviral product sales increased 15 percent to $8.14 billion from $7.05 billion in 2011, reflecting sales growth of 21 percent in the U.S. and 6 percent in Europe.

Source: Gilead press release. Gilead Sciences announces fourth quarter and full year 2012 financial results. (4 February 2013).

http://www.gilead.com/press

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ViiV stops development of NNRTI lersivirine

On 5 February 2013, in a letter to community organisations, ViiV Healthcare announced that it has stopped the development programme of the investigational NNRTI lersivirine. [1]

The letter states: "After much deliberation about how to proceed with lersivirine, it was determined that the compound would not provide an improvement over existing medicines in the NNRTI class, and that R&D resources for ViiV Healthcare should prioritize efforts to identify compounds that further HIV treatment. We remain committed to exploring candidates that will advance HIV treatment and contribute to improving outcomes for people living with HIV".

It continued: "Individuals currently enrolled in trials to investigate lersivirine will be switched to an alternative HIV treatment regimen upon study discontinuation. However, if there are individuals that are benefiting from lersivirine for whom an appropriate alternative treatment option cannot be prescribed, we will continue to offer lersivirine until such time that they are no longer deriving clinical benefit".

This coincided with the publication in JAIDS of 48-week results of a phase 2b study comparing lersivirine to efavirenz in treatment naive patients. [2]

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FDA update atazanavir label to include risk of gallstones and kidney stones and new drug interactions

Several changes were made recently to the US label for atazanavir (Reyataz).

This focused on inclusion of nephrolithiasis and/or cholelithiasis in the section on side effects, adding nephritis, and added new information on drug interactions regarding coadministration with boceprevir, carbamazepine, phenytoin, phenobarbital, lamotrigine and voriconazole.

For full details see the revised full prescription information.

Source: FDA list serve. Recent changes to the Reyataz (atazanavir sulfate) capsule labeling. (8 February 2013).

http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm339009.htm

Nelfinavir non-renewal of marketing authorisation in the EU

The marketing authorisation for nelfinavir (Viracept) ended on 23 January 2013 and is no longer valid in the EU. [1]

This was expected, as last year, manufacturers in the EU, Roche Pharmaceuticals, announced that it was not going to reapply. The original authorisation was granted in January 1998 and was subsequently renewed for additional 5-year periods in 2003 and 2008.

Despite having reduced potency compared to other protease inhibitors, nelfinavir was once widely prescribed and did not require ritonavir boosting. Although a paediatric formulation was available, the volume of powder required for reconstitution limited its use by children. However, nelfinavir was the only available protease inhibitor in many countries, until reduced price heat-stable lopinavir/ritonavir (Aluvia) was launched in 2006.

The dramatically reduced use was not helped by a manufacturing problem that resulted in product recall and a brief discontinuation of supply in 2007. [2]

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TREATMENT STRATEGIES

Why the "when to start" question is complex and informed by limited evidence: a response to Dr Myron Cohen

Simon Collins, HIV i-Base

Introduction

This article was prompted by contributions to the "when to start" debate that avoid both it's complexity and the lack of evidence for benefits at higher CD4 counts. This issue has broad concern for HIV positive people, doctors and health workers, and public health policy.

While this is principally a response to an online interview with the respected researcher Dr Myron Cohen [1], many of the points are similar to other presentations and articles about earlier treatment.

In such examples, a dramatic change in policy – a public health approach of universal treatment on diagnosis - is presented as self-evident based on plausible benefits. Neither the lack of evidence to make it possible to evaluate the risk in relation to the benefits, nor the contradictory evidence (generally from large cohort studies) is discussed in detail. This response is to emphasise the need for greater transparency in the evidence for this change in policy, without which HIV positive people and their treatment providers will be unable to make accurately informed choices.

Dr Cohen's interview included interesting ideas about other aspects of treatment: including that we have a wide range of effective drugs, that doctor experience is important to get the best results; and that cure research and pipeline drugs may make today's treatment unrecognisable in ten years time. But the main areas of concern for treatment at high CD4 counts include:

- Overstating the evidence in the guidelines, understating the quality of that evidence and over-simplifying the final recommendations.
- Merging the health benefits of treatment with the impact on reducing transmission, rather than keeping these distinct.
- Suggesting that earlier treatment reduce deaths.
- Ignoring the broad range of individual immune responses to HIV.
- Creating an urgency that is not supported by the very low risks at high CD4 counts and using emotive language to scare people to use treatment.

Guidelines and evidence for the CD4 count at which to start treatment

The interview starts by saying that both the US DHHS and IAS-USA guidelines recommend "immediate" treatment irrespective of CD4 count. Dr Cohen states: "This is a pretty big change, and it represents the accrued benefits, which are very, very strong".

Clearly something major has happened in the guidelines – which is true. However, the implication that this is due to incredibly certain benefits that outweigh the risks is far less clear. There is an emphasis on urgency with "immediate" treatment. We learn that "earlier treatment is better" and that "this is pretty much written in stone".

The context of guideline changes is then presented as a simple linear progression from 200, through 350 and 500 to the US move "to start people immediately" but missing that until 2001, the US guidelines recommended a CD4 threshold of 500, even with AZT monotherapy, noting plausible benefits from starting higher. The reality of side effects and drug resistance dropped the CD4 threshold to 200, with limited use at 200-350 and the improved safety and efficacy of more recent drugs weighted the risk:benefit balance towards earlier treatment. Also, although there are other considerations for starting treatment (hepatitis coinfection, pregnancy, age etc) the focus on CD4 count is helpful for this main discussion.

Even with the best intentions, guidelines produced by experts, can be wrong when adequate data is not available. This lesson should have been learned: we don't yet have the data for risks when CD4 counts are highest. Even less complex, healthier, motivated patients in a clinical trial on the latest combinations fall short of 100% efficacy by 10-30% leading to drug resistance and evidence of harm.

Although few studies since 2009 provide evidence of the benefits and risks of ART at high CD4 counts, US guidelines (ie for an advanced wealthy setting) have switched from 350 to 500 and now to treatment on diagnosis. An example of why the differences between starting at 350 or above 500 are likely to be so slight, is that the large international randomised START study is expected to need to follow more than 4000 patients for six years to see a difference. [2] Also, modelling studies report life-expectancy for HIV positive people normalising to HIV negative populations, were calculated based on starting treatment at 350. [3] Some of the complexities this produces for resource-limited settings are also discussed below.

Table 1 includes the most significant studies and guidelines relating to when to start treatment. Most of the studies struggle to find evidence for benefits at CD4 counts over 500 and most of the guidelines note the limited evidence on which their recommendations are made and the low quality of the evidence. Not all studies are equal and guidelines recognise the vulnerability of recommending treatment at high CD4 counts by grading the strength of the recommendation low because, this is largely based on expert opinion. Every time the recommendation to start treatment at high CD4 counts is stated, it is misleading not to also state that the level of evidence for this is low.

Table 1. Rationale and evidence for earlier treatment

	Study or document	Summary comment	Refs
Randomised clinical trials (RCTs) This type of study provides the most reliable evidence based on both risks and benefits of an intervention.	CIPRA HT-001 (Haiti) (2010)	Clear health and survival benefits were shown from starting at 200-350 vs waiting until less than 200.	[4]
	SMART (naive sub group) (2008)	Waiting until CD4 <250 had an increased risk of serious events compared to the early treatment group (median CD4 440).	[5]
	HPTN-052	Reduced risk of health events when starting at 350-550 compared to waiting until <250 (ie starting late). No difference in survival.	[6]
Cohort studies This type of study is used when RCT data is not available. It usually involves many more people than an RCT but the results are less reliable. This is because without randomisation it is impossible to adjust for the other things that make people who start treatment earlier different from people who start late.	ART-CC (2009)	ART-CC showed combined health and survival benefit from starting at 350-450 compared to waiting until 250-350 but no significant difference in survival. No survival difference when starting at 450-550 compared to 350-450.	[7]
	NA-ACCORD (2009)	Starting at 350-500 reduced the risk of death compared to waiting until <350. Survival benefit reported when starting >500 compared to <500 but very small numbers of deaths so absolute impact of ART is not possible to estimate. The way this study analysed data has also been challenged.	[8]
	HIV CAUSAL (2011)	Estimated that starting at 350-500 has a reduced risk of an AIDS defining illness compared to <350. No difference seen in survival.	[9]
	CASCADE (2011)	No significant difference in illness or death starting at 350-500 compared to <350. No benefit in either health or survival from starting at 500-800.	[10]
	COHERE (2012)	Benefits in health outcomes including deaths were reduced as CD4 category increased. This included people starting at >500 but the paper notes that this is so small as to be of "little clinical relevance for most patients".	[11]
Concern about inflammation	SMART (2008) ANRS (2009)	Growing awareness and concern with period of detectable viral load. Link to increased risk of serious "non-AIDS" events including heart, kidney, liver disease, neurological complications and some cancers. See the 2013 DHHS guidelines below for an excellent summary and discussion but the references (mainly from 113-127 in the when to start section E) outline basis for concern. Only two are from 2011 and most are significantly earlier.	[12, 13]
Key guidelines The guidelines help explain the complexity of the limited evidence. It is important to read the text and not just the table summary recommendations. All three guidelines come to different conclusions based on the same evidence.	US DHHS (2012)	Evidence base of clinical benefits is reduced as CD4 count gets higher. Strongest recommendation is for starting <350. Then for 350-500. The benefits for starting above 500 are based on expert opinion worried about the potential implications of keeping a detectable viral load. Prevention is discussed but clinical benefits are the main focus of these guidelines.	[14]
	IAS-USA (2012)	Recommendation to offer treatment to all patients at any CD4 count. Strongly influenced by the potential impact on reducing transmission. However the strength of evidence was highest for starting at <500. There was only moderate support for starting at >500, and this was based on the lowest rating for evidence.	[15]
	BHIVA (2012)	UK guidelines recommend starting at 350 or before CD4 count drops below 350. Based on lack of randomised data showing earlier benefit and conflicting results from observational studies.	[16]
	WHO (2009, 2012)	WHO treatment guidelines use 350 for clinical benefit based on moderate evidence for clinical benefit. In guidelines for serodifferent couples, ART use for prevention is supported by strong evidence.	[17, 18]

Treatment as prevention and the risks of merging benefits

Even when reviewing the additional benefit from prevention, treatment guidelines are rooted in recommendations that are primarily focused on clinical need. [14, 15, 16]

But the impact of treatment on prevention is an area where new data is strong. Evidence includes several large and important randomised studies, showing a dramatic impact from treatment on reducing the risk of sexual transmission.

One of these studies was HTPN-052, for which Dr Cohen was the lead investigator. HPTN-052 proved clearly that ART dramatically reduces the risk of heterosexual transmission and that the magnitude of protection exceeded that reported by condom studies alone. For this it was ground-breaking. [5]

But on a population level, being HIV positive does not necessarily mean that you transmit HIV. On an individual level, you may not even be having sex. You may be having exclusively safe sex, either by the choice of activity or careful and consistent condom use. Or your partner may also be HIV positive, and HIV transmission is only an issue in the context of drug resistance.

In the context of informed choice, starting earlier treatment to reduce the risk to your sexual partner(s) can be important and can improve the quality of life for both HIV negative and positive people. WHO guidelines developed for resource limited settings recommend ART at any CD4 counts for serodifferent couples to reduce transmission. [18] It can reduce remaining anxiety for both partners and has given many people the peace of mind for improved sexual health. This comes from knowing that even with continued condom use, if a condom breaks, that passing on HIV is highly unlikely.

But the temptation to merge treatment benefits (probably tangible but slight at CD4 counts over 350) and prevention benefits (dramatically reduced for anyone with sustained viral suppression) needs to be resisted.

These are important caveats when considering a public health initiative to treat everyone on the premise that an HIV diagnosis equates to transmitting HIV.

Approximately 40% of ongoing transmissions may occur during primary infection (highly infectious) though this varies from approximately 10%-90% depending on the population being studied and the modelling. This is likely to disproportionately affect epidemics linked to higher number of sexual partners (such as MSM in the UK) and is likely to shift oral sex for gay men from a low to high risk. Another significant proportion of new infections relates undiagnosed chronic infection. The use of earlier treatment is unlikely to have a direct public health impact related to either of these key populations.

Dr Cohen states that in the context of heterosexual transmission "it becomes pretty clear that treatment renders them no longer contagious" but modifies this to "nearly 100% protection when adherent" to recognise that some transmissions still occur. This ignores concerns about drug levels in the genital tract, persistent shedding, lack of data, modelling problems, cost, adherence, the "inconvenient truth" about acute transmissions. These were just some of the reasons that Dr Cohen used to vociferously argue against "The Evangelical Test And Treat Movement" at the BHIVA conference in Autumn 2010. [19]

While that talk was an overly cautious and pessimistic review, it is difficult to see the volume of evidence since 2010 for such a rapid reversal in his views. Even the NA-ACCORD study – controversial in its methodology, but often referenced as observational cohort data supporting earlier treatment at CD4 >500 had been published 18 months earlier (in April 2009).

As supported in most guidelines, access to treatment to reduce transmission should be an option at any CD4 count. The reason for this use of treatment needs to be a clear patient choice.

Health benefits from earlier treatment: does this save lives?

Dr Cohen states that the HPTN-052 study had a "fairly big impact on health and survival", merging very different endpoints.

Although earlier treatment was not associated with harm, the clinical benefits were far less dramatic:

- People in HTPN-052 were starting treatment at a CD4 count of 250 compared to 350-550. So any benefits could be driven by the low start threshold and not the benefit of treating above 350.
- There was no statistical difference in the number of deaths between the two groups (out of nearly 900 people in each group there were 10 deaths in the early treatment group vs 13 in the group that waited until 250), with a p-value of 0.5 showing no difference and no hint of a trend.
- There was no difference in serious "non-AIDS" events such as major organ complications and some cancers that would be expected from reducing viral load and related immune inflammation/activation.
- Higher events were driven by extrapulmonary TB at two study sites in India, with no difference in pulmonary TB. (An important note is that in high TB settings, earlier HIV treatment may reduce the risk of new TB infections).

Survival is a life and death matter. It is clearly important to doctors and patients. Anyone saying that "immediate" treatment for everyone upon diagnosis will reduce deaths, needs evidence to show this. Merging clinical benefits (less sickness - that is relatively minor and treatable) and survival benefits (less deaths) into a combined endpoint in this context is not helpful.

Combining survival and better health is common in studies. Better health is clearly important. But earlier treatment improved health by not getting some symptoms. Earlier treatment, in nearly all the studies in Table 1, did not reduce deaths.

Individual responses to HIV

Dr Cohen recognises that widely different HIV progression rates highlight a downside to universal treatment on diagnosis, but he is happy to treatment people who don't need treatment for the public good.

So while one-third of people progress rapidly, with a CD4 count dropping below 350 within two years of infection, 25% of people maintain CD4 counts higher than 500 for at lest five years and some for considerably longer. [20] A much smaller percentage, called "elite controllers" also have an undetectable viral load without treatment.

This wide diversity of responses to HIV does not argue for the urgency of "immediate" treatment for everyone. The most significant assault from HIV on the immune system probably occurs within the first weeks of infection. The burst of viraemia, commonly above 1 millon copies/mL is highly infectious and decimates CD4 cells based in the gut. Despite this, most people then generate an immune response that holds HIV at bay for many years. While viraemia during chronic infection is not a good thing, and valid concern supporting earlier treatment, quantifying the associated risk has still to be determined.

Earlier treatment clearly maintains higher CD4 counts. But the example of starting at 440 compared to 220 is too easy. The context of immediate treatment needs to aim higher, and with confidence. What about starting at 1100 compared to 900. Or 900 compared to 700. After 15 years experience with ART, the best cohort studies struggle to find consistent evidence for 700 compared to 500.

Similarly, the benefits of treatment may reach a stable ceiling after five or ten years. If this is the case, the argument that over a lifetime there is little difference between 35 or 40 years on treatment becomes flawed. With no clinical urgency for treatment, this might become a difference of between 25 or 40 years, which is significantly different.

Side effects vs untreated HIV

The effective management of side effects is acknowledged as a caution to wider use of treatment, but the data do not exist to weight the risks and benefits. Randomised studies have not been completed and observational cohorts don't collect this data. As examples of risks, all combinations seem to reduce bone density, some people commit suicide on efavirenz, and the mechanism for fat accumulation is still unknown.

Dr Cohen notes that there "may be adverse events (side effects) at higher CD4 counts" but says this will be balanced by the "clinical benefit [...] of protecting organs".

This issue is important - the SMART study showed that people on treatment had fewer serious major organ complications (heart, liver, kidney) and reduced risk of some cancers, if they had a suppressed viral load on treatment, compared to people who interrupted treatment, even at CD4 counts over 350. SMART showed treatment to be far safer than was originally realised, and its results have driven a whole field of research into the implications of untreated HIV.

Damage from ongoing viral replication off-treatment is quite possible, or even plausible. Some studies have shown biomarker differences between even elite controllers and HIV negative people. But this is currently a research hypothesis and we are talking about lifelong treatment, for possible "subtle" differences.

Global health

Global health is only briefly touched on in the interview, but this is important given that in most countries most patients have access to fewer treatment choices. Simplifying the benefits of earlier treatment irrespective of the setting has specific risks.

Concern that WHO guidelines might increase the threshold for treatment from 350 to 500 was the focus of a review in the last issue of HTB. [21] These concerns are not about restricting access to treatment: WHO guidelines already recommend access to treatment for prevention at any CD4 count for serodifferent couples. They are about the risk of harm, in settings where access to resources and choices are dramatically reduced.

Wealthy settings have over 20 approved drugs from at six drug classes. Most countries base treatment on less than six drugs from two, or perhaps three classes. Access to second-line treatment is often extremely limited and is more expensive. Second-line treatment is also less effective because lack of viral load and resistance monitoring means people usually have far higher rates of drug resistance. Third-line treatment is even more rare.

Perhaps 50% of HIV positive people globally still use d4T (stavudine). The benefits of d4T-based treatment will not outweigh the risks of using it in a combination on diagnosis, at 500 or even 350. When this was the option in Western countries, the side effects were so severe that we set our guidelines at 200. When d4T is not in the combination, then 350 has the strongest evidence.

Treatment stock-outs are still common and are likely to pose a much greater safety concern than risks from HIV in someone with a high CD4 count. [22, 23, 24]

HIV positive people taking treatment for clear clinical benefits are most likely to have their treatment fail because of a break in their drug supply. No matter how perfect their adherence to taking meds, if there is a stock out and you are forced to stop treatment, you risk developing drug resistance as drugs levels in your blood fall during the first weeks off treatment. Restarting treatment when the supply returns will have only limited benefit for people in who resistance developed. It is difficult to see uninterrupted lifelong treatment be guaranteed when minimum financial targets for the Global Fund are missed year on year.

In the context of priority, in public health, in lives saved and health maintained, treatment above 350 for clinical benefit is not even on the radar in most resource-limited countries.

Patient choice and the decision to start

To further emphasise the urgency of immediate treatment, Dr Cohen says that the concept of a person being "ready to start" treatment suggests that a doctor-patient discussion to arrive at this position might project "a false sense of security" that "all is well".

This central tenet of treatment guidelines – readiness to start – is one that activists have demanded and supported because of a high risk of failure when the need for treatment and how to use it is not understood. Whether someone is starting treatment on diagnosis, using a CD4 threshold of 500, 350 or 200 – for their personal health or to reduce the risk to their partner – it needs to be an informed choice.

Throughout the interview, language is used that increases anxiety, rather than providing information for an informed choice. This includes the "urgency" discussed above, but also emphasises the fear of the unknown. An HIV diagnosis is still traumatic for most people. It is a life-changing event. The decision to start treatment is similarly important.

Scaring people into the decision, whether for future health risks or on a public health agenda, will help no-one.

Conclusion

The plausibility of potential benefits of treatment on diagnosis has been argued since AZT monotherapy. No virus is better than virus. But at high CD4 counts there is too little evidence to know whether lifelong treatment is better than asymptomatic HIV.

Currently, the evidence (and expert interpretation of the same evidence in different guidelines) still supports equipoise for many people on the question of whether benefits outweigh the risks of earlier treatment at CD4 counts above 350. Results from the START study, expected in 2016, will provide the strongest real data to inform this question. [2]

This doesn't mean nothing can be done until then, but guessing the results – or worst still, pretending the evidence already exists – has a serious risk for being wrong.

HIV positive people should have the option to start treatment at any CD4 count, especially to reduce the risk of transmission to sexual partners. But to be an informed choice, this needs to acknowledge that the evidence for personal health benefits at high CD4 counts has plausibility, but limited data.

Until 2016, a wide range of studies suggest both a low absolute risk from starting earlier treatment if this is an individual's choice and a low absolute risk from deferring until 350 if that is an individual's choice. This is especially important to remember for people enrolled in the START study, who will ultimately help settle this key question.

Simon Collins is a member of the Community Advisory Board for the INSIGHT group that is currently running the START study. This article was based on a previous weblog. [25] Thanks to the HTB editorial board for support and comments.

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TREATMENT GUIDELINES

US (DHHS) ARV guidelines updated: moderate recommendation to treat at CD4 count >500 is based only on expert opinion

Simon Collins, HIV i-Base

The DHHS adult and adolescent treatment guidelines are widely seen as the most important US document to outline optimised care.

Although the guidelines are reviewed throughout the year (the panel has monthly calls), major updates are usually annually and the latest version was released on 13 February 2013. [1]

The document in an important summary of current evidence and as such, it is essential reading to follow changes in the recommendations. It is also important to see which studies over the last year are seen as sufficiently relevant to change care. As good practice, changes since the last significant update from March 2012, are highlighted in the PDF file with yellow background.

The guidelines are extensively reference for their evidence base and the writing panel includes leading US doctors and advocates.

The main changes in this update are listed below.

- In the introduction, in addition to reducing mortality and morbidity, ART is effective at reducing risk of transmission. Also that less than one third of HIV positive people in the US have an undetectable viral load, predominantly due to undiagnosed and failure to link to care. Discussions about health and prevention benefits of treatment should be started when someone is first diagnosed.
- The most significant change, perhaps, is to recommend ART for all patients irrespective of CD4 count, including early infection (defined as within six months of infection). The rating for this is BIII for people in chronic infection but counter-intuitively BII for early infection. The B rating makes this a "moderately strong" recommendation. The quality of evidence rating for early treatment (the II) comes from "one or more well-designed, non-randomised trials or observational cohort studies with long-term clinical outcomes". The quality of evidence for treatment at high CD4 counts in chronic infection is less reliable, being only "expert opinion".
- Although the priority in the guidelines is the medical benefit for the patient, the impact of treatment on prevention of sexual transmission is frequently stressed and is part of the combined decision to recommend earlier treatment. The evidence rating for reducing heterosexual transmission in AI and is AIII for "other risk groups".
- HCV coinfection includes a stronger recommendation to use ART including at CD4 counts >500 and in people with cirrhosis. HCV serology has also been added to list of recommended tests after HIV diagnosis.
- A paragraph on long-term slow progressors and elite controllers recommends treatment if viral load is detectable >200-1000 copies/mL or if the CD4 count is declining and notes higher levels of immune activation and inflammation markers (compared to HIV negative controls).
- All four preferred first-line combinations include the dual nucleoside option of tenofovir/FTC.
- The guidelines include a new discussion on the advantages and disadvantages of the choice for the other components of a combination: efavirenz, atazanaivr/ritonavir, darunavir/ritonavir and raltegravir (ordered by FDA approval date).
- The panel still strongly caution against the use of efavirenz in women who are not using contraception or who wish to conceive. For women who become pregnant while taking efavirenz, switching to an alternative drug is not recommended, because the period of risk if the first

5-6 weeks of pregnancy, usually prior to knowing about the pregnancy. Use of AZT is no longer recommended for women whose viral load is <400 copies/mL at delivery. The incidence of transmission is referenced at less than 0.5% in the context of the mothers viral suppression at delivery.

- Elvitegravir, coformulation with cobicistat, tenofovir and FTC (tradename Stribild, previously Quad) has a page to expand on why this is not currently a preferred combination, and to detail prescription restrictions.
- New discussions are included about the use of treatment in early infection, combining acute and recent infection with a definition of within six months of infection. This section emphasises that treatment is recommended for all HIV positive people but that in early infection "definitive data are lacking as to whether this approach will result in long-term virologic, immunologic, or clinical benefit". The references for this come from the ACTG 5217, SPARTAC and Primo-SHM studies that reported small short term benefits from a period of treatment in early infection (from 12 – 48 weeks). However, the guidelines use these studies to recommend lifelong treatment as strongly as they discourage interrupting treatment later.
- Drug resistance testing is recommended for integrase resistance in people using integrase-based combinations. Previously this was just considered.
- Tropism testing prior to prescribing a CCR5 inhibitor now includes genotype alternatives to phenotype tests.
- Drug interactions tables are updated with main chances relating to integrase inhibitors, and also to recently approved treatment for hepatitis C.
- Although cost of treatment is not directly addressed in the guidelines, Appendix B Table 8 list the suggested wholesale price (SWP) for individual ARVs, coformulations, and fixed dose combinations.

C O M M E N T

It is important to note that the recommendation to treat at any CD4 count above 500 is only rated at BIII. This is a moderate strength recommendation but evidence grading of III is based on the least reliable evidence (expert opinion, with no evidence either from randomised studies or observational cohorts).

It is also notable that references to the positive impact of treatment on prevention are included throughout the document and that both the strength of recommendation (A rather than B) and quality of evidence (graded as I rather than III) are stronger for this use of ART than clinical benefits.

For individual treatment decisions about when to start, these two benefits have to be discussed separately. For a further discussion on the complexities of the "when to start" debate, please see the article earlier in this issue of HTB ("Why the "when to start" question is complex and informed by limited evidence: a response to Dr Myron Cohen").

The inclusion of routine HCV screening on HIV diagnosis coincided with a new US study reporting a prevalence of 6% of HCV coinfection in a cohort of MSM followed from 1997 to 2009, and an incidence rate of 1.6/100 person years (95% CI 0.97–2.30) in approximately 400 men with more than one test. Only one-third of infections were in men who reported injecting drug use as a potential risk. [2]

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SIDE EFFECTS & COMPLICATIONS

No impact of ART on progression or regression of anal squamous intraepithelial lesions

Simon Collins, HIV i-Base

Results from a French study of 94 HIV positive gay men who were followed prospectively, prior to starting ART, reported a lack of regression of AIN precursor lesions associated with anal cancer and no beneficial association with increased CD4 counts on ART.

This study, from Christophe Piketty and colleagues was published as a concise communication in the 28 January 2013 edition of AIDS. [1] Participants were enrolled from the Hôpital Pitié-Salpetrière, Paris between March 2006 and October 2007.

Patients were evaluated for anal cytology, histology and anal HPV DNA at 3 months prior to starting cART (baseline), month 12 and month 24 of ART. Anal cytology was classified as normal, atypical squamous cell of undetermined significance (ASCUS), atypical squamous cell that cannot rule out high grade SIL (ASC-H), low grade SIL (LSIL) and high grade SIL (HSIL). A single pathologist was responsible for all histology results and the most severe results were used.

Median (IQR) baseline characteristics included age 39.4 years (IQR 33.3-43.4), time since HIV diagnosis 2.3 years (IQR 1.0 – 3.9), CD4 count 301 (IQR 242 - 339) cells/mm^3 and viral load 4.9 (IQR 4.3 – 5.2) log copies/mL.

In data from a sub-set of about 70 patients, median age at first intercourse was 20 (IQR 18-24) years and 66% had had more than 40 lifetime partners. Sexual activity included similar percentages of people having insertive and receptive anal intercourse, with approximately 45% estimated 1-100 times and 45% 100-1000 times. Only 7% estimated more than 1000 sexual experiences. Approximately 31% had a prior history of anal warts. 34% were current smokers and 16% were former smokers.

At baseline, 59% (45/76) of patients had an abnormal cytology results, with LSIL in 36% (27/76) and HSIL in 9% (7/76). After follow-up, these rates were 59% (40/68), 34% (23/68) and 15% (10/68) at month 12 and 52% (36/69), 33% (23/69) and 9% (6/69) at month 24, respectively.

The prevalence of any lesion at baseline was similar in patients with HPV-16 infection vs other oncogenic HPV genotypes (63% vs 53%, p=0.469) but HSIL prevalence was significantly different (18% vs 0%, p=0.013).

There was no significant relationship between ART, baseline or change in CD4, or viral suppression and the rate of acquisition or disappearance of anal lesions at any timepoint. Among patients with no lesion at baseline, 10 patients (35.7%) exhibited a SIL at month 12 (n=7 LSIL and n=3 HSIL). At month 24 these figures were n=5 LSIL and n=1 HSIL. Regression of anal lesions was observed, without specific therapeutic intervention, in all five patients with HSIL at baseline (n=4 to LSIL and n=1 to normal) at month 12; n= 2 ASC-H, n= 2 LSIL and n=1 normal at month 24.

At month 24, regression of the severity of lesions was observed in 44% (18/) patients with a lesion at baseline and new lesion occurrence was observed in 37% (10/27) without a lesion at baseline.

Ref: Piketty C et al. Lack of regression of anal squamous intrapathelial lesions despite immune restoration under cART. AIDS. 2013 Jan 28;27(3):401-6. doi: 10.1097/QAD.0b013e32835ad2cb.

http://journals.lww.com/aidsonline/Abstract/2013/01280/Lack_of_regression_of_anal_squamous.10.aspx

Osteonecrosis in HIV positive patients is associated with increased levels of CRP and D-dimer

Simon Collins, HIV i-Base

A retrospective case control study of 43 HIV positive patients with MRI-confirmed osteonecrosis of the femoral head (n=26 symptomatic, n=17 asymptomatic) had significantly elevated levels of the biomarkers C-reactive protein (CRP) and D-dimer compared to a control group of 50 HIV positive patients with negative MRI results.

This was a US study by Caryn Morse and colleagues from the National Institute of Health Clinical Centre and results were published as a concise communication in the 20 February 2013 edition of AIDS. [1]

All participants were already enrolled in other NIH studies, including a natural history study of osteonecrosis,

CRP is an inflammation marker commonly associated with cardiovascular disease and D-dimer is a coagulation degradation product and both have been associated with increased risk of mortality and serious complications in HIV positive cohorts, independently of CD4 and viral load.

Samples were used from osteonecroisis diagnosis (+/- 2 months) and from at least 6 months prior to and post diagnosis for the active group, with the control using samples from the time of negative MRI and 6 months later. Values below the detection limit of the assay were assigned a value of 0.21 mg/mL for D-dimer and of 0.16 mg/L for CRP.

Although baseline characteristics (at time of MRI) was similar for both groups, significant differences included longer median (range) duration of HIV infection (11.7 (1.6–19.5) vs 8.8 (0.4–16.4) years, p=0.003) and lower median (Range) CD4count (465 (12–1117) vs 686 (71–1705) cells/mm3, p=0.008) for the active vs control group respectively. Most participants were male (~90%) and on ART (~90%) with only 50% in each group having viral load <50 copies/mL. A high percentage of both groups had prior use of IL-2 (40% vs 60%, respectively).

Median levels of both D-dimer (0.32 vs 0.22 mg/mL; p=0.016) and CRP (2.52 vs 1.23 mg/L; p=0.003) were significantly higher in the active vs control group and remained significant after adjustment for viral load and anticardiolipin antibody status.

However, in linear regression analysis, the patterns of elevations were different for each biomarker after adjusting for viral load. D-dimer increased from the prediagnosis to diagnosis time point only in the osteonecrosis group (from 0.2 ug/L to 0.4 ug/L vs 0.2 ug/mL in controls). CRP levels remained stable (slope = zero) in each group over time. No difference was seen in D-dimer or CRP levels between the asymptomatic and symptomatic patients in the osteonecrosis group.

In the discussion, the authors noted that elevations in D-dimer are associated with the development of osteonecrosis, but that CRP elevation predate the development of osteonecrosis, suggesting that at-risk patients have persistently higher levels of chronic inflammation; and that both markers could potentially help identify patients at higher risk of osteonecrosis.

Ref: Morse CG et al. Elevations in D-dimer and C-reactive protein are associated with the development of osteonecrosis of the hip in HIV-infected adults. AIDS 27(4):591–595. 20 February 2013. doi: 10.1097/QAD.0b013e32835c206a. http://journals.lww.com/aidsonline/Abstract/2013/02200/Elevations_in_D_dimer_and_C_reactive_protein_are.11.aspx

Cognitive disorders are common in French cohort but are not HIV-related

Asya Satti, HIV i-Base

A French study has reported that neurocognitive impairment (NCI) was common in a group of unselected HIV positive adults, but that this was not related to either HIV or HIV treatment.

The study highlighted the importance of preventative measures such as control of cardiovascular risks, and the screening of anxiety and depression, in addition to effective ART. This will become increasingly important with an ageing population and increasing life expectancy.

This was a prospective study from Fabrice Bonnet and colleagues from the ANRS Aquitaine Cohort that consecutively enrolled 400 patients from five clinics between 2007–2009, and is notable for the inclusion of an MRI substudy for white and grey matter volumes. Results were published in the 28 January 2013 edition of AIDS. [1]

The study included standard intensive neuropsychological and cognitive assessment including difficulties in everyday life, plus medical history that included drug, alcohol and substance use.

If NCI was present, the severity was then categorised as asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) or HIV associated dementia (HAD), based on a score defined against a demographically adjusted normative score using US norms in at least two ability domains, without any symptoms.

Baseline characteristics included median age 47 years (42-53), median CD4 cell count 515 cells/mm3 (350-700) and 79% of patients were male. Approximately half acquired HIV as MSM, 37% heterosexual and 15% from IDU. Most (89%) were on ART and 85% had viral load <400 copies/mL. Although 24% were diagnosed as AIDS stage, only 5% had neuro AIDS. Coinfection with HCV or HBV was 22% and 7%, respectively.

The study reported NCI in 58% (95%CI 53.5 – 63.4%) of participants (234/400) with severity categorised as 20% ANI, 31% as MND and 7% with HAD. Neurocognitive tests detected similar rates of NCI in people reporting symptoms (62%) or no symptoms (57%). Motor function difficulties also related to poor cognition.

In multivariate analysis, symptomatic NCI was independently associated with (Odds Ratio; 95%CI): history of neurological AIDS event (OR 4.46; 95%CI 1.59, 14.9); lower level of education (OR 3.39; 95%CI 1.48, 7.80), anxiety (OR 2.93; 95%CI 1.67, 5.14), depressive symptoms (OR 2.11; 95%CI 1.23, 3.63), and any history of brain damage (OR 2.05; 95%CI 1.18, 3.58).

Perhaps surprisingly, symptomatic NCI was still reported in 18% (36/192) patients who had none of these associated factors,

No association was reported between NCI and HIV related factors including CD4 cell count and nadir, viral load, hepatitis coinfection, use of either efavirenz or AZT, or, notably, with CPE score. While generalised anxiety, depressive symptoms, alcohol dependence and neurological disease were all found to be related (a P-value of 0.46 and 0.004 respectively).

In the 178 patients with evaluable MRI scans, NCI of any category was associated with significantly reduced grey matter volume [650.9 (95% CI 639.7–662.1) vs. 627.3 (95%CI 614.8 – 639.9); p=0.006], and this remained significant when 14 people with previous CNS injury were excluded from the analysis (p=0.03). Although a trend appeared to relate to grey matter volume and severity of NCI, this was not statistically significant (p=0.098).

A significant association between cognition and poor lower limb muscle performance: 58% of patients with NCI also had lower limb muscle performance evaluated by 5STS test vs. 46% of those with no NCI (P=0.04). Those with symptomatic NCI (MND and HAD), 63% of them had a poor 5STS test performance compared to 47% of those with without symptomatic NCI (P=0.004). Poor lower limb performance in HIV-infected patients may be as a result of muscle function rather than NCI as patients performed well in balance tests.

C O M M E N T

This study is notable for being a representative clinic cohort with reasonable size data but reported similar prevalence to that seen in other European and US studies, which tended to be in selected populations.

Nearly everyone in the study was associated with some level of dysfunction (if the positive cognitive test results for people with no cognitive complaints are included) raising the difficulty of interpreting the practical significance in the absence of an HIV negative control group.

Although most dysfunction was either asymptomatic or mild, 8% of people in this well treated cohort had severe cognitive disorder categorised as HIV-associated dementia.

Ref: Bonnet F et al. Cognitive disorders in HIV-infected patients: are they HIV-related? AIDS 2013, 27:391–400. (28 February 2013).
http://journals.lww.com/aidsonline/Abstract/2013/01280

PAEDIATRIC CARE

Once-daily option for paediatric use of darunavir/ritonavir

On 1 February 2013, the FDA approved revisions to the darunavir (Prezista) tablet and oral suspension label to include paediatric use.

This included once daily dosing in treatment-naïve subjects 3 to less than 18 years of age and once-daily dosing in treatment-experienced subjects 3 to less than 18 years of age with no darunavir resistance associated substitutions.

Weight-based dosing tables are included by age, weight and treatment experience.

For full details please see the full label and/or online infromation from the FDA list serve.

Source

FDA list serve. Prezista (darunavir) tablet and oral suspension: pediatric dosing. (1 February 2013).

http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm337778.htm

TUBERCULOSIS COINFECTION

Tuberculosis MVA85A vaccine trial shows lack of efficacy in infants

Richard Jefferys, TAG

On 4 Feburary 2013, results from the phase IIb trial of the MVA85A vaccine in 2,797 infants in South Africa (given as a booster following BCG immunisation) were published in the Lancet. [1]

The vaccine proved safe but, disappointingly, failed to show signifcant efficacy. However, as the researchers note, this was the first infant efficacy trial of a new TB vaccine since BCG was last assessed as part of the Chingleput trial in 1968; as such, it is a major milestone for the field, and analyses of the results, including assessments of the immune responses induced by the vaccine, will make a vital contribution to advancing the development of new vaccine candidates.

Results from trials in adults are pending, and it remains uncertain if the lack of efficacy in infants will be mirrored in the adult setting.

MVA85A is a recombinant attenuated version of the vaccinia virus (cowpox) combined with TB antigen 85A. It was developed at Oxford University and is being evaluated as a booster of preexisting immune responses to antigen 85A, which are present in most people either as a result of BCG vaccination or natural exposure to TB.

Ref: Tameris MD et al. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. The Lancet, early online publication. 4 February 2013. doi:10.1016/S0140-6736(13)60177-4.

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2813%2960177-4/abstract

Lancet commentary:

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60137-3/fulltext

Press release from trial sponsors:

http://www.aeras.org/newscenter/downloads/news/aeras_news_1344.pdf (PDF)

i-Base/TAG annual TB pipeline report:

http://www.pipelinereport.org/TOC/tuberculosis-vaccine

BASIC SCIENCE

CD4 T cells specific for different pathogens vary in susceptibility to HIV infection

Richard Jefferys, TAG

When it comes to susceptibility to HIV infection, not all CD4 T cells are created equal.

There are a variety of factors that have been shown to influence how readily HIV gains entry and replicates, with the best-described distinction being between activated CD4 T cells, which are highly susceptible, and resting CD4 T cells, which are relatively resistant. The particular types of cytokines and chemokines that a CD4 T-cell makes have also been shown to influence the efficiency of HIV infection.

Less well understood is the influence of antigen specificity—the pathogen being targeted by the CD4 T cell. Evidence has been published showing that TB-specific CD4 T cells are highly susceptible [1], whereas those responding to the viral infection CMV are relatively resistant [2] (with this resistance being associated with the release of beta-chemokines capable of binding the CCR5 receptor and blocking HIV entry). A study by Haitao Hu and colleagues from the US Military HIV Research Program has now explored this issue further by looking at the susceptibility of various pathogen-specific CD4 T cells and the relationship with the genes that the different cells express. [3]

The results confirm that CMV-specific CD4 T cells are highly resistant to HIV, but not just due to release of beta-chemokines: gene expression analyses revealed that the cells also upregulate several innate antiviral factors such as IFIT1 (a protein that recognises a particular form of viral RNA). Because of these factors, CMV-specific CD4 T cells displayed reduced susceptibility to HIV infection even when the researchers used antibodies to neutralise any effect of beta-chemokines. In contrast, CD4 T cells specific for Tetanus Toxoid (TT) and Candida exhibited a pro-inflammatory Th17-type profile and were highly permissive to HIV infection. The researchers suggest that these differences in susceptibility may contribute to the well-documented relationship between differing levels of immune deficiency and risk of specific opportunistic infections; i.e. candidiasis is typically an early sign of immune deficiency whereas active CMV disease almost exclusively occurs at extremely low CD4 T cell levels.

Another important implication of the study is that HIV vaccines should aim to induce HIV-specific CD4 T cells with a profile that resembles CMV-specific responses. The researchers speculate that there may be a connection between their observations and the fact that the best results obtained to date in the stringent SIV/macaque model of vaccination have involved a CMV-based vaccine vector. [4]

Several research groups—including those of Louis Picker at the Oregon Health & Science University and Rafick-Pierre Sekaly at the Vaccine & Gene Therapy Institute in Florida—are now working to develop CMV-based HIV vaccine vectors with the aim of conducting human studies in both the therapeutic and preventive contexts.

Source

TAG Web Blog. CD4 T cells specific for different pathogens vary in susceptibility to HIV infection. TAG web Blog. (6 February 2013).
http://tagbasicscienceproject.typepad.com/

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RESEARCH UPDATES

START study increases sample size: additional 600 participants to be older than 35

Simon Collins, HIV i-Base

The international START study is on track to enrol the last of the initially proposed 4000 participants by May 2013. However, an additional 600 patients are due to be enrolled, which will require fewer final events and still have the study reporting primary results within three years.

As detailed in the study protocol, a blinded assessment of the event rate and baseline entry criteria was performed to review whether the projected event rate in the two arms combined was matching actual events during the enrollment phase, in order to modify the study numbers if this has an impact on the power of the study.

This analysis showed that event rates are lower than originally estimated and this could imply that the persons enrolled are healthier than assumed. The ongoing safety of both arms is clearly supported by this low event rate. Enrolment of the last 600 persons older than 35 years will assist in raising the event rate.

Conversely, the CD4 count when entering the study was higher than projected. The wider difference in CD4 counts between the deferred and immediate arms than originally projected reduces the number of endpoints needed in order to answer the study question: only 213 rather than 370 endpoints will now be required to retain 90% power on the primary endpoint of the difference between the two approaches in serious AIDS and non-AIDS events including mortality.

Continued adherence to the two strategies in the next three years (i.e. immediate vs deferred initiation of ART) is now an important focus of the ongoing study.

The projected minimum follow-up time for START remains unchanged at three years, with result still expected in 2016. The next review by the study DSMB will be in May 2013.

http://www.insight-trials.org

OTHER NEWS

US Senate supports bill to allow HIV positive organ donations to HIV positive recipients

Simon Collins, HIV i-Base

On 20 March 2013, the US Senate approved legislation that should end the long-standing ban against HIV positive people donating organs.

This is the first stage for the HIV Organ Policy Equity (HOPE) Act. [1]

The ban has been in place since 1998 and has prevented HIV positive people participating in living donor programmes to other HIV positive partners. [2]

The bill was endorsed by the American Medical Association.

Sources

1. Boxer, Coburn Praise Senate HELP Committee Passage of the HOPE Act.
   http://boxer.senate.gov/en/press/releases/032013.cfm
2. New York Times. A new push to let HIV patients accept organs that are infected. (11 April 2011).
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Update on AllTrials campaign for publication of full research results: PhRMA unhappy but GSK sign up

The previous issue of HTB included information about a new campaign calling for the publication of the results (that is, full clinical study reports including negative ones) from all clinical trials – past, present and future – on all treatments currently being used. [1]

Clearly unhappy, the US-based pharmaceutical membership and public relations organisation PhRMA has countered with a press statement from. [2]

It was timely that two days later GSK announced its support for the AllTrials campaign. [3]

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   http://www.gsk.com/media/press-releases.html

FUTURE MEETINGS

Conference listing 2012/13

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

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

19th Annual (BHIVA) 2013

16th – 19th April 2013, Manchester.

http://www.bhiva.org

14th International Workshop on Clinical Pharmacology of HIV Therapy

22 – 24 April 2013, Liverpool, UK.

http://www.virology-education.com

48th International Liver Congress (EASL 2013)

24 – 28 April 2013, Amsterdam.

http://www.easl.eu

Intl Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies

4 – 8 June 2013, Toronto

http://www.informedhorizons.com/resistance2013

7th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2013)

30 June – 3 July 2013, Kuala Lumpur, Malaysia.

http://www.ias2013.org

53rd ICAAC

10 – 13 September 2013, Denver, USA.

http://www.icaac.org

14th European AIDS Conference (EACS)

16 – 19 October 2013, Brussels, Belgium.

http://www.europeanaidsclinicalsociety.org

20th IAS World AIDS Conference

20-25 July 2014, Melbourne, Australia

http://www.aids2014.org

12th International Congress on Drug Therapy in HIV Infection

2-6 November 2014, Glasgow

http://www.hiv11.com

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website: 2012 update for PDA access

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

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

http://www.i-Base.info

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

Publications and regular subscriptions can be ordered online.

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

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

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

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

An average of 200,000 pages from individual ISP accounts contact the website each month, with over 6000 hits a day.

Non-technical treatment guides

i-Base treatment guides

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

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

- Introduction to combination therapy (April 2013)
- HIV testing and risks of sexual transmission (February 2013)
- HIV and quality of life: side effects & complications (July 2012)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009) - *currently only online.*

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.

HTB West Balkans

HIV Bilten is an edition of HTB in Bosnian, Monteragrin, Croatian and Serbian, for the West Balkans, produced by Q Club.

Why we must provide HIV treatment information

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

Translations of i-Base publications

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

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

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

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

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

Advocacy resources

Online treatment training for advocates

http://i-base.info/ttfa

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

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

UK CAB: reports and presentations

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

http://www.ukcab.net

Phoneline and information services

Treatment information request service - 0808 800 6013

i-Base runs a specialised treatment information service.

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

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

Online Q&A service

An online question and answer service that now has over 3000 questions and comments online. Questions can be answered privately, or with permission, can be answered online.

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

Other resources

Treatment 'Passports'

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

Generic clinic forms

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

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

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

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

Order publications and subscribe by post, fax or online

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

http://i-base.info/order

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

htb(e)

HIV TREATMENT BULLETIN (e)

HTB(e) is the electronic version of HTB, which is published six times a year by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered by fax or post using the form on the back page or directly from the i-Base website:
http://www.i-Base.info
by sending an email to: subscriptions@i-Base.org.uk
Editor: Simon Collins
Contributing Editor: Polly Clayden

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

HIV i-Base receives unconditional educational grants from Charitable Trusts, individual donors and pharmaceutical companies.All editorial policies are strictly independent of funding sources.

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http://www.i-Base.info

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

HIV i-Base

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

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