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CONTENTS

EDITORIAL 2
CONFERENCE REPORTS 3
7th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 30 June - 3 July 2013, Kuala Lumpur
- Introduction
- WHO 2013 guidelines: what about the missing formulations?
- WHO 2013 guidelines: when the risk:benefit may not favour starting at CD4 count of 500
- Efavirenz at 400 mg compared to standard 600 mg dose has similar efficacy with fewer side effects
- Dolutegravir update: treatment experienced patients and drug resistance
- Elvitegravir/cobicisat/tenofovir/FTC: Stribild studies at IAS 2013
- Non-standard combinations: NRTI-sparing combinations
- ARVs and bone health: the role of NRTIs in second-line therapy
- No viral load rebound off-ART following stem cell transplant: two "cure" cases using reduced intensity conditioning chemotherapy and CCR5 d-32 negative donors
- HIV cure research: further capsules at IAS 2013
- Partner-dependent immune differences may protect against HIV infection

CONFERENCE REPORTS 20
5th International Workshop on HIV Paediatrics, 28-29 June 2013, Kuala Lumpur
- Introduction
- Vertical transmission continues to decline in UK and Ireland
- Decline in late preterm delivery with vaginal birth in Europe
- High loss to follow up among asymptomatic women starting ART in pregnancy in Option B+ programme
- Decreased growth in ART exposed uninfected infants in Botswana
- Antiretrovirals, doses and formulations for children

CONFERENCE REPORTS 27
International Workshop on HIV and Hepatitis Virus Drug Resistance and Curative Strategies, 4-8 June 2013, Toronto
- Introduction
- Higher intracellular concentrations with tenofovir alafenamide (TAF) overcomes K65R and other key NRTI resistance in vitro
- Tentative phenotypic cut offs for dolutegravir: guidance for use with integrase resistance
- S/GSK744 and long-acting formulation indicate broadly similar resistance profile to dolutegravir

ANTIRETROVIRALS 31
- Dolutegravir approved in the US

TREATMENT ACCESS 32
- Ending global use of d4T: UNITAID to tip market to safer alternatives
- TRIPS extension for least developed countries
- Community request Gilead to study and develop separate formulation of new tenofovir prodrug

BASIC SCIENCE AND CURE RESEARCH 34
- Sad news regarding attempt to duplicate the cure achieved in Timothy Brown
- ART reduces HIV reservoirs in elite controllers: implications for cure research

PREVENTION AND TRANSMISSION 35
- Bangkok Tenofovir Study: US CDC recommends oral PrEP for injection drug users

OTHER NEWS 36
- CROI website: vital community and research resource vanishes
- FDA guidance for industry HIV development and trials

ON THE WEB 36
- TAG report: Immune system, HIV, and ageing
- RITA! summer issue: HIV and cardiovascular disease

FUTURE MEETINGS 37
DONATION FORM 39

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EDITORIAL

This bumper issue of HTB largely reports from three important medical meetings.

The 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention took place in Kuala Lumpur at the beginning of July. We include reports on the 2013 WHO guidelines, lower dose efavirenz (400 mg), dolutegravir, Stribild and several small NRTI-sparing studies. Cure research had a high profile with two new possible "cure" cases plus other studies. We include a report on the role of partner-dependent immune responses on HIV transmission and on the potential for generic versions of pipeline HCV drugs.

News from the 5th International Workshop on HIV Paediatrics includes the all time lowest level reported for vertical transmission of 0.46% in 2010.

And reports from the International Workshop on HIV and Hepatitis Virus Drug Resistance and Curative Strategies include important data on tenofovir alafenamide (TAF), dolutegravir and S/GSK744.

Treatment Access includes the good news that UNITAID has committed to help end the use of d4T. Less good, that Gilead might not develop TAF in a stand-alone version.

The Southern African HIV Clinicians Society

Since its inception in 1997, with a membership of approximately 250 members, the Southern African HIV Clinicians Society has

grown to a membership of over 15,000 in the Sub Saharan region and internationally - a clear recognition of the services and support provided.

The Southern African HIV Clinicians Society is the largest special interest group within the South African Medical Association (SAMA).

It is also the largest HIV interest group in the world.

The Society is thrilled to be part of the HIV Treatment Bulletin South initiative. This is a valuable publication for all Health Care

Practitioners. This publication has essential, current and scientific information about research and HIV treatment updates with particular implications for clinical practice.

For more information about the Society or on how to become a

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CONFERENCE REPORTS

7th IAS Conference on HIV Pathogenesis, Treatment and Prevention

30 June - 3 July 2013, Kuala Lumpur

Simon Collins, HIV i-Base

Introduction

It was somewhat unnerving, in an understated way, that the IAS news was dominated by the launch of the WHO 2013 treatment guidelines, upstaging another WHO publication heralding that close to 10 million people in low- and middle-income countries are now on ART. [1, 2]

The anticipated level of interest for the launch was so underestimated that even after moving to a room double the original size of the first satellite meeting, it was still standing room only. Our first reports cover these guidelines and some of their implications.

Opening plenary

The tone and context for the rest of the conference was set by Steve Deeks in the opening plenary lecture: the benefits of ART for those with access to modern effective drugs dramatically extends life but residual inflammation on ART may be clinically relevant, especially in an ageing population. [3]

After adjusting for all traditional risk factors, inflammatory biomarkers remain elevated during long-term ART and a single elevated biomarker (either IL-6 or d-dimer) predicts excess risk of morbidity or mortality ten years later. [4]

Several other studies, including the VA database suggest that that HIV accounts for a 1.5-fold increased risk for cardiovascular events, [5] but as inflammation predicts a wide range of complications including frailty, lymphoma, type-2 diabetes, cognitive function and mortality in general population studies this is a caution that is the increasing focus of research.

The interventions that Deeks currently recommends (to us and to his patients) are simple: exercise to keep physically active and switch to a Mediterranean diet. To be healthy at 70 years old you need to start when you are 40 (though not suggesting it is ever too late).

Also, optimistically, the international and collaborative research efforts targeted to an HIV cure make this an increasingly tangible goal. The two-day pre-meeting to IAS 2013 on cure research highlighted a broad range of approaches including use of dendritic cell vaccines developed from a patients individual viral proteins and approaches to target viral latency including the panobinastat study currently running in Denmark. [6, 7]

We of course report much more: paediatrics, pregnancy, PMTCT, new drugs, complications and transmission.

Many of the key oral presentations are available as webcasts, but unfortunately not all. Online coverage as we went to press is patchy and it is disappointing that many important sessions may not be posted online. Similarly, although many slide presentations are available, many are not.

However, all abstracts are online through the link to the Programme At a Glance online database for the meeting and contact details for many researchers are also available.

http://pag.ias2013.org/PAGHome.aspx

The year the conference has also posted webcasts from the press conferences on YouTube, including for the late-breaker sessions.

http://www.youtube.com/user/iasconference

The following reports are included in this issue of HTB and more will follow next issue.

- WHO 2013 guidelines: what about the missing formulations?
- WHO 2013 guidelines: when the risk:benefit may not favour starting at CD4 count of 500 cells/mm^3
- Efavirenz at 400 mg compared to standard 600 mg dose has similar efficacy with fewer side effects
- Dolutegravir update: treatment experienced patients and drug resistance
- Elvitegravir/cobicisat/tenofovir/FTC: Stribild studies at IAS 2013
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- HIV cure research: further capsules at IAS 2013
- Partner-dependent immune differences may protect against HIV infection
- Pipeline oral HCV drugs and generic global access: need to mirror ARV programmes

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IAS 2013: GLOBAL TREATMENT ACCESS

WHO 2013 guidelines: what about the missing formulations?

Polly Clayden, HIV i-Base

The launch of the WHO "Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection" at IAS 2013 caused quite a stir. [1] Glimpses of the top line recommendations in the run up to their release provoked much discussion - particularly about when to start – which continued throughout the conference.

Unlike previous editions of the guidelines, the consolidated guidelines combine recommendations for adults and adolescents, pregnant women and children. They also make recommendations on operations and service delivery.

They call for countries to start treatment in all HIV positive adults with a CD4 count of 500 cells/mm^3 or less, and to start at any CD4 count in several populations. The recommendation to start earlier plus widening other criteria immediately increase the number of people eligible for treatment from 16.7 to 25.9 million. The recommendations are based on a mix of evidence for the benefit to individual health, reduction in transmission risk, operational considerations and aspiration.

"Earlier, safer and simpler antiretroviral therapy can push the HIV epidemic into irreversible decline", the press release announced. This review in HTB only briefly summarises the "earlier" recommendations, which have been discussed at length elsewhere (although any offer of treatment to a healthy, asymptomatic person makes little sense without modern antiretrovirals), and focuses on the "safer and simpler" aspects of the recommended antiretroviral options.

At times the guidelines swerve between aspirational – for children options are largely based on formulations that are not yet commercially available – and unambitious – in the case of the omission of a generally preferred adult PI conversely because a suitable formulation is not currently available – but largely give us plenty to push for, including drugs and formulations not yet included.

Treatment and management of adults and adolescents in 2013 guidelines

When to start?

- At a CD4 count of 500 cells/mm^3 or less. People with 350 cells mm^3 or less and/or WHO clinical stage 3 and 4 are prioritised.
- At any CD4 count in people with active TB or HBV co-infection with evidence of severe chronic liver damage.
- At any CD4 count in people with HIV negative partners.
- All pregnant and breastfeeding women - those meeting the eligibility criteria for treatment should remain on lifelong ART.
- In generalised epidemics particularly, lifelong treatment is recommended for all pregnant women. Some countries can consider stopping ART after the risk of vertical transmission is over.

What to start?

Adult first-line recommendations are certainly simple with a reduced number of preferred regimens. Triple fixed dose combinations (FDCs) of the preferred regimen efavirenz (EFV), tenofovir disoproxil fumarate (TDF) and 3TC are available, as are those for the alternative ones. See Table 1.

Table 1. WHO Guidelines 2013: recommended ART regimens

1st line	TDF + 3TC (or FTC) + EFV preferred including pregnant women. AZT alternative to TDF. NVP alternative to EFV.
2nd line	ATV/r or LPV/r preferred. + TDF + 3TC preferred backbone if AZT or d4T 1st line. + AZT + 3TC preferred if TDF 1st line.
3rd line	No specific recommendations: INI or 2nd generation PI or NNRTI are mentioned.

There is a strong recommendation that "countries should discontinue d4T use in first-line regimens because of its well recognised metabolic toxicities". The guidance for programme managers' section also includes a box with key implementation considerations for phasing out d4T. What is not discussed is when to start in settings where a prompt transition from d4T has not occurred and is not happening - an estimated one million people in developing countries are still receiving this drug – see the related article by Simon Collins below.

UNITAID recently announced an initiative to enable better access to TDF-based FDCs by stimulating market competition and reducing prices by at least 30%. [2] Current annual costs are over 30 percent more for a TDF-based FDC than a d4T-based one - respectively US$ 130 vs US$ 79 per person per year [3] – this initiative should help to spur along more rapid phase out.

The recommendation to start with EFV includes pregnant women and a number of people have remarked that this is complicated to explain to health workers as the labeling for EFV still says that it is contraindicated in pregnancy.

Widespread EFV use can provoke concern from communities, particularly people that have experienced or witnessed bad CNS side effects. The ENCORE1 study presented at the conference which found 400 mg non-inferior to the standard dose of 600mg also found significantly fewer participants discontinuing treatment due to EFV-related side effects and fewer reporting them in the lower dose arm. [4, 5] This approach is promising and the 400 mg dose might be a better component of future FDCs but more information is needed on the durability of the lower dose in the presence of concomitant rifampicin.

For second-line boosted PIs the guidelines recommend lopinavir/ritonavir (LPV/r) and atazanavir/ritonavir (ATV/r).

The usually preferred boosted PI, darunavir/ritonavir (DRV/r) is only included in a footnote – puzzlingly in the same sentence as the suboptimal one saquinavir/ritonavir (SQV/r) – which says: "DRV/r can be used as an alternative PI and SQV/r in special situations; neither are currently available as heat-stable fixed-dose combinations, but a DRV + RTV heat-stable fixed-dose combination is currently in development".

In contrast, US Department of Health and Human Services (DHHS) and BHIVA guidelines both recommend ATV/r and DRV/r as preferred PIs and have LPV/r as an alternative. [6, 7]

WHO's own systematic review including six clinical trials comparing the three boosted PIs used for second line concluded that there was no evidence to support changing the recommendations from the 2010 guidelines. This was despite noting that two of the studies showed better virological response and retention in care for people receiving DRV/r than LPV/r, and its use in high-income settings.

The decision was not based on efficacy, safety, tolerability or sequencing but on the availability of a generic, heat-stable, FDC of DRV/r at a comparable price.

Several generic companies have heat-stable, co-formulated DRV/r in development but they might be reluctant to make the investment without a potential market. FDCs with heat stable RTV are not easy to produce. In the case of both LPV/r and ATV/r, a few attempts were necessary to get a suitable formulation within the regulatory limits of bioequivalence, so the companies will consider this an expensive risk. To have an FDC included in the Expressions of Interest (EOI) list of WHO prequalification (PQ), it needs to be in the guidelines – although there is likely to be an EOI later this year despite this cautious inclusion in a footnote.

If there were some countries prepared to adopt DRV/r, UNITAID could consider an intervention similar to what CHAI previously implemented with ATV/r – which broke the LPV/r monopoly, opened up a competitive ATV/r market, and dramatically increased access to second-line treatment. [8] Notably, in contrast to the 2013 approach to DRV/r, the 2010 guidelines recommended ATV/r before a suitable heat-stable FDC was available - WHO PQ and FDA tentative approval for the first ATV/r FDC occurred in November 2011.

There is also potential to reduce the current annual patient cost of DRV/r from US$900 to below US$350 – if it is used in volumes comparable to LPV/r – with process chemistry, dose optimisation and reformulation. [9] Stronger language from the guidelines on DRV/r would encourage investment in this work, as well as generic manufacture, country adoption, and donor investments to scale-up second-line treatment.

SQV/r is a mystifying inclusion. It is not a preferred or alternative option in DHHS or BHIVA guidelines because of a high pill burden and its initiation requires dose escalation and ECG monitoring due to its association with QT interval prolongation.

It is mentioned in the context of concomitant TB treatment at 400/400 mg twice daily. SQV/r is contraindicated with rifampicin at 1000/100 mg twice daily due to drug-induced hepatitis with marked transaminase in a study with HIV negative volunteers. [10] For 400/400 mg, the only available data is a conference abstract. In this Brazilian study 15/20 naïve patients receiving SQV/r 400/400 mg twice a day with TB treatment dropped out; 14/15 due to adverse effects (mainly hepatic and gastrointestinal). The authors did not recommend this regimen.

Although the relevance of this inclusion is very low as the use and procurement of SQV/r is virtually non-existent – with the occasional exception of west Africa for HIV-2 – it is inappropriate that it is mentioned in the same sentence as DRV/r.

Treatment and management of children in 2013 guidelines

When to start?

Infants and children should initiate antiretroviral therapy:

- Less than five years old regardless of CD4 count or WHO stage. Strong recommendation for children up to one year and conditional from one to five years.
- At five years and older with 500 CD4 cells/mm^3. Strong recommendation 350 cells/mm^3 and below, and conditional 350 to 500 cells/mm^3.
- With severe or advanced symptomatic disease (WHO stage 3 or 4) regardless of age or CD4 count.
- With a presumptive HIV diagnosis below 18 months.
- With active TB. As soon as possible within eight weeks following the start of TB treatment regardless of CD4 or WHO clinical stage.

What to start?

First-line for infants and children less than three years old:

- LPV/r-based regimens regardless of previous NNRTI exposure. If LPV/r is not feasible, NVP-based.
- Consider substituting LPV/r with an NNRTI after sustained virological suppression (defined as viral load less than 400 copies/mL at six months, confirmed at 12 months from starting treatment). Conditional recommendation.
- Children who develop active TB while on LPV/r- or NVP-based regimens should be switched to ABC + 3TC + AZT during TB treatment. They should switch back to the original regimen when their treatment for TB is completed.

The backbone should be one of the following (in order of preference): ABC or AZT + 3TC; d4T + 3TC.

First-line for children three years and older:

- EFV preferred and NVP alternative.
- Less than 12 years (or weighing less than 35 kg) the backbone should be (in order of preference): ABC+3TC; AZT or TDF + 3TC or FTC. Conditional recommendation.
- Adolescents 12 years (weighing more than 35 kg) should align with adults, the backbone should be: TDF+ 3TC or FTC; ABC or AZT + 3TC.

Which Second-line?

- After first-line NNRTI failure, a LPV/r regimen is preferred.
- After failure of first-line LPV/r, children less than three should remain on the regimen with improved adherence support.
- After failure of first-line regimen containing ABC or TDF + 3TC or FTC, the preferred backbone is AZT + 3TC.
- After failure of first-line regimen containing AZT or d4T + 3TC or FTC, the preferred backbone is ABC or TDF + 3TC or FTC.

Missing triple fixed dose combinations

By contrast, the recommendations for children are not so simple and very aspirational. In order to make the simplified first and second line recommendations for children feasible across all age groups nine possible regimens are needed, which could be facilitated with six triple FDCs. Only one (AZT/3TC/NVP) is currently available. [12] See Table 2.

Table 2. Triple FDCs needed for WHO 2013 ART recommendations for children

FDC	Doses	Status and comments
AZT/3TC/NVP	60/30/50 mg	Available
ABC/3TC/NVP	60/30/50 mg	Alternate 1st line.
ABC/3TC/EFV	120/60/ 100 mg	Preferred 1st line >3 to 10 years
TDF/3TC/EFV	75/75/ 150 mg	Preferred 1st line >10 years
AZT/3TC/LPV/r	30/15/40/ 10 mg	Preferred 1st line <3 years. Preferred second line >3 years.
ABC/3TC/LPV/r	30/15/40/ 10 mg	Preferred 1st line <3 years.

Sources: WHO recommended urgently needed formulations Table 6, Annex 7: Dosages of recommended antiretroviral drugs. Juneja S. Licensing technology and intellectual property for the development of paediatric formulations.

ABC/3TC/NVP is quite far along but ABC/3TC/EFV might not be feasible because of tablet sizes. EFV/3TC/TDF should be possible will scaled down or scored versions of adult tablets.

The LPV/r based combinations are also underway.

For older children on second line, heat stable ATV/r aligned with adults would probably be preferable to LPV/r.

The challenges with the current formulations – particularly the LPV/r syrup currently available for infants and young children – and pipeline paediatric antiretrovirals are described in the 2013 i-Base/TAG Pipeline Report. [13]

A satellite meeting sponsored by the Drugs for Neglected Diseases initiative (DNDi) – who are currently developing a granule formulation of LPV/r with Cipla - The Medicines Patent Pool and UNITAID also focused on some of the shortcomings with current formulations. [14]

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WHO 2013 guidelines: when the risk:benefit may not favour starting at CD4 count of 500

Simon Collins, HIV i-Base

There was overwhelming interest in the new and consolidated WHO 2013 guidelines when they were launched in a WHO satellite meeting prior to the opening of the 7th IAS conference - even though many of the key changes were already expected. [1]

One of the reasons why the guidelines generated so much discussion was the decision to recommend a higher CD4 threshold for starting HIV treatment. This modest increase on paper - moving from 350 to 500 cell/mm^3 - is based on the hoped for merger of clinical, prevention and operational benefits of earlier treatment.

This even upstaged the preceding satellite session, launching the WHO evaluation and update on current global access that highlighted the much more significant news that close to 10 million people in low- and middle-income countries are now taking HIV treatment. [2] The two issues are closely connected though, because by raising the CD4 threshold, the number of people in need of treatment has risen from 16 million to 25 million.

The recommendation to raise the CD4 threshold to 500 is stated as "strong", and supported by a "moderate" level of evidence that many think errs on the generous side. Using PICO questions (Population Intervention Comparison Outcome) and the systematic data reviews required for the GRADE system for producing evidence-based guidelines, only two randomised clinical trials (SMART and HPTN052) were judged suitable to inform this question. Importantly, both used sub-analyses rather than primary endpoints, they most importantly compared earlier treatment to deferring to a CD4 count of 250 (and not 350), and neither study was primarily designed to look at the timing of when to start treatment. [3] This meant that cohort data was used to help answer the question of when to start and the contradictory results from these studies should have lowered the rating for the quality of evidence rather than increased it. [4]

This recommendation in the guidelines may therefore be based on higher quality evidence (from randomised studies) that ART reduces transmission. With this mix of individual and public benefits, the evidence from the public benefits is stronger and has driven the change. Another factor, perhaps even more important, is that it may have operational benefits by keeping people in care after testing.

This makes the guidelines aspirational. It also makes them political. Both of which are good things. They show a drive to lead global health that is activist in spirit. Wanting to narrow the gap between WHO guidelines and Western guidelines is also good, although it is important to recognise the greater size of the epidemics in the poorest countries such that "a public health" rather than "individual patient" approach is needed. Things change slowly in global health and if the data are not currently available to prove the benefit of starting treatment at 500 rather than 350, there is a good chance that it will be available in a couple of years. On this at least, WHO will be ahead of the game, although it could be difficult if the benefit from early ART is not as great as some people expect. It would just have been better if the guidelines stated this, instead of stating so emphatically that the clinical benefits are "firmly rooted in evidence".

The detailed data set used to inform the guidelines - likely to run into several hundred pages - is due to be published in August. This limits the ability to look in detail at the evidence, process and methodology until then, by which time the mainstream media are likely to have lost interest.

When resources are limited - when are they not limited? - the guidelines state that people with a CD4 count <350 should have priority access to treatment. They also recommend that ART should be available universally irrespective of CD4 count (ie at counts higher than 500) for three important groups: pregnant women, children less than five years old, and HIV positive people in relationships where HIV transmission is a risk.

In this bold move, WHO are establishing the global urgency for broader access to treatment. They have produced an ideal rather than be restrained by settings with the most limited access. "WHO recommends earlier HIV treatment" was not a bad headline from global news agencies. [4, 5] This message could help lead to earlier testing and earlier access to treatment. It might also maintain pressure on governments to keep HIV as a high priority by setting a target by which national treatment programmes would be assessed.

The interesting history of the moving CD4 threshold is not discussed. In 1987, with the approval of AZT, the US DHHS guidelines recommended a CD4 threshold of 500. It stayed at 500 until 2000 when the threshold dropped first to 350 and then to 200 based on the side effects of early treatment, including d4T. As newer and better drugs became available, this increased back to 350 in 2007 and returned to 500 in 2009. In 2013 however, US guidelines recommended treatment irrespective of CD4 count, even when above 500, though acknowledging the evidence base was only "expert opinion". Whether what has been proposed for the US will work in very different settings, with different access to drugs and monitoring will be the long-term test. It is worth noting however that even in the US, most people start treatment far later than 500 cells/mm^3, and the aspirational aspect of the US guidelines was to encourage earlier and routine testing and so limit late diagnosis.

This highlights a more serious issue with the WHO guidelines. The benefit from broader and earlier ART, is dependent on the quality and range of the drugs being used and related issues including drug supply and monitoring. But although the guidelines very clearly and emphatically call for better care - for example by phasing out d4T - they don't go into details about how this affects the decision of when to start. They lack the same careful data-based analysis of the impact that commonly faced real-world factors - such as continued use of d4T - or the likelihood of a stock out - would have on the risk:benefit assessment. This data is readily available because it was used to draft earlier guidelines in countries when d4T was an acceptable standard of care in the West.

The operational benefits from expanding the criteria to access treatment are important. Once diagnosed, people who start treatment may be more likely to be retained in care - and current loss from care is a big concern.

But from this perspective, WHO could have dropped the CD4 count criteria altogether. The threshold of 500 is as arbitrary as 350 and current studies are looking at immediate treatment (at any CD4 count) compared to waiting until 350. This would have been a bolder move - but then we'd be back to the difficult detail of the lack of evidence. Loss to care may be more directly reduced by decentralising health care and this is part of the challenge for countries moving to Option B+ for pregnant women.

Table 1: Situations when a CD4 threshold of 500 cells/mm^3 might not have a risk:benefit advantage over starting at 350

Factor	Concern	Comment
d4T used in first-line treatment.	Mitochondrial toxicity: peripheral neuropathy, facial lipoatrophy, lactic acidosis, pancreatitis.	The CD4 threshold for starting treatment in Western countries when d4T was standard of care was 200-350. For a person with CD4 counts <500 but >200 and certainly >350 the risk of HIV-related complications is considerably lower than the risk of debilitating and lifelong d4T-related side effects. The global move to replace d4T with tenofovir is likely to change local access with the next two years. On a lifetime balance, deferring treatment until non-d4T options are available is recommended, and is urgent.
If AZT is only option.	Anaemia, lactic acidosis, facial lipoatrophy.	Although AZT is still widely used in resource-limited settings, if this is the only first-line option, similar concerns to d4T are important. Facial lipoatrophy (loss of facial fat) is a side effect of AZT, albeit at a reduced rate. Similar concerns about the risk:benefit ratio apply for people with CD4 counts above 350. AZT is also currently more expensive than tenofovir.
Efavirenz side effects	Limited alternatives for people with serious intolerance.	The side effect profile for efavirenz is well described in Western settings where approximately 30% of people switch to an alternative. Even if severe psychiatric reactions effect <5% of people, this would be significant in population terms. In some settings (Option B+) have no alternative to efavirenz.
Stock-outs and NNRTI-based ART with some NTRIs.	Drug resistance following interruption of treatment.	Some combinations have a higher risk for developing resistance if treatment is stopped (all drugs at the same time). This especially concerns NNRTI-based combinations (including FDCs) with NRTIs that have shorter half-lives (ie twice-daily dosing). Stopping these combinations risks a period of NNRTI monotherapy when resistance can easily develop. The assessment of risk:benefit for earlier treatment in a setting where stock-outs are common and tenofovir is not available may make the risk of drug resistance during a drug interruption outweigh the benefit from earlier treatment. This will further depend on the likelihood of a stock-out (5%, 10%, 20% chance per year etc), the normal length of stock out (greater than a few days to a week will provide time for resistance), and whether alternative options are in place for stock-outs (for example, emergency supply of NRTIs for staggering time for stopping treatment or access to PI/r to cover the NNRTI pharmacologic "tail" etc).
Limited options for second-line and third-line therapy.	Need for treatment if first-line fails.	If second-line therapy is not readily available this has an implication for planning treatment. First-line treatment might not work for 5-10% of people, even with good adherence. This is not a reason not to use treatment on an individual level but on a population level needs to be included as a disadvantage of earlier treatment. In a setting where virological failure is unlikely to be detected early due to limited access to viral load testing, extensive resistance would develop on first-line treatment for little or no clinical benefit.
Treatment as prevention: reducing infectiousness.	Is HIV transmission a concern?	The recommendation to treat at 500 is based on reduced risk of transmission. If this does not affect you, this will change the weight of evidence recommending earlier treatment. For example: if you currently always use condoms, if your partner(s) are HIV positive (and drug resistance is not a concern), if you are not currently sexually active, etc. There may be clinical benefits from earlier treatment, but this is based on expert opinion rather than evidence from clinical studies. If treatment is being used to reduce infectiousness, guidelines (including WHO, US, UK and EACS) recommend ART can be used irrespective of CD4 count.
Stability of current CD4 count above 350 and "normal" levels.	Individual immune responses to HIV means 350-500 may be normal for some people.	This is a complex issue to integrate into public health guidelines but is an important detail. The reference range for a "normal" CD4 range is approximately 420 - 1600 cells/mm^3, based on the 95% range but varies by test, laboratory and background population. This means a significant minority of people would fit the criteria to start treatment prior to any evidence of immune damage from HIV. This emphasises the importance of CD4 monitoring. As several research groups have recently proposed using 900 as a new target for "normal" levels, this issue will become more important. For someone with a "normal" CD4 count less than 500 it is difficult to see how ART could increase this further.

Finally, two indications of the effectiveness of ART at a CD4 threshold of 350 cells/mm^3, can perhaps minimise the urgency of this question. Firstly, studies reporting that ART normalises life expectancy for someone newly infected, albeit in uncomplicated cases - was based on a threshold of 350. [7]

Secondly, the START and TEMPRANO clinical trials, that will provide evidence from well powered randomised studies on both the risks and benefits of immediate treatment compared to waiting until 350, are both large studies requiring many years of follow-up. [8, 9]

START for example is expected to need to follow more than 4000 people for 3-6 years in order to see a difference between starting above 500 or waiting until 350. The guidelines explicitly mention the importance of both studies providing essential data to inform the decision on when to start treatment.

For settings where current standard of care does not match the US, a suggested appendix for when a CD4 threshold of 500 cells/mm^3 may not be appropriate to start treatment is included in Table 1.

C O M M E N T

In the bigger picture, the move to broader ART access is a good thing and the profile of the 2013 WHO guidelines have already helped in this. The leading role they are taking for global health is real and important.

Access to earlier treatment on a global scale is probably more important than the detail of whether to start at 350 or 500 - or even whether there should be a CD4 threshold at all.

The guidelines should also take in to account the differences between well resourced and resource-limited settings and that the HIV epidemic is so much greater in the latter needing a public health not individual approach.

In the detail, people who decide to start treatment earlier in their infection should be able to do this based on a risk:benefit assessment of the treatment options available when they start. Otherwise, nothing will have been learnt from mistakes that Western guidelines have made in the past.

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IAS 2013: ANTIRETROVIRALS

Efavirenz at 400 mg compared to standard 600 mg dose has similar efficacy with fewer side effects

Simon Collins, HIV i-Base

Results from the ENCORE1 study comparing efavirenz at a reduced compared to standard dose in treatment naive patients, were presented as an oral later breaker by Rebekah Puls from the University of New South Wales, Sydney. [1]

This was a double-blind, placebo-controlled, non-inferiority trial that randomised 636 patients (1:1) to efavirenz dosed at either 400 mg (n=324) or 600 mg (n=312). Tenofovir/FTC was used as the dual RTI backbone for all patients, with participants taking four pills daily because efavirenz/placebo used 200 mg capsules.

Entry criteria included CD4 50-500 cells/mm^3 and viral load >1000 copies/mL. The primary endpoint was virological suppression to <200 copies/mL at week 48, with follow-up planned until week 96. Non-inferiority was determined using a lower margin of –10%.

Both arms were well matched and baseline demographics included mean (+/-SD) age 36 (+/-10) years, mean CD4 count 270 (+/- 100) cells/mm^3 (75% were <350 cells/mm^3) and viral load was 4.7 (+/- 0.8) log/copies/mL. The majority of patients were asymptomatic (>80% CDC stage A). This was an international study and approximately one third of participants were African, one third were Asian and one third were Caucasian.

At week 48, there were no significant differences by ITT analysis, with 94% vs 92% of patients having undetectable viral load in the 400 mg vs 600 mg group respectively (difference 1.8 (95% CI 2.1, +5.8), p = 0.36, NS). Very similar results were reported when stratified by baseline viral load above or below 100,000 copies/mL (all >90%). There were no differences between in the slope of viral decline, with overlapping plots at each of the week 4, 12, 24, 36 and 48 time points (p=0.35, NS).

The mean change in CD4 counts was slightly higher in the 400 mg arm (by +25 (95%CI 6, 44) cells/mm^3; p=0.009).

Slightly lower rates of discontinuation were reported for the 400 mg arm (10% vs 14%) but this was not related to distribution of general side effects which were similar (approximately 47% with grade 1-2; with 2-3% grade 3-4; 7% with SAE; all p = NS).

However, significantly fewer patients discontinued treatment due to efavirenz-related side effects (rash, CNS, GI but not psychiatric) from the 400 mg arm (1.9% vs 5.8%; difference –3.9 (95%CI: –6.96, –0.95); p = 0.01) and fewer patients reported these side effects (37% vs 47%; difference –10.5% (95%CI: –18.2, –2.8); p=0.008).

C O M M E N T

The potential to use a lower efavirenz dose has been suggested for many years and this was one of the drugs suggested for use in "Micro-HAART" about a decade ago by Andrew Hill, one of the ENCORE1 investigators. [2]

A more recent review article on the potential for dose optimisation for resource-limited countries is also available online. [3]

It is probably also significant that the first efficacy and safety data from the randomised ENCORE1 study has only been presented as the marketing patent for efavirenz in Western countries is about to end. This drug for this study was a generic version of efavirenz produced by Mylan as the patent holder would not support this research.

These results are provocative. Rates of viral response were high in both arms, with the slightly improved tolerability in the 400 mg arm not coming at the cost of lower efficacy. The ethnic balance in the study does not suggest that the results are limited to lower weight/BMI, although this analysis was not presented. Further PK and sub-analyses are planned.

The use of four pills in this study (rather than a single tablet formulation) may make the potential cost savings important for rich as well as resource-limited countries.

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Dolutegravir update in treatment experienced patients and drug resistance

Simon Collins, HIV i-Base

Several studies presented new or updated information on dolutegravir.

This new integrase inhibitor has potential advantages over raltegravir by being a once rather than twice-daily drug, and over elvitegravir by not requiring PK boosting. Of note, dolutegravir with a twice-daily dose retains activity against early but not late resistance to raltegravir and elvitegravir and may rescue some patients who fail on first-line integrase inhibitors.

Dolutegravir also seems to have an interesting resistance profile that may limit the accumulation of further integrase mutations, although in vivo data are still scarce due to low numbers of patients who have experienced virological failure. Primary mutations to dolutegravir appear to significantly reduce viral fitness, but unlike with other antiretrovirals this does not seem to be restored by later development of compensatory mutations.

Dolutegravir has already been submitted to the US and EU regulatory authorities and a decision on approval is expected before the end of 2013.

SPRING-2 study: dolutegravir is non-inferior to raltegravir at 96 weeks in treatment-naive patients

Francois Raffi from Nantes University Hospital, presented 96-week results from the randomised, double-blind, placebo controlled phase 3 SPRING-2 study in 827 treatment-naive patients, with data presented for 411 patients in each arm. Results were stratified by baseline viral load above or below >100,000 copies/mL) and by investigator selected used of either tenofovir/FTC or abacavir/3TC (used by 60% and 40% of patients respectively). [1]

This was a largely male and white study population in patients with early-stage HIV. Approximate baseline characteristics for the study included median age of 36 years, 85% male, 85% white and 10% African American. Median viral load and CD4 count were approximately 35,000 copies/mL and 360 cells/mm^3 respectively. No figures for the range or IQR were provided for the median values. However, 28% of patients had baseline viral load >100,000 copies/mL and 12% had a CD4 count <200 cells/mm^3. Approximately 2% and 10% were coinfected with hepatitis B and C respectively.

At week 96, viral suppression in the dolutegravir (50 mg once daily) vs raltegravir (400 mg twice daily) arms was 81% versus 76% achieving undetectable viral load (<50 copies/mL (difference 4.5%; 95% CI: -1.1%, 10.0%). This compared to rates of 88% vs 85% patients respectively at week 48 (difference was 2.5%; (95% CI: -2.2% to 7.1%). Median CD4 cells/mm^3 increases from baseline were also similar between arms (+276 vs +264 cells/mm^3).

In the stratified analyses, responses were similar in each arm

for patients with baseline viral load <100,000 copies/mL but were significantly better for dolutegravir in the >100,000 copes/mL group (78% vs 63% achieving viral load to <50 copies/mL).

There were no differences between arms when abacavir/3TC was used as the background RTIs but dolutegravir was significantly better when tenofovir/FTC was used (86% vs 77% respectively). When both baseline viral load and RTI choice were factored together dolutegravir was significantly more effective compared to raltegravir only with tenofovir/FTC use in the >100,000 copies/mL group: 81% (62/77) vs 61% (47/77), respectively.

Side effects were similar: 13-15% (nausea, headache, diarrhea, and nasopharyngitis) and 2% of patients in each arm discontinuing due to side effects, predominantly during the first year. From week 48, only three patients stopped due to tolerability (one case each of hepatitis C, suicide attempt and hepatotoxicity, all in the raltegravir arm).

Virologic non-response occurred less frequently on dolutegravir (5% vs 10%) and at virologic failure, with no resistance (from the limited resistance test results available) in the dolutegravir arms compared to n=1 (integrase resistance) and n=4 people (NRTI resistance) in the raltegravir arm. These results continued to support dolutegravir non-inferiority at week 96.

SAILING study: dolutegravir is superior to raltegravir in treatment-experienced, integrase naive patients

Week 48 results from the phase 3 randomised, placebo controlled, SAILING study comparing doultegravir to raltegravir in 715 treatment-experienced (with resistance to two or more classes) but integrase-naive patients were presented in a late breaker oral presentation by Pedro Cahn from Fundación Huésped, Buenos Aires. [2] The results were broadly similar to the 24-week interim analyses that was presented at CROI 2013. [3] The 48 week full study has also just been published in the Lancet. [4]

Dolutegravir was dosed at 50 mg once-daily with raltegravir dosed at 400 mg twice-daily. Background combinations included up to two other drugs, one of which had to be fully active, and were individually optimised by baseline resistance test and treatment history. Approximately 30% were women, 50% white and 40% African/American.

At baseline, approximately half the patients in each arm had CD4 counts <200 cells/mm^3 and 50% had resistance to three or more classes. Baseline viral load for patients on currently failing therapy was approximately 15,000 copies/mL with 30% failing at >50,000 copies/mL. Only 20% of patients using darunavir/ritonavir had no primary PI-associated mutations.

Viral efficacy (<50 copies/mL) at week 48 (primary endpoint) favoured dolutegravir over raltegravir (71% vs 64%; difference (95% CI): 7.4% (0.7%, 14.2%); p=0.03), adjusting for baseline viral load, darunavir/r use without primary PI mutations and baseline phenotypic sensitivity score for the background regimen. CD4 changes were similar at +162 vs +153 cells/mm^3 in the dolutegravir vs raltegravir arms.

None of the subgroup analyses favoured raltegravir, but dolutegravir was statistically superior in patients with viral load greater than 50,000 copies/mL in the darunavir/r group with primary PI mutations and in patients with a PSS score of 2 or higher.

Virologic failure occurred less frequently in the dolutegravir arm (6% vs 12%) with <1% vs 5% for virologic non-response and 5% vs 7% for viral rebound.

Although resistance occurred at low levels in each arm, fewer patients failed with integrase resistance (1% vs 5%; p=0.003) or to background regimen (1% vs 3%) in the dolutegravir (n=2/354; both with R263K, one also with V260I, but this conferred <2-fold change in IC50) vs raltegravir (n=10/361) groups. [5]

Tolerability was good in both arms, with <1% reporting grade 4 events: one case each of hepatotoxicty and renal failure in the dolutegravir arm and one case each of rash, pancreatitis, hepatitis and suicide ideation in the raltegravir arm. Mean increases in serum creatinine were greater with dolutegravir (+11.1 vs +5.1 umol/L).

VIKING-3 study: dolutegravir in integrase experienced patients

Perhaps the most important dolutegravir study at IAS 2013 was the single-arm VIKING-3 in integrase-experienced patients. [6] This provided information on likely options for people with more extensive drug resistance, including people who have failed on raltegravir or elvitegravir containing combinations. Dolutegravir was added to current failing regimens (integrase inhibitors were stopped) at 50 mg twice-daily for the first 8 days before background treatment was optimised at day 8 and dolutegravir was continued.

Baseline characteristics included 23% women, 21% HBV or HCV coinfection and 27% African American, with a median CD4 count of 140 (range 19-1110) cells/mm^3, 56% with CDC class C, and a median 13 years prior ART (range 0.3 - 25 years).

Participants had previously used a median of 14 ARVs (range 3-25) including prior darunavir/r (73%), etravirine (56%), T20 (49%) and maraviroc (32%). Class resistance included >/=2 NRTIs (75%), >/+ 1 NNRTI (70%) and >/+ 2 PIs (62%). All patients had evidence of integrase resistance (68% at baseline, 32% documented).

This analysis provided results for 183 patients at week 24 and 114 patients with data at week 48. Overall, viral load <50 copies/mL was achieved by 69% of patients at week 24 and 56% at week 48, with virologic non-response of 27% and 39% at week 24 and 48 respectively.

Results by primary integration mutations and Overall Susceptibility Score (OSS) at baseline are detailed in Table 1 and showed reduced responses when Q148 was present with two or more other integrase mutations (p<0.001), but a less clear relationship with OSS. The active drug in most cases was an NRTI.

Table 1. VIKING-3: Percentage of people with <50 copies/mL at week 24 by baseline integrase mutations and OSS of background regimen (n=161)

Baseline IN mutations	OBR OSS=0 n/N (%)	OBR OSS=1 n/N (%)	OBR OSS=2 n/N (%)	OBR OSS>2 n/N (%)	Total n/N (%)
No Q148	4/4 (100%)	35/40 (88%)	40/48 (83%)	17/22 (77%)	96/114 (84%)
Q148+1	2/2 (100%)	8/12 (67%)	10/17 (59%)	0	20/31 (65%)
Q148+≥2	1/2 (50%)	2/11 (18%)	1/3 (33%)	0	4/16 (25%)

Response by dolutegravir sensitivity at baseline was 82%(98/120), 56% (14/25) and 11% (1/9) in the < 4-fold, 4-10 fold and >10-fold reduced sensitivity groups respectively.

In a separate analysis, phenotypic response cut-offs for dolutegravir of <9.45, 9.45-25.99 and >25.99 were derived for full (>1 log), intermediate and non-responses. See later report in HTB from the Drug Resistance Workshop. [7]

Tolerability was generally good with side effects similar to earlier reports using 50 mg once-daily dosing.

A separate poster reported renal safety from two Phase 3 studies. Renal events in the dolutegravir arms were comparable to control arms. Dolutegravir produces a small non-progressive increase in serum creatinine in the first two weeks of treatment that remains stable afterwards that can affect eGFR. However, no increases in median urinary albumin/creatinine ratios were observed over 48 weeks. [8]

Drug resistance in integrase-naïve patients

Very few treatment-naïve or integrase-naïve patients have experienced virologic failure using dolutegravir. However, it is notable that even when suboptimal responses or viral rebound occurs, that mutations in the integrase gene are rare – even out to 96 weeks in the SPRING-2 study reported above. Information on the potential resistance profile for dolutegravir is therefore largely based on in vitro studies.

Mespléde and colleagues from Mark Wainberg's group at McGill University, Québec – rather than ViiV or GSK – are suggesting that this may be related to dolutegravir's long intracellular half-life. In vitro, multiple pass selection studies in the presence of increasing concentrations of dolutegravir, generate the R263K mutation, which is often associated with the secondary mutation H51Y which further decreases susceptibility to the drug and is associated with reduced integration and impaired viral replication. Other secondary mutations in vitro include M50I and E138K. These secondary mutations not only do not compensate for reduced replication but, in further in vitro assays, both R263K and R253K/H51Y impaired the development of resistance to 3TC and nevirapine. [9, 10]

Two patients in the dolutegravir arm in the SAILING study developed R263K at virological failure however, and this should caution that resistance can develop in naïve patients, even though this had <2 fold impact on IC50 (and perhaps might be overcome by increasing to a 50 mg twice-daily dose). [5]

If the resistance profile continues to be strong in clinical practice, when monitoring is less intense and so viral failure is detected later, this could have important implications for using dolutegravir in first-line therapy.

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Elvitegravir/cobicisat/tenofovir/FTC: Stribild studies at IAS 2013

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Several posters at the IAS conference presented generally supportive results for the fixed-dose integrase inhibitor-based combination of elvitegravir/cobicistat/tenofovir/FTC (Stribild).

A poster from Frank Post from University College London and colleagues looked at the concern about renal safety. [1]

The current license for Stribild restricts use to patients with creatinine clearance (CrCl) based on estimated GFR >/= 70 mL/min as this was an entry criteria in the registrational phase 3 studies.

The new study was a phase 3, open-label, multicenter, two-cohort study in HIV positive patients with CrCl from 50 to 89 mL/min. The analysis for Stribild was based on 33 treatment naive patients and the analysis for cobicistat was based on 73 people who were virally suppressed on stable PI/r-based combinations who switched ritonavir to cobicistat.

Baseline CrCl (median [IQR]) was 73 mL/min (65 to 81) and 71 mL/min (62 to 81) in the Stribild and cobicistat cohorts, with small reductions at week 24 in both groups (-5 mL/min [-13 to 1] and -4 mL/min [-7 to 2] respectively).

No changes in actual GFR (rather than estimated GFR) were reported in the small number of patients (n=14) who had this measured. No renal events were reported, although three patients discontinued Stribild due to reduced CrCl, which resolved on stopping treatment; none with features of proximal tubulopathy.

David Cooper from St Vincent's Hospital, Sydney and colleagues presented pooled analyses from two registrational phase 3 studies (n=1408 including active and control patients). They reported similar rates of viral suppression and clinical results by gender, age (above vs below 40 years old) and race (white vs non-white); and by baseline CD4 and viral load. [2]

These results were supported by pooled pharmacokinteic analyses from earlier studies in the development programme in HIV positive and HIV negative people. This study pooled results from nine studies for elvitegravir and tenofovir and from 16 studies for cobicistat. No differences were seen in a wide range of demographic and HIV factors including by race (white/black/Asian/Latino/Hispanic), baseline viral load (above and below 100,000 copies/mL) or CD4 count (above or below 200 cells/mm^3). [3]

Early results from a 48 week study from one of the many switching studies currently supported by Gilead were presented as a poster. [4]

The study enrolled 48 patients who were stable (viral load <50 copies/mL for greater than six months - median duration was 34 months) on raltegravir-based combinations. At week 24 all patients maintained viral load <50 copies/mL.

Finally, a study of a post-hoc analysis of the impact of less than 95% adherence with Stribild compared to Atripla was also presented as a poster. [5]

Median adherence, assessed by pill count through to week 96, was 98% in each arm. However, <95% adherence was reported by 26% vs 25% and <90% by 7% vs 11% in the Stribild vs Atripla groups respectively. There were no statistically significant differences in rate of viral suppression by adherence level between the two treatment groups.

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Non-standard combinations: NRTI-sparing combinations

Simon Collins, HIV i-Base

A number of small studies presented results at IAS 2013 on combinations that are not widely used or recommended in first or second line therapy.

The studies were small, underpowered and often without comparator arms but they show an interest in broadening options which may become possible with drugs approved from five classes. None will change guidelines that are currently based on using 2NRTIs plus an NNRTI/boosted PI/integrase inhibitor.

Maraviroc + raltegravir maintenance

Cotte and colleagues reported initial results from using a four drug initial combination of maraviroc 300 mg twice-daily, raltegravir 400mg twice daily and tenofovir/FTC. Patients with viral suppression to <50 copies/mL at week 24 then dropped the NRTIs and continued on only maraviroc plus raltegravir. [1]

Although this study plans to enroll 40 patients, an interim analysis of the first ten patients at week 24 was required prior to enrolling the full group.

Median baseline CD4 cell count and viral load was 457 cells/mm^3 [range 366-929] and 4.0 log copies/mL [range 2.7-4.5].

All patients were men with median age 41 years [range 25-54]. Entry criteria included CCR5 tropism and no drug resistance.

All patients had undetectable viral load at week 24 and remained suppressed out to week 48 on the reduced combination. One blip result at week 44 (56 copies/mL) was re-suppressed without treatment change.

Raltegravir + darunavir/r

In another NRTI-sparing approach, the RADAR study included 85 treatment-naive patients starting on darunavir/ritonavir (800 mg/100mg once-daily) who were randomised to include either raltegravir (400 mg twice daily) or tenofovir/FTC (300 mg /200 mg once-daily).

A high rate of drop out/loss to follow-up (~20%) resulted in poorer virological responses in the primary endpoint for the raltegravir vs tenofovir/FTC arm in the ITT analysis (62.5% vs 83.7% achieved viral load <50 copies/mL at week 48; p=0.045). However, most of the virological failures in the raltegravir arm had viral load <200 copies/mL. [3]

A secondary endpoint looking at bone changes favoured the NRTI-sparing arm (sub-total BMD: +1.02% vs. -0.76%, p=0.002). Changes in bone formation and resorption markers at week 16 were predictive of these BMD changes at week 48.

Boosted PI monotherapy: darunavir/r vs lopinavir/r

A small randomised study in treatment-naive patients compared boosted PI monotherapy with darunavir/r (n=40) and lopinavir/r (n=33). [6]

At week 48, by ITT analysis, 77.5% (31/40) and 66% (22/33) patients respectively had viral load <50 copies/mL (p=0.302, treatment difference 10.8% [IC95% -12.6;34.2]). Side effects were similar to the expected profiles for each drug. The median (IQR) change of CD4 cell count seemed numerically lower with darunavir: +3 (-204, 99) vs 71 (-49, 144) cells/mm^3 although this was not statistically significant (p=0.164).

Switch to etravirine plus raltegravir

Results from a single-arm observational study reported on 91 patients stable on standard three-drug combination and without NNRTI resistance at a single centre in France who from 2008 switched to etravirine plus raltegravir. Reasons for switching included metabolic toxicity/lipodystrophy, renal impairment or toxicity prevention. [7]

Median (IQR) follow-up was 11.5 months (4.6-22.7) with 65 and 48 patients reaching 6 and 12 months of follow-up respectively, generally maintaining viral suppression.

Five patients had virological failure, after a median (IQR) 7 months (6-16) following the switch. These five patients had previously used NNRTIs and 4/5 reported prior NNRTI treatment failure. Of the 18 other discontinuations, five were associated with side effects related to either drug.

Once-daily etravirine plus darunavir/ritonavir

Although combinations including etravirine and darunavir/r plus optimised background regimens were the basis for regulatory approval (the DUET 1 and DUET 2 studies) their use without other drugs and specifically without NRTIs has not been previously reported.

This study also notably used etravirine at a 400 mg once-daily dose (although approved as a twice-daily drug, recent PK data may support once-daily use). [8]

This was a 48-week single arm study included 42 treatment experienced patients and 12 patients who were treatment naive with transmitted drug resistance. All patients had to show genotypic sensitivity to both drugs.

Virological response rate at week 48 was 89% by ITT analysis that did not include resuppressed blips as treatment failure. However, response rates were lower by standard ITT (74%), TLOVR (72%) and FDA snapshot (69%) analyses. Seven patients discontinued due to virologic failure (2/2 with resistance results had etravirine mutations) and four due to side effects.

COMMENT

Although the numbers are small, the study from Cotte et al sounds interesting for people unable to take NRTIs. However, this is a twice-daily combination for first treatment, when once-daily combinations are usually preferred. This combination is unlikely to offer any cost saving.

The RADAR study is similar to the earlier ACTG 5262 single arm study of darunavir/ritonavir plus raltegravir that reported a 16% failure rate at week 24 and 26% failure at week 48, with poorer outcomes for patients who had baseline viral load >100,000 copies/mL.

However, given the higher effectiveness of darunavir/ritonavir monotherapy (88% <50 copies/mL at week 96 in the MONOI study and 82% at week 48 in the MONET study) these differences may have been related to more difficult to treat US patients. [4, 5]

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IAS: SIDE EFFECTS

ARVs and bone health: the role of NRTIs in second-line therapy

Simon Collins, HIV i-Base

The final clinical late-breaker oral presentation at IAS 2013 reported significantly less reduction in bone mineral density (BMD) after a year on an NRTI-sparing combination in a randomised study compared to standard NRTI-containing treatment. [1]

Bone health is an unresolved complication of HIV and ART that bucks the trend for the generally beneficial impact of treatment to reduce both HIV-related and serious non-AIDS complications, mediated by reduced immune inflammation and activation. Although few individual drugs have been associated with greater reductions in BMD, ART itself, irrespective of the individual drugs has a negative impact on BMD compared to people not taking antiretrovirals. [2]

The current study, presented by Jennifer Hoy from Monash University, Melbourne was a substudy of a second-line therapy trial that randomised adults (>16 years-old) failing first-line NNRTI-based therapy to either NRTI-sparing combination of lopinavir/r plus raltegravir (n=108) or to the standard of care combination of lopinavir/r plus two NRTIs (n=102).

This was an international, 96-week, open label, non-inferiority trial, with an assumption that raltegravir would have less impact on BMD. The primary endpoint of the main study was viral suppression (<200 copies/mL) at week 48. The bone substudy was run at 8/37 sites with access to DEXA scans, in South Africa, India, Malaysia, Thailand and Argentina with a primary endpoint of changes in BDM between baseline and week 48 and additional bone-related secondary endpoints. BMD was measured at proximal femur and lumbar spine (L2-L4) measured by a standard protocol. Covariates in the multivariate analyses included: age, sex, ethnicity, BMI, smoking, blood pressure, HIV and ART markers (randomised treatment arm, CD4 counts, viral load, prior and on-study use of tenofovir and duration of use), body composition parameters (fat and lean mass) and other parameters influencing bone mass (e.g. hypogonadism, corticosteroids).

The two groups were well balanced for most demographics and baseline characteristics and included 50% women, but the NRTI-sparing arm had slightly fewer men (42% vs 54%) and fewer current smokers (13% vs 22%). Baseline CD4 count and viral load for the study population as a whole was 202 (IQR 104 – 307) cells/mm^3 and 4.1 (IQR 3.5 – 4.7) log copies/mL respectively, indicating a wide range of clinical management: approximately 25% of patients were switching first-line treatment with either a CD4 count below 100 cells/mm^3 or a viral load >50,000 copies/mL.

Approximately 51% were Asian, 43% African and 6% Caucasian. Also importantly, approximately 65% had BMI <20 and only 10% >30 kg/m2. Patients had been on treatment for a median of 3.4 years (IQR 2.0 – 6.0) and current NRTI-use included d4T (48%), AZT (34%) and tenofovir (17%). Approximately 45% of people used tenofovir in their second-line therapy.

Baseline rates of osteopenia and osteoporosis respectively were 20% and 1.5% in the proximal femur and 30% and 5% measured at the lumber spine.

At week 48, significant differences in mean (95%CI) BMD changes were reported for the NRTI-sparing vs control arms respectively: with reductions of -2.9% vs -5.2% in the proximal femur [difference -2.4% (-3.5 to -1.2); p=0.0001] and -2.0% vs -4.2% in the lumber spine [difference -2.1% (-3.3 to-0.6); p=0.0006], adjusting for sex, BMI and smoking status. Similar and consistent differences were reported for changes in T-score and Z-score at each body site, although there were no significant differences in the odd ratio for the risk of developing new cases of osteopenia or osteoporosis.

In the multivariate analyses, lower nadir CD4 count (p=0.0173), tenofovir use (p=0.0001), BMI (p=0.0002) and vigorous exercise in the previous week (p=0.0157) were significantly associated with changes in BMD at both proximal femur and lumber spine. The exercise finding was unexpected and was not discussed further, though the explanation for this finding is unclear. Both prior (p=0.0303) and current (p=0.0002) use of tenofovir were significant.

C O M M E N T

For adult care, if HIV was acquired after bone density had peaked, the impact of ART is more likely to be a longer-term concern, overlapping the complexities of reduced BMD and increased frailty with ageing, and several studies have already reported that HIV is associated with an increased risk of fractures. [4]

For children, adolescents and young adults, when HIV and treatment may have reduced natural bone development before peaking by age 30 years, this may become a caution from the

use of earlier ART. Further research may support interventions to manage bone health that maximises the period of bone growth in order to prepare for reduction that will occur much later in life.

The BMD substudy of the START trial will provide a valuable longitudinal dataset to look at the impact of HIV, treatment and age. [3]

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IAS 2013: CURE RESEARCH

No viral load rebound off-ART following stem cell transplant: two "cure" cases using reduced intensity conditioning chemotherapy and CCR5 d-32 negative donors

Simon Collins, HIV i-Base

Three cases of HIV positive people, who underwent stem cell transplant (HSCT) to treat leukemia, were presented by Timothy Henrich of Harvard Medical School as a late-breaker. [1]

After intensive tests failed to show evidence of ongoing viral replication, two of the three patients stopped HIV treatment as part of an analytic treatment interruption. Follow-up to week 8 and 15 has failed so far to isolate evidence of viral load rebound.

Unlike the widely reported case of Timothy Brown who has remained off treatment for more than five years without viral rebound following myeloablative chemotherapy, these patients did not use a donor with CCR5-delta-32 genetic deletion that protects against HIV infection and which was attributed to the functional cure in that case. [2] They also continued ART before, during and after the transplant with follow-up prior to stopping treatment of 4.5 and 2.7 years.

The two patients that have responded successfully underwent reduced intensity conditioning (RIC) chemotherapy post-transplant that involves non-ablative slightly milder chemotherapy without total body irradiation (therefore retaining some of the patients own immune cells) or antithymocyte globulin (which also clear host immune cells). This is considerably less aggressive that the procedures undertaken by Timothy Brown but it is still associated with an approximately 15% two-year mortality.

Both patients are male but with very different HIV histories. The first was infected perinatally and had been on long-term ART. In 2006, he was diagnosed with stage 4 Hodgkins disease that relapsed following standard chemotherapy and he underwent autologous RIC HSCT in 2007 with a partially mismatched donor and response included graft versus host disease (GVHD) that subsequently worsened.

The second patient was sexually infected in the mid 1980s and had remained off-treatment until 2003 when he was diagnosed with a diffuse large B-cell lymphoma that responded to chemotherapy and ART. In 2006, he developed stage 4 Hodgkins lymphoma and following disease recurrence after chemotherapy and salvage chemotherapy, he underwent autologous HSCT in 2007. In 2010, he developed a myelodysplastic syndrome, likely related to previous chemotherapy, and underwent an RIC matched HSCT which also resulted in complicated GVHD response.

GVHD in both patients was managed by sirolimus and tacrolimus, with prednisone used when initial GVHD response worsened. Both patients are currently stable. The difficulty of recovering HIV DNA in PBMCs at 8-17 months post-transplant was reported in detail at the IAS conference in Washington in 2012 and was published this year as an open access article in JID. [3, 4]

In both patients, HIV DNA was detected in PBMCs prior to and 2-3 months after transplant but not following full engraftment. An updated summary this year on the attempts to recover HIV DNA now covers assays using 5 million PBMCs that have been repeated up to 30 times for each patient or in rectal tissue (for one patient), prior to the decision to stop ART.

Residual pre-transplant cells now constitute less than 0.001% of PBMCs post-HSCT and may represent circulating non-hematopoietic cells but donor cells now clearly constitute the majority population. Also, no strong HIV-specific immune responses were generated from HLA-specific or pooled HIV-1 peptides before or after transplant.

HIV has so far failed to be detected in plasma (using less than 1 copy/mL assays), in cells (in millions of cells with sensitive testing), or in gut tissue (which is one of the compartments that cure researchers believe is a sanctuary site).

The researchers suggested that two aspects of their protocol may be important. Firstly, that the role of GVHD may be critical in clearing host cells post-transplant, especially as host cells are not cleared by irradiation or antithymocyte globulin, and secondly, that continuing on ART for several years after the transplant may also have prevented reinfection while allowing clearance of any residual reservoir of HIV-infected cells.

Unfortunately, a third patient enrolled in the study protocol died from recurrent lymphoma six months after HSCT, highlighting the serious risk of the complications for any patient considered suitable for this type of treatment.

Further details on this presentation are limited, as neither the webcast from this session nor the presentation slides have yet been posted to the conference website. This article will be updated when these become available. [5]

In the press conference, Henrich emphasised the importance of continued careful follow-up in these patients and that the potential for very delayed rebound, even out to 1-2 years, was supported by modeling studies presented at CROI 2013. [6, 7] Also, that while this is not a realistic option for most people, this research may inform cure research on how low viral suppression needs to go and for further understanding the innate immune responses that are likely to be needed for functional cure in chronic HIV infection.

C O M M E N T

Although currently off-ART for only 15 and 7 weeks, if these results are sustained this would make the chance to cure HIV a more realistic possibility for HIV positive patients requiring HSCT as it removes the need to source and match CCR5-d32 deleted donors.

While these cases seem very promising, even with the RIC chemotherapy this remains a complex procedure and a salvage response to previously non-responsive or relapse first-line chemotherapy.

Viral dynamics of untreated HIV suggest that four months would be sufficient in most cases to detect new viral replication. However, researchers in this case are cautious about suggesting that these patients are functionally cured. Individual cases - not in the context of HSCT - include later rebound when virus is detectable in less than 1.7 billions cells, following more than ten years of viral suppression and starting ART during primary infection. [8]

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HIV cure research: further capsules at IAS 2013

Richard Jefferys, TAG

In addition to the cases of treatment discontinuation following stem cell transplantation (Hendrich et al, reported above) the focus on cure research was one of the strong themes on the conference and it featured in many of the sessions.

A case report from Jan van Lunzen and colleagues in Germany, described a 67 year-old man who was treated with ART three months after infection and one month after seroconversion (when his CD4 was <500 cells/mm^3 and viral load was >1 million/copies/mL). In 2004, after 5.5 years on ART he stopped therapy and has maintained undetectable viral load (<20 copies/mL) for nine years and currently has a stable CD4 count >900 cells/mm^3. [1]

This case had previously been briefly described in a presentation at the 2011 HIV Persistence Workshop. [2] Although HIV DNA and RNA cannot be detected in plasma, PBMC, gut or CSF, experiments involving the transfer of purified CD4 T cells to humanised mice have revealed the presence of replication-competent virus.

Jan van Lunzen's case appears to have some similarities with the 14 individuals in the well-publicised VISCONTI cohort, in that it involves post-treatment control of HIV. [3] However, HIV DNA remains detectable in all VISCONTI participants and they have been reported to have weak HIV-specific CD8 T cell responses. In contrast, van Lunzen found broadly directed HIV-specific CD8 T cells along with strong HIV-specific CD4 T cell responses—as measured by proliferation—in his case (no data on HIV-specific CD4 T cell responses in the VISCONTI cohort has been reported yet). The German research group also opted to designate the outcome as a "functional cure" whereas the researchers involved in VISCONTI have more conservatively described their study subjects as achieving "virological remission."

This semantic tangle highlights important and arguably somewhat neglected issues in HIV cure research: the need to create more rigorous definitions of the terms being used and the need to obtain broader consensus about their appropriate application. It should also be noted that reports of post-treatment control are not new; one of the first widely publicised instances was an individual in Berlin (the first so-called "Berlin patient") who was treated during acute infection and maintained viral load below 50 copies/mL after a subsequent interruption. This case also involved use of hydroxyurea and was published as a letter in the New England Journal of Medicine in 1999. [4]

Although this person was still off ART in 2003, reported by Bruce Walker during a presentation by at IAS 2003, there have not been any updates recently (although the individual is one of the

subjects of a forthcoming book along with the person now more associated with the Berlin patient moniker, Timothy Brown). [5] There have also been a smattering of other reports such as those from Renslow Sherer and colleagues at the 2000 CROI, [6] but the extent of the virological control in these individuals appears to have been variable and it is unclear how they might compare to newer cases. The term "virological remission" shows up as far back as 1996 in an abstract from the 11th International AIDS Conference. [7]

To address the shortcomings in current knowledge of post-treatment control, the VISCONTI researchers (led by Asier Sáez-Cirión) announced at an IAS 2013 satellite symposium that they are launching an international collaborative effort to collect data on individuals maintaining low or undetectable levels of HIV off ART. [8]

The inclusion criteria are:

- Treatment initiation with VL >2000 HIV-RNA copies/mL, whatever the timing of infection
- Treatment for more than 12 months
- Viral control after treatment interruption below 400 copies/mL for at least 12 months

Researchers and clinicians who may have candidates for inclusion are encouraged to email <visconti@anrs.fr> for inclusion.

One of the anticipated presentations at IAS 2013 was Martin Tolstrup's first report of data from a phase I trial of an HIV latency-reversing candidate, the HDAC inhibitor panobinostat (earlier this year the trial was the subject of an erroneous but very widely distributed article in the Daily Telegraph claiming that an HIV cure was months away). [9]

Fifteen individuals on long-term suppressive ART participated in the study, receiving a cyclic dosing regimen of 20mg of panobinostat three times a week, every other week, for a total of eight weeks. The primary endpoint is changes in cell-associated HIV RNA, however that data is reportedly being reevaluated at the current time. Tolstrup was able to present one of the secondary endpoints, changes in low-level HIV viraemia as measured by a qualitative (not quantitative) nucleic acid detection system (the PROCLEIX ULTRIO Plus Assay, which is used for blood screening). The results of this assay indicated a significant increase in the proportion of participants with detectable low-level HIV RNA after receipt of panobinostat. [10]

While adding to the evidence that HDAC inhibition can coax HIV out of latency, the results are preliminary and do not shed light on the thorny question of what proportion of latently infected cells are responding to the intervention.

Additional presentations on cure research are included below with hyperlinks to the conference website.

Press conference: Towards an HIV cure

http://www.youtube.com/watch?v=Wo8NdKWVdhU

Towards an HIV cure symposium

http://www.iasociety.org/Default.aspx?pageId=687

http://www.iasociety.org/Web/WebContent/File/HIV_Cure_Abstract_Book_IAS2013.pdf (PDF of abstract book)

Immune activation in HIV (MOBS01)

http://pag.ias2013.org/session.aspx?s=86

Multi-faceted aspects of acute HIV infection (MOPDA01)

http://pag.ias2013.org/session.aspx?s=11

What drives disease progression and limits CD4 recovery? (MOAA01)

http://pag.ias2013.org/session.aspx?s=56

Viral and immune-targeted interventions: hit me with your best shot (TUAA01)

http://pag.ias2013.org/session.aspx?s=18

The roles of secondary lymphoid tissues in HIV infection: what do we know and don't know? (TUSY01)

http://pag.ias2013.org/session.aspx?s=60

ANRS satellite symposium: what can we learn from post-treatment controllers? (TUSA03)

http://pag.ias2013.org/session.aspx?s=42

Approaches to HIV cure in children and youth with perinatal HIV infection. (WESY0107)

Persaud D. (not webcast, rapporteur summary only)

http://pag.ias2013.org/session.aspx?s=69

Late Breaker Track A (WELBA)

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IAS 2013: HIV TRANSMISSION

Partner-dependent immune differences may protect against HIV infection

Simon Collins, HIV i-Base

An interesting poster at IAS 2013 looked at the association between HLA incompatability of sexual partners as a mechanism for protection against sexual transmission. [1]

Wim Jennes from the Institute of Tropical Medicine, Antwerp presented results from a study of 108 Senegalese couples enrolled in a cohort in Dakar. This included 35 sero-different couples, 35 where both partners were HIV positive and 38 where both partners are HIV negative.

The hypothesis for potential protection was based on the role that killer immunoglobulin-like receptors (KIR) which regulate natural killer (NK) innate immune responses in susceptibility to HIV infection and that KIR respond to HLA expression on target cells. The group has previously published on how KIR/HLA patterns could explain protection from HIV in a group of multiply-exposed HIV negative sex workers. [2]

KIR contain two or three external Ig-like domains (2D, 3D) with either long (2DL, 3DL) or short (2DS, 3DS) tails, corresponding to their function as inhibitory or activating receptors, respectively and can have strong or weak binding affinities to specific HLA.

NK cells from HIV negative donors were co-cultured with HIV positive patient-derived CD4 cells to look at NK cell-mediated CD4 T-cell killing as a function of KIR/HLA.

In terms of autologous NK cell function and KIR frequencies, HIV negative partners (in the serodifferent group) had significantly lower levels of 2DL3 (p=0.001) and higher levels of both 2DL2 (p=0.036) and 2DS2 (p=0,049) compared to HIV positive people (partners in the HIV positive couples). When looking at KIR/HLA frequencies, HIV-negative people were more frequently KIR2DL2 hmz (centromeric KIR BB) and HIV positive people were more frequently KIR2DL3 hmz (centromeric KIR AA).

Allogenic NK cell function, targeting incoming HIV-infected cells from the HIV positive partner, regulated by allogeneic KIR/HLA compatibility between partners (based on studies from stem cell transplants) showed similar associations. HIV-different couples showed a higher frequency of a missing self KIR/HLA combination while HIV-concordant couples showed a higher frequency of a matched KIR/HLA combination. 2DL1+C1/C1 was present in approximately 3% vs 22% and 2DL3/L3+C1/C2 in 33% vs 3%, in HIV positive vs HIV-different couples respectively. In multivariate analysis, matched and missing self allogeneic KIR/HLA combinations, but not recipient KIR genotype, independently predicted couple HIV status.

In the in vitro studies with HIV negative cells, significantly higher levels of alloreactive NK cell-mediated CD4 killing were seen for missing self KIR/HLA combinations.

COMMENT

The complexity of factors that compound to allow or block sexual transmission are numerous and complex, and range from biomedical determinants to behavioural risks. In terms of individual per-exposure risks reference ranges (approximately 1 in 200-500 in someone not on treatment) suggest that HIV is a difficult virus to transmit.

Conversely, only one exposure is needed for transmission to occur. Anecdotally, some people are unlucky in this corresponding to a single unprotected risk while others remain protected after numerous risks over many years with an HIV positive partner, even when condoms are not used.

Although free virus is usually referred to as the cause of infection, HIV-1 transmission may occur at least in part via HIV infected cells from the sexual partner. These cells can penetrate deeply in the recipient's mucosal tissues and continue to produce infectious virus. The relative contribution of free virus and infected cells in causing transmissions is not known. The current hypothesis from this group is that the allogeneic KIR/HLA mismatches protect against these incoming infected cells.

Once infection is established, even if this is by free virus from the sexual partner, they suggest that an early mucosal infection in the recipient could then still be cleared by autologous activating KIR/HLA genotypes in the recipient partner. They also speculate that that alloreactive KIR/HLA combinations target free virus from the sexual partner, because free virus is known to carry the HLA molecules from the host cells in abundance on the viral membrane. The mechanism for this requires further study.

A previous analysis of these couples, published in PLoS One, reported a high phylogenetic linkage between the positive couples (74% linked, 13% indeterminate, 13% unlinked) that corresponded to interview data on behavioural risk. [3]

Also, that although condom use is now high in the serodifferent couples, and that many of the HIV positive partners have suppressed viral load due the ART, the negative partners still represent selected survival because they went through a period of high infection risk (when HIV status was not known, no condom

use and no ART). These issues are expanded on in the published findings from this study in the journal Blood. [4]

This research provides insight into further understanding the genetic factors affecting transmission and is important for highlighting how these may be specifically partner dependent.

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CONFERENCE REPORTS

5th International Workshop on HIV Paediatrics

28-29 June 2013, Kuala Lumpur

Introduction

The International Workshop on HIV Paediatrics is into its fifth year now an annual fixture, held immediately before the IAS conference.

The meeting provides an excellent opportunity to present work on a subject that often gets overlooked at the larger conferences.

Presentations are a mix of plenary talks, abstracts, clinical case studies and discussions. This year's meeting was excellent which a strong emphasis on clinical considerations. Topics included cure, adolescents, Option B+, retention in care, long-term complications and TB. There were also presentations on the new WHO guidelines focusing on the paediatric and pregnancy recommendations.

Workshop materials including the programme and abstract book for online viewing are available from the previous meetings section of the Virology Education website.

The abstracts of the 5th International Workshop on HIV Paediatrics are published in Reviews in Antiviral Therapy & Infectious Diseases 2013_7:

http://regist2.virology-education.com/abstractbook/2013_7.pdf

The slides are online but the meeting is not webcast:

http://regist2.virology-education.com/2013/5HIVped/28june.html

Co-submission of abstracts to both IAS 2013 and this workshop is possible, so there is some overlap. If there is a webcast of an oral presentation from that meeting we have also included a reference and link.

Articles in this issue include:

- Vertical transmission continues to decline in UK and Ireland
- Decline in late preterm delivery with vaginal birth in Europe
- High loss to follow up among asymptomatic women starting ART in pregnancy in Option B+ programme
- Decreased growth in ART exposed uninfected infants in Botswana
- Antiretrovirals, doses and formulations for children

Vertical transmission continues to decline in UK and Ireland

Polly Clayden, HIV i-Base

The rate of vertical transmission of HIV continued to inch its way down further between 2007 and 2011 than in previous years, according to data presented at the 5th International Workshop on HIV Pediatrics.

Claire Thorne from the Centre of Epidemiology for Child Health, UCL Institute of Child Health, London presented findings from the National Study of HIV in Pregnancy and Childhood (NSHPC) – a population-based surveillance study. In the UK and Ireland children born to HIV-positive mothers are followed up to establish their own HIV status. Dr Thorne presented analyses including live singleton births born 2000 to 2011 and reported to the NSHPC by March 2013.

In 2000 to 2006, the vertical transmission rate in diagnosed women in the UK and Ireland was already very low at 1.2%. The investigators compared this previous rate to that from 2007 to 2011 and looked at different treatment and mode of delivery scenarios. They examined the association between ART with three or more antiretrovirals and the probability of transmission using generalised additive models.

There were 12,487 singleton live births to HIV positive women between 2000 and 2011. Of 6377 births in 2007 to 2011, 72% were to women diagnosed prior to becoming pregnant compared to 46% in 2000 to 2006, $p<0.001$.

The majority of women (96%) received ART in pregnancy in 2007 to 2011 compared to 82% in the earlier time period; of these 41% started treatment before conception, compared to 25% in 2000 to 2006, both comparisons $p<0.001$.

There was an increase in the proportion of women with an undetectable viral load closest to delivery (median 23 days,

IQR 9-42), respectively 76% and 57% in the later and earlier periods, p<0.001.

Women started ART significantly earlier in 2007 to 2011 at a median 22.7 weeks gestation than in 2000 to 2006 at a median 25.7 weeks, and twice as many had planned vaginal deliveries, 31% compared to 14%, both comparisons p<0.001.

The overall vertical transmission rate in 2007 to 2011 was 0.57% (33/5788; 95% CI 0.42-0.84%), which was significantly lower than in 2000 to 2006, p<0.001. Incomplete data from 2010 to 2011 shows the rate reached 0.46% during the most recent year examined.

Excluding breast fed infants and/or those with clear evidence of post natal transmission, the proportion attributable to short duration of ART or lack of treatment has declined from 77% to 24% in the earlier and later time periods respectively, p<0.001.

Transmission rates in 2007 to 2011 in women on ART were: 0.2% (3/1720) in those with planned vaginal delivery, 0.6% (12/2050) with elective caesarean section and 0.5 (7/1360) with emergency caesarean section. Intrapartum/postpartum transmission rates were: 0.05% (2/3915) in women with viral load <50 copies/mL at a median of 23 days before delivery, 1.0% (97/684) in those with 51-4000 copies/mL and 2.9% (13/447) in those with >400 copies/mL. The investigators noted that it was improbable that either of the two transmissions, which occurred despite ART or undetectable viral load were in utero transmissions (both infants tested negative at birth).

The probability of vertical transmission among 6507 pregnancies delivered 2000-2011 by duration of ART was modelled, this declined sharply with each additional week of treatment up to about 10 weeks duration, levelling off at 0.4% after about 13 weeks of ART.

Overall, vertical transmission rates in the UK and Ireland continued to improve in recent years, reaching the all time lowest level of 0.46% in 2010, despite an already very successful programme. This was mostly due to a reduction in transmissions associated with starting ART late or receiving no of ART in pregnancy, as well as an increase in the proportion of women on ART at conception.

Ref: Townsend CL et al. Mother-to-child transmission of HIV continues to decline in the UK and Ireland. 5th International Workshop on HIV Pediatrics. 28 - 29 June 2013, Kuala Lumpur, Malaysia. Late breaker oral abstract. O_09.

http://regist2.virology-education.com/2013/5hivped/docs/16_Thorne.pdf (PDF slides)

Decline in late preterm delivery with vaginal birth in Europe

Polly Clayden, HIV i-Base

Late preterm deliveries have decreased in Europe since guidelines recommending vaginal delivery were published.

Claire Thorne showed findings from the European Collaborative Study (ECS) in EuroCoord and the Swiss Mother & Child HIV Cohort Study (MoCHiV) conducted to explore the effect of updated national guidelines in Europe on rates of late preterm delivery (defined as 34 to 36 completed gestational weeks) in HIV-positive women delivering between 2000 and 2010.

National guidance recommending vaginal delivery for women with undetectable or very low viral load, changed in Europe between 1999 and 2010. BHIVA guidelines changed in 2008.

Data conflict on the association between maternal HIV, preterm delivery and ART. The majority of preterm infants are born at 34 to 36 weeks gestation ie late preterm. In the general population, around 30% to 35% of preterm births are due to maternal or foetal indications, with induced labour or elective caesarean section. Compared to infants born full term, late preterm infants are physiologically and developmentally immature with higher rates of mortality and morbidity.

The study was a pooled analysis of data from eligible HIV positive women enrolled in the two European cohorts with a live birth between 2000 and 2010. Deliveries were stratified pre- or post-publication of national guideline change and preterm delivery rates were calculated.

Overall, 2663 mothers and 3013 deliveries were included from 10 countries; 80% (2402) delivered before and 611 20% (611) after the guidelines changed.

The women were 43% white and 48% black with a median age of 32 years (IQR 27-360) at the time of delivery. The majority (72%) were diagnosed with HIV before they became pregnant.

Overall, 76% of women received ART with 24% on ART at conception and the remainder receiving it in the first or second trimesters. Mono or dual ARV prophylaxis was used by 11%, 4% received ARVs but the strategy was unknown and 9% received nothing.

Comparing the pre-guideline with post-guideline groups: ART use increased from 72% to 90%; the proportion of women receiving no ARVs declined from 10% to 4% and mono/dual therapy decreased from 13% to 2%. The proportion of vaginal deliveries increased from 25% to 52% and elective caesarean section rates decreased from 65% to 27%. The overall rate of preterm delivery decreased from 22.8% to 12.5%. The investigators observed a decrease of late preterm deliveries from 16% to 7% after the change of guidelines, p=0.05.

Dr Thorne explained that prior to guideline changes, nearly three-fifths of late preterm deliveries were delivered by elective caesarean section, the majority with maternal HIV as the indication. Concerns about potential preterm delivery led to iatrogenic preterm delivery with elective caesarean section to avoid intrapartum risk with labour/rupture of membranes. Change in mode of delivery policy led to reduction in this strategy and in turn a decrease in proportion of late preterm infants.

It is to be expected that late preterm delivery rates in HIV positive women will continue to decline as increasing proportions of women with undetectable viral load deliver vaginally.

Ref: Aebi-Popp K et al. Vaginal delivery as option for HIV infected women: decreasing late preterm delivery rates in a European cohort collaboration. 5th International Workshop on HIV Pediatrics. 28 - 29 June 2013, Kuala Lumpur, Malaysia. Late breaker oral abstract. O_14.

http://regist2.virology-education.com/2013/5hivped/docs/25_Thorne.pdf

High loss to follow up among asymptomatic women starting ART in pregnancy in Option B+ programme

Polly Clayden, HIV i-Base

Loss to follow up is high in pregnant women not otherwise indicated for treatment starting ART in Malawi's Option B+ programme.

Lyson Tenthani showed findings from an analysis of retention in care of HIV positive pregnant and breastfeeding women started on ART in the Malawi Option B+ programme by the Ministry of Health Malawi and IeDEA South Africa. [1] This was a late breaker presentation at the 5th International Workshop on HIV Pediatrics.

Malawi pioneered the Option B+ strategy - ie all pregnant and breastfeeding women starting lifelong ART - in 2011. It has led to a massive 763% increase in HIV positive pregnant women receiving ART. [2] But there are concerns about acceptability, retention and adherence particularly among asymptomatic women.

This cohort study analysed facility- and patient-level data from sites enrolled in the national electronic ART register across the country. The investigators used meta-analyses, logistic regression and competing risk survival models to examine at site- and patient-level predictors of loss to follow-up.

The evaluation included facility level data on a total of 21,939 women from 540 sites and patient-level data on 28,428 women from 19 ART sites with electronic medical record system.

At 6 months after starting ART 82% of women were alive on ART and 17% were lost to follow up – a small proportion had either died or stopped ART.

In multivariate analysis controlling for age, facility type and random effects for site Option B+ women starting ART in pregnancy were 5 times more likely to be lost to follow up with no follow up visit than patients initiating treatment with low CD4 and/or WHO stage 3/4. Option B+ women starting during breastfeeding were twice as likely to have no follow up visit. See table 1: Option B+: predictors of loss to follow up.

Notably 41% of patients had no CD4 data - one of the reasons for starting B+ Malawi was because of lack of access to CD4 testing.

Table 1. Option B+: predictors for loss to follow up

	No follow up visit	
Indication	OR (95%CI)	p-value
Low CD4 or stage 3/4	ref	<0.0001
B+ pregnant	5.18 (4.35-6.17)	
B+ breast-feeding	2.26 (1.83-2.80)	
Pregnant and low CD4 or stage 3/4	1.88 (1.23-2.90)	

Lost at second visit		Lost during 3-8 months on ART	
OR (95%CI)	p-value	SHR (95% CI)	p-value
ref	0.1972	ref	0.0091
1.90 (1.46-2.48)		0.91 (0.67-1.24)	
0.90 (0.64-1.27)		0.60 (0.42-0.85)	
0.45 (0.18-1.10)		0.61 (0.31-1.19)	

SHR: Substitution hazard ratio

Performance across sites was variable, overall 37% of sites did well with less than 10% of all patients lost to follow up six months after starting ART but 33% of the sites had greater than 20% loss to follow up.

Analyses of site level predictors for loss to follow up in 368 sites revealed Ministry of Health sites did less well (faith based as reference) OR 1.19 (0.94-1.50), p=0.04 as did central hospitals (health centre as reference) OR 2.7 (0.92-7.94), p=0.47, that is larger sites with higher proportions of B+ women.

COMMENT

If ever there was a job for the community!

Most Option B+ patients who were lost to follow up started ART on the day of their diagnosis and never came back. Unsurprisingly these women were less likely to return to clinics than pregnant women who started treatment after a little time to come to terms with their HIV status (OR 1·7, 95% CI 1·4-2·2).

Much of the discussion following the presentation focused on understanding the barriers to retention in care and including preparation and support for women in Option B+ programmes. The sites with a low rate of loss to follow up - demonstrating that good retention in care can be achieved - need to be scrutinised for generalisable strategies.

The crucial role of treatment literacy and preparation for women, starting from the first visit, cannot be emphasised more.

There are many excellent models of community support, treatment education, adherence clubs and one to one peer support. These programmes need to be taken seriously, communities must be included in their design and funding must cover their successful execution.

A related presentation at IAS 2013 from Uganda also showed high loss to follow up among women associated with rapid initiation of ART. [3]

This study compared women starting ART in ANC to those starting in labour. In this programme 190 women tested positive and 92% started ART in the ANC; 82% returned to receive their CD4 results. There were also 162 women who started in labour and only 12% of these women returned. Although there is no opportunity to

delay ART initiation at this very late stage of pregnancy, the same attention to support and education is likely to improve this tiny proportion of women returning to the facility.

http://pag.ias2013.org/Abstracts.aspx?SID=22&AID=2187

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Decreased growth in ART exposed uninfected infants in Botswana

Polly Clayden, HIV i-Base

In utero ART exposure is associated with significantly lower weight and length at 24 months of life in HIV-exposed uninfected infants compared to those with AZT exposure.

Poor growth has been reported in HIV-exposed uninfected infants exposed to ART in utero compared to AZT but this phenomenon has not been looked at longer term.

Kate Powis presented data from a comparison of uninfected, breast fed infants participating in clinical trials in Botswana to find out if in utero exposure to AZT vs ART results in different growth outcomes.

The Mashi and Mma Bana studies enrolled HIV positive pregnant women from the same four sites. In both trials infant weight and length measurements were routinely taken until 24 months of age.

The analysis included singleton infants born at term to mothers receiving ART or AZT for at least two weeks before delivery, breastfed and remaining HIV negative at 18 to 24 months with weight/length measurements at 24 months.

Infants/children were measured a birth, monthly through 6 months and every 3 months starting at 9 months to 24 months of age. Weight-for-age (WAZ), length- for-age (LAZ), and weight-for-length (WLZ) z- scores were derived from WHO Child Growth Standards. WAZ, LAZ and WLZ were compared by antiretroviral exposure at 24 months using t-test and linear regression.

Data for 513 ART exposed and 3003 AZT exposed children were included in the analysis. Median maternal CD4 count at enrollment was 392 and 324 cells/mm^3 in mothers receiving AZT and ART respectively, p<0.001. Median duration of infant in utero exposure to AZT or ART was 5.7 weeks and 12.0 weeks respectively, p<0.001; mean months breastfed was 5.1 and 5.2, respectively, p= 0.41; and mean birth weight was 3.16 kg and 3.04 kg respectively, p<001.

In unadjusted analysis, at 24 months, mean WAZ and LAZ were significantly lower in ART exposed infants while mean WLZ did not differ significantly: WAZ -0.51 (95% CI -0.61 to -0.42) vs -0.28 (95% CI -0.40 to -0.17), p=0.002; LAZ -1.00 (95% CI -1.11 to -0.90) vs -0.71 (95% CI -0.89 to -0.61), p=0.001 and WLZ -0.02 (95% CI -0.11 to +0.08) vs +0.09 (95% CI -0.05 to +0.23), p=0.21.

In multivariate analysis, adjusted for maternal CD4, viral load enrollment site, in utero ARV exposure duration and maternal BMI at 1-month postpartum, in utero ART exposure remained significantly associated with lower mean LAZ, effect estimate AZT vs ART +0.54 (95% CI +0.28 to +0.80), and WAZ, +0.41(95%CI +0.19 to +0.63), p<0.003.

By sex, the weight and height differential for girls were +0.61 kg, p=0.01, and +2.11 cm, p<0.001, and for boys +0.48, p=0.02 and +1.35 cm, p=0.02.

Dr Powis suggested that limitations of the study included differences between cohorts in timing of maternal ARV initiation by gestational age and Mashi infants received twice daily AZT thoughout breastfeeding while Mma Bana infants were exposed to maternal ART through breast feeding. There was also no control group of HIV-unexposed infants.

Ref: Powis K et al. In utero HAART exposure associated with decreased growth among HIV-exposed uninfected breast fed infants in Botswana. 5th International Workshop on HIV Pediatrics. 28 - 29 June 2013, Kuala Lumpur, Malaysia. Late breaker oral abstract. O_11.

http://regist2.virology-education.com/2013/5hivped/docs/22_Powis.pdf (PDF slides)

This study was also presented as a poster at the 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 30 June - 3 July 2013, Kuala Lumpur. Poster available.
http://pag.ias2013.org/abstracts.aspx?aid=1113

Antiretrovirals, doses and formulations for children

Polly Clayden, HIV i-Base

Both the 5th paediatric workshop and the 7th IAS conference had excellent presentations on pipeline antiretrovirals, dosing strategies and formulations.

Some of the studies made an appearance at both meetings – as oral or poster presentations - as co-submission was encouraged. The IAS session "Expanding ARV options for children: first line and beyond" was webcast. [1]

This report combines presentations from both meetings.

Atazanavir

Atazanavir (ATV) powder boosted with ritonavir (RTV) liquid once daily plus optimised dual NRTI background therapy is effective in ART-naïve or experienced children aged 3 months to 6 years

with no additional safety issues to previous ATV paediatric and adult studies. [2, 3]

Atazanavir is currently approved for children aged 6 years and above. PRINCE 1 is an ongoing phase 3b prospective, international, multicentre, open label, two-stage clinical trial - 48-week data were presented. This trial has been ongoing since 2010

The study enrolled ART-naive or -experienced (without prior ATV use) children with viral load ≥1000 copies/mL. There were two dosing regimens: stage 1 - ATV powder boosted with RTV liquid, based on 3 weight bands (see dosing table 1) and stage 2 – switch to ATV capsules after 48 weeks on ATV powder or when they reached 6 years or ≥25 kg. Stage 1 efficacy and safety were presented.

Table 1. ATV powder/RTV liquid dosing table

Weight (kg)	ATV dose (mg)	RTV dose (mg)
5 to <10	150	80
10 to <15	200	80
15 to <25	250	80

A total of 56 children were enrolled, 46 completed stage 1, and 45 made the transition to stage 2. The majority (68%) of children were from Africa. At baseline, they were a median age of 28.5 months (range 3 to 65), with mean viral load and CD4 counts of 4.62 $\log^{10}$ copies/mL and 1192.6 cells/mm^3; 61% were ART-naive.

Using modified intent-to-treat analysis, at week 48, 33 (61%) children had viral load <50 copies/mL, and 40 (74%) had viral load <400 copies/mL. Viral suppression increased with higher weight: 48% in the 5 to <10 kg compared to 71% in the 15 to < 25kg weight band had viral load <50 copies/mL.

There was no significant difference between ART-experienced and -naive children in rate of viral suppression, with 60% and 62% <50 copies/mL respectively. Mean CD4 count change from baseline was 397 cells/mm^3, respectively 550, 225 and 374 cells/mm^3 in the increasing weight bands.

By week 48, 14 children had virological failure, 57% were ART-naïve and 43% ART-experienced. Nine had paired genotypic data (baseline and on treatment) and 6 paired phenotypic. This showed no acquired phenotypic resistance to ATV, ATV/RTV or any NRTI or NNRTI. One child developed phenotypic resistance to saquinavir. No child developed any major PI substitution to ATV or ATV/RTV.

There were no new or unexpected safety events and no deaths. Eleven children (20%) had on treatment SAEs. Five children (9%) discontinued due to AEs, 4 were in the 5 to <10 kg group. Seven (13%) had hyperbilirubinaemia-related AEs and 3 cardiac disorders, 2 were considered related to the study treatment.

Through 48 weeks on ATV powder, common AEs occurred in 52 children (93%); the most frequent being upper respiratory tract infections (36%), diarrhea (36%) and vomiting (29%).

The PRINCE 2 study of ATV powder in 3 months to <11 in 95 children years is ongoing. A PK, safety and efficacy analysis of the combined data sets will be conducted.

Darunavir

Darunavir/ritonavir (DRV/r) plus an optimised background regimen was effective in treatment-experienced children, with no new safety concerns compared to adults at 48-weeks in the ARIEL trial. [4]

The primary 24-week analysis from this phase 2, multicentre, international trial led to the approval of DRV/r for treatment experienced children aged 3 to <6 weighing at least 10 kg.

Children enrolled in ARIEL had been on ART for 12 weeks or more with viral load >1000 copies/mL and less than three darunavir-associated mutations.

They initially received DRV oral suspension at 100mg/mL plus RTV 20/3mg/kg twice daily with an optimised background regimen. Following pharmacokinetic (PK) analysis after two weeks of receiving this dosing regimen and Data and Safety Monitoring Board recommendations, children weighing <15 kg and 15 to < 20kg were given DRV/r 25/3mg/kg and 375/50mg twice-daily respectively.

The 48-week analysis included 21 children with a median age of 4.4 years (range 3-6) at enrollment. Their mean baseline viral load was 4.34 copies/mL, median CD4 count 927 cells/mm^3 and CD4 percentage 27.7%.

The majority of the children received two background NRTIs and two children received three NRTIs.

At week 48, 81.0% of children had viral load <50 copies/mL and 85.7% <400 copies/mL (ITT-TLOVR). Notably at 24 weeks only 57.1% of children had achieved virological suppression <50 copies/mL but 81.0% were <400 copies/mL.

Two children with baseline DRV mutations (L33FL and L76V) had viral load <50 copies/mL at 24 and 48 weeks. There were 3 virologic failures at week 48 (2 never suppressed; 1 rebounder); of the 2 with paired baseline/endpoint genotypes, neither developed PI nor NRTI mutations. Both remained susceptible to DRV and other NRTIs in the background regimen.

There was one AE possibly related to DRV (ECG QT prolongation), and one discontinuation due to grade 2 vomiting probably related to RTV. Two children had grade 4 AEs (stenosing tenosynovitis and asthmatic crisis), both considered serious but not related to the study treatment. All laboratory abnormalities were grade 1 except for one grade 3 neutropenia, which had been present at baseline and was not considered treatment-related.

A small Thai pilot study looked at PK and efficacy of once daily compared to twice daily dosing of DRV/r in older children and adolescents. [5]

Treatment-experienced children and adolescents receiving DRV/r twice daily in optimised regimens, with no prior DRV-associated mutations, and virologically suppressed (<400 copies/mL) for at least 6 months were enrolled.

Twelve-hour blood sampling (pre-dose and 2, 4, 6, 8 and 12 hours post-dose) for PK was performed at enrollment. DRV/r was then switched to once daily dosing and 24 hour sampling (as previously but with 18 and 24 hours post dose) was repeated 2 weeks later. Twice daily DRV/r doses of 375/100, 450/100, and 600/100 mg were increased to once daily doses of 450/100, 600/100, and 900/100 mg, respectively.

DRV/r PK parameters were calculated using non-compartmental analysis. CD4 counts and viral load were measured at baseline and at 12, 24, 36 and 48 weeks.

Eight children and adolescents with a median age of 16 years (range 11.0-18.9) were evaluated. Their median CD4 count was 806 cells/mm^3 (range 621-1200). DRV AUC0-24h with twice daily and once daily dosing was 59.6 (range 38.5-139.3) and 51.5 (range 20.7-117.7) mcg.hr/mL, respectively. The C12h and C24h DRV concentrations were 1.4 (range 0.7-4.9) and 0.7 (range 0.2-2.4) mg/L, respectively.

PK parameters for RTV were: AUC0-24h with twice daily and once daily dosing 8.8 (range 3.3-11.1) and 6.9 (range 0.7-9.3) mcg. hr/mL , p=0.95; C12h and C24h 0.33 (range 0.2-0.5) and 0.08 (range 0.03-0.12) mg/L, respectively, p<0.001.

All children had DRV concentrations above the IC50 for wild type virus (0.055 mcg/mL) while receiving either once or twice daily dosing.

Six of eight children had viral load <50 copies/mL at all tests during the 48 weeks.

Maraviroc

Maraviroc (MVC) is a CCR5 antagonist, approved to treat adults and adolescents aged 16 years or more with CCR5-tropic HIV but not yet approved for paediatric use.

Data were presented from 94 participants in the ongoing A4001031 study in treatment-experienced children and adolescents aged 2 to <18 years. [6]

This is an open-label, two-stage (stage 1: dose-finding; stage 2: safety/efficacy), age-stratified, non-comparative, multicentre study to evaluate the safety, tolerability, and PK of MVC plus optimised background therapy.

Participants are enrolled into one of four cohorts by age and formulation: cohort 1, ≥2 to <6 years/liquid (n=13); cohort 2, ≥6 to <12 years/tablet (n=27); cohort 3, ≥ 6 to 12 years/liquid (n=12), and cohort 4, ≥ 12/tablet (n=42).

Those eligible have viral load >1000 copies/mL, on stable or no therapy and have experienced >6 months in at least two ARV classes.

Dosing is complex and determined by body-surface area (BSA) and concomitant medications**.** Dose adjustment occurred if average concentrations were <100 ng/mL at Week 2. Doses ranged from 50-450 mg twice daily.

A total of 75/94 participants were followed for 48 weeks. At the time of analysis 49 were still on treatment and 26 discontinued MVC, 14 with virological failure and evidence of non-adherence - which was more frequent in adolescents - and 3 participants with virological failure had tropism shift. Of those remaining on treatment, 52% and 40% had viral load <400 and 50 copies/mL respectively.

AEs occurred in 60 (63%) participants and 10 (10.6%) were grade 3 or 4. There were no deaths and 3 discontinuations due to AEs. Most common (>10%) AEs were: infection and infestations (49%), gastrointestinal disorders (36%), nervous system disorders (14%), reproductive system and breast disorders (13%), and skin and subcutaneous tissue disorders (12%).

MVC PK from this study was presented separately. [7] This sub study using PK profiles from 51 participants found BSA-based dosing with CYP3A4 inhibitors scaled from the 300 mg adult dose provides MVC exposures achieving the target Cavg >100 ng/mL in all cohorts.

Non-inhibitor ART regimens are still under evaluation and PK data suggests that doses are likely to be higher than the initial adult BSA scaled dose.

Enrollment in A4001031 will continue out to five years.

Efavirenz

Efavirenz (EFV) plus NRTI backbone combination is the preferred WHO first line antiretroviral therapy for HIV-positive children more than 3 years and weighing above 10 kg.

WHO weight band dosing reduces the proportion of children with EFV concentrations below target compared to FDA, but this is achieved with a higher proportion having concentrations above target and in turn a higher risk of toxicity, according to a study comparing the two dosing guidelines using a population PK approach. [8] See Table 2.

Table 2: Efavirenz dosing guidelines

Dose	Body weight	
	FDA	WHO (2010/2013)*
200 mg	10 to <15 kg	10 to <14kg
250 mg	15 to <20 kg	14 to <25
300 mg	20 to <25 kg	
350 mg	25 to <30 kg	25 to <35
400 mg	30 to 40 kg	
600 mg	≥ 40 kg	≥ 35 kg

* The study used 2010 dosing guidance – this is unchanged in the 2013 revision.

This analysis included EFV plasma concentration data from 190 children (623 plasma samples); 40 had 24-hour PK sampling data available. EFV was given according to FDA weight band recommendations. Population PK was estimated using nonlinear mixed effects modelling.

Median age was 7.2 years (0.1* to 12.2), bodyweight 16 kg (5 to 42), and efavirenz dose 300 mg (200-600). *The investigators noted that this child at the lowest end of the range first received dual NRTI before starting EFV at 5.4 years.

A one-compartment PK model was used with delay absorption. Weight influenced EFV apparent oral clearance and volume of distribution and allometric scaling significantly reduced the interindividual variability.

The estimated median AUC0-24 was 49 mg/L.hr (8 to 296). A predicted EFV C12 was 2.3 mg/L (0.07 to 11.9). Of 190 children, 16 (8%) had predicted EFV C12 below 1 mg/L (subtherapeutic range) and 12 (6%) above 4 mg/L (toxic range) with FDA dosing. No serious adverse events were reported.

Simulations predicted similar proportions of children with C12 between 1 mg/L and 4 mg/L with both dosing guidelines. Proportions of children with C12 in the subtherapeutic range were reduced across all weight bands with WHO compared to

FDA dosing, respectively: 8 vs 16%, 11 vs 14%, 12 vs 16% and 8 vs 15% in the 14 to <15 kg, 15 to <20 kg, 25 to 32.5 kg and 35 to 40 kg groups; but proportions in the toxic range increased, respectively: 39 vs 25%, 33 vs 24%, 28 vs 21% 42 vs 21%.

A previous study of Thai children an 11% frequency of CYP2B6 TT genotype (EFV concentration >6 mg/L), genotypes were not determined in this one but several children had EFV concentrations >6 mg/mL which could be explained by this phenomenon.

Safety data on EFV in children dosed according to the WHO weight bands are needed.

Lopinavir/ritonavir

Using 70% of lopinavir/ritonavir (LPV/r) standard dose in heat stable tablet formulation for maintenance therapy was non-inferior to standard dose in a Thai study. [9]

This was a multicentre, randomised, open-label trial conducted at 11 sites in Thailand. Children and adolescents aged < 18 years weighing 25-50 kg with viral load <50 copies/mL were randomly assigned to FDA -recommended standard dose or low dose of LPV/r.

LPV/r doses for children 25 to 35 kg were 300/75 mg or 200/50 mg, and >35 to 50 kg were 400/100 mg or 300/75 mg twice daily. The primary endpoint was the proportion of children with viral load <50 copies/mL at 48 weeks. Secondary endpoints were LPV Ctrough and the proportion of children with dyslipidemia.

The study enrolled 199 children, with mean age of 13.4 years (SD 2.2) years, and CD4 of 787 (319) cells/mm^3; 98 were randomised to standard and 101 to the low dose arm. The NRTI backbones were AZT/3TC (47%), AZT/ddI (18%), TDF/3TC (16%) and others (20%).

Loss to follow up was 7 (3.5%) participants - 3 in the standard and 4 in the low dose arms.

At 48 weeks, by intention to treat analysis, the proportions of participants with viral load <50 copies/mL were 91.8% in the standard and 88.1% in the low dose arms, difference -3.7% (95% CI -12.0 to 4.6%), p=0.38. Eight participants had viral load >400 copies and factors associated with this were poor adherence (aOR 3.3) and weight 35 to 50kg (aOR 3.6).

Median LPV Ctrough at week 48 were 6.9 (range 0.3. to 20.4) and 5.2 (0.2 to 11.8) mg/dL, standard and low dose respectively. Fourteen (7.3%) had Ctrough < 1 mg/dL (4 in standard and 10 in low dose arms, p = 0.1).

More children in the standard arm had cholesterol > 200 mg/dL (34.4 vs 20.6%, p=0.03) and triglyceride > 150 mg/dL (60.4 vs 44.3%, p =0.03) than those in the low dose arm.

Once daily abacavir and 3TC

Data from Thailand demonstrated non-inferiority of abacavir (ABC) and 3TC once daily compared to a twice daily regimen in children. [10]

ABC and 3TC are approved for once daily use in adolescents aged 12 and above and adults, but not yet in younger children.

Previous studies in European and African children found similar PK for once and twice daily ABC and 3TC.

This was a single-arm, open- label, crossover study, conducted in 30 Thai children and adolescents aged <18 years, weighing >14 kg, viral load <50 copies/mL, and HLA B5701 negative. ABC and 3TC daily doses by weight were 300 and 150 mg for 14 to <20 kg, 450 and 300 mg for 20 to <25 kg, and 600 and 300 mg for >25 kg.

The study used originator ABC and 3TC scored tablets. Intensive PK sampling was performed following 14 days of each dose. GMR (90% CI) of AUC0-24 and Cmax were compared.

At baseline, participants were a median age 8.8 years (IQR 6.6-11.3) years, weight 21.9 kg (IQR 11.9-30.6) kg and CD4 count 841(IQR 580-1073) cells/mm^3.

ABC and 3TC was given with EFV (60%), LPV/r (37%), or NVP (3%). No children had SAEs or laboratory abnormalities during the PK study.

GM of AUC0-24 for once and twice daily ABC were 14.43 and 10.65 mg·h/L, which gave a GMR 1.36, (90% CI 1.19-1.55). For 3TC, these values were 17.70 and 18.11 mg·h/L, GMR 0.98 (90% CI 0.84-1.14).

GMR of ABC Cmax for once and twice daily was 2.84 mg/L (90% 2.28-3.53); 3TC was 1.69 mg/L (1.35-2.09).

ABC AUC0-24 once daily was higher overall but lower in the 14 to 20 kg weight band. 3TC AUC0-24 once and twice daily was bioequivalent – there was higher 3TC exposure in Thai children compared to historical data in children and adults but no toxicities were observed.

The study demonstrated the non-inferiority of once daily ABC and 3TC compared to twice daily and provides further support for this dosing regimen in children.

Fixed dose combination: 3TC/NVP/AZT

A generic dispersible fixed dose combination (FDC) of 3TC/NVP/AZT for children is bioequivalent to the originator liquids. [11]

Mylan (formerly Matrix) tested dissolution of 3TC/NVP/AZT 30/50/60 mg FDC tablets in 0.1N HCl /Type II/75 rpm/900mL media. Bioequivalence was tested in 48 healthy adults aged 18 to 50 under fasting conditions. Originator liquids were used as reference: Epivir solution, Viramune suspension and Retrovir syrup.

The tablet has a short disintegration time and disperses quickly in water - after 10 minutes, 98 to 100 of the API was dissolved.

In the bioequivalence study all participants were randomised to receive a single dose of either the FDC or reference products during period 1 and then the other after a washout period of 21 days. Very intensive sampling was performed up to 72 hours. The relative bioequivalence is shown in table 3.

Table 3: Relative bioequivalence (% of reference) of 3TC/NVP/AZT tablets to originator liquids

	Cmax	AUC(0-t)	AUC (0-inf)
3TC	105.51 (95.49 -115.54)	98.42 (90.69 -106.15)	98.59 (91.15-106.03)
NVP	102.52 (98.18 - 106.86)	100.55 (99.07 - 102.04)	-
AZT	99.37 (91.16 - 107.58)	101.12 (97.83 - 104.41)	101.27 (98.09-104.46)

The study found the time/concentration curves for the dispersible tablet and the reference products were indistinguishable, demonstrating equal bioavailability.

C O M M E N T

Data from PRINCE 1 has taken its time – adult ATV approval was in 2003 and for older children 2008. Presumably data from the combined sets from PRINCE 1 and 2 will eventually be submitted for approval. Whether there will be generic heat stable versions of ATV/r for children remains to be seen.

DRV/r might also be a good second line option for children over three who started on NNRTIs if suitable heat stable generics were available.

As with adults maraviroc will be far to complicated to use for all but a few treatment experienced children in rich countries.

According to this model, the risk of EFV toxicities seems quite high with WHO weight band dosing. This is not ideal particularly with double the proportion in the toxic range in the higher weight band, ie older children and adolescents who are most likely to receive it.

The Thai data for ABC and 3TC once daily reinforces that from ARROW and the PENTA studies. ViiV are submitting ARROW and PENTA data for a once daily indication for children (particularly with a view to producing a scaled down paediatric once daily FDC of dolutegravir plus these two NRTIs).

Finally, indisputable bioequivalency data for the only paediatric FDC recommended in the new WHO guidelines that is currently available.

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CONFERENCE REPORTS

International Workshop on HIV and Hepatitis Virus Drug Resistance and Curative Strategies

4-8 June 2013, Toronto

Introduction

This annual meeting had developed from its previous focus on HIV drug resistance to include resistance to hepatitis C and developments in cure research.

The meeting has a diverse and interesting programme and the organisers helpfully post the programme, abstract books and links to some of the oral presentations online.

Reports in this issue of HTB include:

- Higher intracellular concentrations with tenofovir alafenamide

(TAF) overcomes K65R and other key NRTI resistance in vitro

- Tentative phenotypic cut offs for dolutegravir: guidance for use with integrase resistance
- S/GSK744 and long-acting formulation indicate broadly similar resistance profile to dolutegravir
- One in five people with recent HIV infection in Spain have X4/R5 mixed tropic virus

Conference website:
http://www.informedhorizons.com/resistance2013

Abstract book:
http://www.intmedpress.com/journals/avt/abstract.cfm?id=2658&pid=88

Presentations:
http://www.informedhorizons.com/resistance2013/presentations.html

Higher intracellular concentrations with tenofovir alafenamide (TAF) overcomes K65R and other key NRTI resistance in vitro

Simon Collins, HIV i-Base

Results of a careful study suggest that the new tenofovir prodrug will become an essential goal for global treatment for at least the next decade. [1] The study was presented at the International Workshop on HIV and Hepatitis Drug Resistance held in Toronto from 6-8 June 2013. [2]

Tenofovir alafenamide (TAF) is a prodrug that has greater viral activity compared to tenofovir disoproxil fumerate (TDF) - by approximately an additional 0.5 log copies/mL in treatment naive patients - and which achieves intracellular concentrations of tenofovir diphosphate in PBMCs that are 5-7 fold higher and tenofovir (TFV) plasma concentrations that are 90% lower.

First in vitro results on the resistance profile for TAF suggest that this improved cell targeting results in a resistance profile that overcomes common NRTI resistance including the K65R mutation associated with high level resistance to tenofovir, the MDR Q151M and T69ins mutations and other mutation combinations including thymidine analogue mutations (TAMs). This is based on TAF achieving intracellular 95% inhibitory quotient (IQ95) levels that are five times higher with TAF compared to TFV.

Christian Callebaut and colleagues from Gilead created a large panel of reverse transcriptase mutation complexes derived from patients samples previously tested in the Monogram single-cycle phenotypic assay, including multiple combinations, with and without M184V, K65R, Q151M, T69ins and multiple TAMs and performed multi-cycle HIV infections to establish TAF activity against these viral isolates, Viral breakthrough experiments were subsequently performed, passaging HIV infected MT-2 cells every 4-5 days for 4 weeks to establish antiviral activity and related in vitro phenotypic cut-offs for TAF compared to TFV. The EC50 and EC95 values for each compound were used to establish intracellular IQ95 values, and target levels of 1 uM and 50 uM for TAF and TFV respectively.

TAF activity was highly inversely correlated with phenotypic fold change, loosing sensitivity when reaching 15-20 fold changes, with this requiring greater than three TAMs. The group also looked at two higher concentrations for each complex allowing an opportunity to see whether higher dosing might overcome further resistance.

Table 1 includes six of these complexes with the corresponding fold change in the single-cycle infection Monogram assay and mutli-cycle MT-2 cell exposure, and the time to viral breakthrough over 28 days if this occurred.

These in vitro results suggest that TAF is likely to be active against HIV that has developed resistance to TDF and other NRTIs and provide the first evidence for clinical advantages from the advanced formulation that are more than theoretical.

Table 1: Selected examples from panel of nucleoside mutation complexes

Virus ID	Category	Mutation complex	FC Monogram	FC MT-2 cells	Time to breakthrough (days)	
6	3 TAMS	M41L, L210W, T215Y	1.8	3.8	TAF >28 days	TFV 13 days
11	K65R	K65R, M184V	1.8	6.1	TAF >28 days	TFV 4 days
15	K65R/Q15M	M41L, A62V, K65R, T69ins, K70T, L74V, V75I, Y115F, F116Y, Q151M, M184V	2.4	3.3	TAF >28 days	TFV 8 days
30	T69ins	D67E, T69SSG	4.5	10.1	TAF >28 days	TFV 4 days
31	5 TAMs	M41L, D67N, T69D, L210W, T215Y, K219R	4.5	21.9	TAF 8 days	TFV 4 days
34	5 TAMs	M41L, D67N, L210W, T215Y, K219R	5.8	14.7	TAF 8 days	TFV 4 days

C O M M E N T

These data support the importance of developing TAF as an individual drug to ensure a solid dataset with a wide range of ARVs. This should be in addition to the current development programme for TAF that so far prioritises coformulations and fixed dose combinations over the single compound.

Hopefully these results will encourage Gilead to recognise that future access to TAF should not be restricted to co-bundled formulation with other compounds owned by this company and its partners. There will be an ethical urgency for patients with

existing drug resistance in both wealthy and resource limited countries to be able to have access to this new formulation.

Table 1: Virologic response at day 8 by FC cut-off

	Observed response					
Est. FC cut-off	Full	Intermediate	None	Total	PPV	NPV
< 9.45	136 (77%)	16 (9%)	4 (2%)	156 (88%)	136/156 (87%)	10/15 (67%)
9.45-25.99	5 (2%)	2 (1%)	5 (3%)	12 (7%)	159/168 (95%)	
> 25.99	0	0	3 (2%)	3 (2%)		3/3 (100%)
Total **	146 (82%)	19 (11%)	12 (7%)	177 (100%)		

** 6/177 patients had no FC at baseline

Ref: Callebaut C et al. Antiviral activity of tenofovir alafenamide (TAF) against major NRTI-resistant viruses: improvement over TDF/TFV is driven by higher TFV-DP loading in target cells. International Workshop on HIV and Hepatitis Virus Drug Resistance and Curative Strategies, 4-8 June 2013, Toronto. Oral abstract 23.

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http://www.informedhorizons.com/resistance2013/pdf/Presentations/Callebaut.pdf (PDF slides)

Tentative phenotypic cut offs for dolutegravir: guidance for use with integrase resistance

Simon Collins, HIV i-Base

Several presentations presented new data relating to the investigational integrase inhibitors dolutegravir.

The most important of these included a correlation of baseline fold change (FC) in IC50 with change in plasma viral load following 8 days of monotherapy, plotting individual patient responses based on baseline integrase resistance. [1]

This analysis, presented by Cindy Vavro and colleagues from GlaxoSmithKline, was from the VIKING-3 study in treatment-experienced patients with integrase inhibitor resistance, using dolutegravir at a dose of 50 mg twice daily for 8 days as functional monotherapy (while on current failing treatment), before switching to optimised background therapy.

Mean reduction in viral load at day 8 in 183 patients was -1.43 log copies/mL (95% CI -1.52, +1.34; p<0.001) with 82% of patients dropping by greater than 1 log copies/mL.

Phenotypic cut offs for dolutegravir were derived based on viral response at day 8. These were defined in the study as full (>1 log), intermediate (0.5-1.0 log) and none (<0.5 log) with FC

(95% CI) of <9.4 (5.98, 15.88) and ≥25.99 (15.92, –), for full and intermediate responses respectively.

Table 1 summarises Day 8 observed responses by these FC sensitivity at baseline, which resulted in a negative predictive value of 67% for people with FC <9.45 who would still not have a full response and a positive predictive value of 87% (136/156).

In this planned interim analysis of patients with 24 week results,

63% of those with baseline FC <9.45 (72/114) had viral load suppressed to <50 copies/mL. No patients with FC >9.45 at baseline achieved <50 copies/mL at week 24. Response rates were also closely related to integrase mutations at baseline, with Q148H/K/R present in 57 (31%) patients, usually with additional mutations. Pre-specified integrase mutations (with primary integrase mutations in bold) were: H51Y, **T66A/I/K**, L68V, L68I, L74I/M/R, **E92Q/V,** Q95K, T97A, G118R, E138A/K/T, G140A/C/S**, Y143C/H/R,** P145S, S147G, **Q148H/K/R**, V151I/L, S153F/Y, **N155H**, E157Q, G163R/K, G193E, R263K.

In multivariate analysis, three baseline mutations were most significantly associated with reduced day 8 response: Q148H/K/R (by –0.47 log); p=<0.001), L74I (by –0.27 log; p=0.037) and E138E/K/T (by –0.25 log; p=0.052). There was also a high correlation between Q148H/K/R and G140A/C/S (p<0.001).

When Q148 mutations were not present at baseline, 92% participants achieved >1 log reduction by day 8. This dropped to 71% when Q148 was present with one out of G140A/C/S, L74I or E138A/K/T and to 45% when two or more of these mutations were also present. The 24-week response rates for each of these baseline resistance categories was 79%, 45% and 11% respectively. The investigators noted that confidence intervals for FC values were either wide or not obtained and that this limited certainty of the results, but commented that this was partly related to high rates of viral efficacy and low numbers of patient with higher FC values in the current dataset.

In the Q&A after the presentation, Brendan Larder suggested that it would be more important to use the dataset to establish the cut-off that determined 100% response rates rather than the 69% presented. This improved sensitivity would clearly help management of patients who are unlucky enough to have already developed drug resistance to raltegravir or elvitegravir.

A poster from the VIKING-3 study presented an analysis of the resistance that developed in 35/183 (19%) based on interim results in 31/35 of these patients with paired baseline and week 24 samples. [2]

Treatment emergent resistance developed in 15/31 of these patients, with 13/15 having a Q148 mutation at baseline or in archived samples. Newly emergent Q148 mutations occurred in four patients, with 3/4 having archived Q148 and detection at day 1 occurring in the other. Dolutegravir fold-change increased from baseline to point at viral failure by >2 fold in 13/15 people with newly emergent resistance with >8-fold increases in 7/31 (23%) of patients.

An interim 24 week analysis from the phase-3 SAILING study, comparing raltegravir to dolutegravir in treatment-experienced but integrase-naïve patients, reported fewer protocol-defined failures in the dolutegravir arm (14/354 vs 34/361: 4% vs 9%). Additionally, that two patients on dolutegravir-based treatment had viral rebound with mutations at codon R263. [3]

These two cases sub-optimal ART and/or dolutegravir levels with one patient entering the study on a combination with only one additionally sensitive drug (efavirenz). Both patients experienced viral rebound prior to week 24, one with R263R/K at week 16 and one with V260I/R262K at week 24, but both osolates retained low IC50 fold changes to raltgravir an dolutegravir. A separate in vitro analysis suggested that dolutegravir binding remains prolonged (>50 hours) in the presence of both these complexes and that this might explain the relatively high genetic barrier to resistance.

Finally, a poster looked at the evolution of integrase resistance mutations in the Monogram clinical isolate library with raltegravir resistance during two periods - from August 2008 to December 2009 (n=273) and from January 2010 to December 2011 (n=806). This was to give an indication of how resistance may be changing in the clinic setting. [4]

In general the percentage of both individual mutations and more complex combinations, was reduced in the second time period. They reported that 662 (93.9%) of raltegravir-resistant isolates had dolutegravir FC <10 and that only 13 isolates (1.8%) had dolutegravir FC >25. This was interpreted as reflecting prompt switching away from raltegravir in patients who developed early resistance on raltegravir-based combinations who did not achieve viral suppression to <50 copies/mL.

Most of these isolates retained sensitivity to dolutegravir with significantly reduced FC sensitivity to dolutegravir compared to raltegravir, but this was based on definitions for primary and secondary mutations that have since been updated based on the VIKING-3 results described above. [2] This study found a similar correlation to dolutegravir sensitivity based on presence of Q148 and contribution of additional changes at G140, E138 and L74.

C O M M E N T

In addition to identifying the role of key integrase mutations more accurately and the likely response to dolutegravir, these results further caution against continuing to use raltegravir or elvitegravir in combinations that are not maximally suppressing viral load. Continued use increases the risk or more complex integrase resistance that will limit the option to use dolutegravir.

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S/GSK744 and long-acting formulation indicate broadly similar resistance profile to dolutegravir

Simon Collins, HIV i-Base

The first resistance data on the follow-on integrase inhibitor to dolutegravir, a Long Acting Parenteral (LAP) formulation of S/GSK1265744, was included as an oral presentation at the workshop. [1]

Although GSK744 is being developed in an oral formulation, most attention has been focused on a long acting injection with potential indication for both treatment and prevention with rilpivirine, which also has both oral and long acting formulations.

Pharmacokinetic results last year reported that plasma concentrations of GSK744-LAP remained above the IC90 for at least three months following a single intramuscular or subcutaneous injection at doses of 200 mg or higher. [2] The potential for use as PrEP was shown by impressive results earlier this year that generated full protection in a macaque study following multiple rectal exposure. [3]

Previous in vitro studies also supported a resistance profile that retains sensitivity to raltegravir and elvitegravir associated mutations. [4]

At the workshop new data were presented showing that, as with raltegravir, GSK744 effectively inhibits HIV integration and reduces LTR-circles without impacting levels of viral DNA. No further mutations emerged when GSK744 was passaged for 56 days with raltegravir-associated single site directed mutations E92Q or N155H. However, further mutations developed with the Q148H/K/R pathway although the associated reduced fold change (FC) sensitivity (FC 5.6 with Q148R and FC 5.1 with Q148R) could be overcome by higher dosing.

C O M M E N T

The resistance profile for GSK-744 appears similar to dolutegravir, rather than being a compound that could salvage dolutegravir resistance. This should inform the approach both to future studies and to proposed integrase sequencing.

Current studies with GSK-744 include an ongoing safety study

with rilpivirine LA in HIV negative volunteers and an induction/ maintenance study (starting with GSK-744 plus two RTIs and switching to GSK-744 plus rilpivirine maintenance) in treatment naive patients. [5, 6]

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ANTIRETROVIRALS

Dolutegravir approved in the US

Simon Collins, HIV i-Base

On 12 August 2013, the FDA approved dolutegravir (50 mgtablets), a new integrase inhibitor to be used in combination with other antiretroviral drugs [1, 2]

The indication for use in adults and children aged 12 years and older weighing at least 40 kg (approx. 88 lbs).

Approval is based on results from four phase 3 studies whose results have already been reported in HIV Treatment Bulletin (HTB): [3]

• SPRING-2: dolutegravir (once-daily) vs raltegravir (twice-daily) with investigator chosen dual NRTIs (abacavir/3TC or tenofovir/FTC)
• SINGLE: dolutegravir plus abacavir/3TC vs efavirenz/tenofovir/FTC (Atripla) in treatment naïve patients
• SAILING: dolutegravir (once-daily) vs raltegravir (twice-daily) with investigator chosen background regimen in treatment-experienced but integrase-naive patients on currently failing combinations; and
• VIKING-3: dolutegravir (once-daily) with investigator chosen background regimen in treatment- experienced patients with resistance to raltegravir or elvitegravir.

The indication for children older than 12 years is based on a 24-week open- label label study in integrase-naïve patients.

Dolutegravir is dosed 50 mg once-daily for naïve and integrase-naïve patients and at 50 mg twice-daily for patients who are integrase-experienced. Twice-daily dosing is also required for naïve and experienced patients when coadministered with efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin to overcome UGT1A/CYP3A inducing by these drugs.

Dolutegravir should be taken 2 hours before or 6 hours after takingcation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.

Side effects include hypersensitivity reactions and worsening liver enzymes in patients with HIV and hepatitis B and/or hepatitis C coinfection.

Dolutegravir can be taken with or without food.
For prescribing details see the full product information. [4]
Dolutegravir is marketed by ViiV Healthcare and has the trade name Tivicay.

COMMENT

US approval of this long-awaited new integrase inhibitor is welcomed and it is clearly supported by good efficacy and tolerability results. At a low milligram dose it also has the potential to be co-formulated with other ARVs and a Fixed Dose Combination (FDC) with abacavir/3TC is already underway.

Although dolutegravir is active against HIV that is resistant to raltegravir or elvitegravir, even using twice-daily dose it is not enough to overcome extensive integrase resistance. The prescribing information notes that poor virologic response was observed in subjects treated with 50 mg twice daily with Q148 mutations plus two or more additional integrase inhibitor-associated mutations including L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R. [4, 5]

Also, although indication is to take with or without food, drug levels are increased when taken with a meal, especially if this has a higher fat content (AUC increased by 33%, 41%, and 66% when administered with low-, moderate-, or high-fat meals, respectively, compared with fasting). [6]

Given the need for a twice daily dose in integrase inhibitor experienced patients to increase drug exposure it would be interesting to know whether taking with food to maximise the PK levels in patients with existing integrase inhibitor mutations would affect outcomes.

Dolutegravir was submitted to the European regulatory agency at the same time as to the FDA and a decision is expected later this year. [7]

As with all new drugs, how widely dolutegravir will be used will depend on pricing. Unfortunately, the US price has set this as second-line rather than first-line therapy and higher than other integrase inhibitors.

The time it takes for approval, generic manufacture and accessible pricing of dolutegravir in low and middle income countries remains to be seen.

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TREATMENT ACCESS

Ending global use of d4T: UNITAID to tip market to safer alternatives

Simon Collins, HIV i-Base

On 11 June 2013, UNITAID announced in a press statement that it was committing USD $77 million to end of the use of the archaic HIV drug d4T (stavudine) and replace it with tenofovir which is a newer more effective alternative. [1]

Although d4T was widely used in Western countries during the first years of combination therapy, it has been much less used this century, due to the high rates of serious side effects. These include peripheral neuropathy (painful nerve damage that limits mobility), peripheral lipoatrophy (loss of fat cells, notably in the face, arms, legs and buttocks), lactic acidosis (rapid onset, high fatality) and pancreatitis.

About one million people in low-income countries are estimated to still be using d4T due to its lower cost (approximately $79 per year for a d4T-based combination compared to $130 for a tenofovir-based one). [2]

The UNITAID initiative aims to change the current pattern of drug use by reducing the demand for d4T which will in turn increase the price. Conversely, the price for the replacement drug will fall by a further 30%. This project is in strategic collaboration with the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria. The new tenofovir-based treatment regimen is recommended by WHO.

The press release states "UNITAID's proposed intervention would address this challenge through negotiating with manufacturers for lower prices and temporarily subsidising the difference between stavudine and tenofovir-based treatment. Various stakeholders would be involved with implementing this proposal, including UNITAID, WHO, the Global Fund, and the Presidents Emergency Plan for AIDS Relief (PEPFAR)".

UNITAID in an international funding initiative from the governments of Brazil, Chile, France, Norway and the United Kingdom that identifies new sources for funding - 50% of it's funding comes from a levy on air-tax - to be used in innovative health interventions, working with partners on important issues of public health, including HIV, TB and malaria. [3]

COMMENT

This initiative should be widely publicised. Cost still drives access to health care in most countries, but it is unacceptable that d4T continues to be so widely used just because of a lack of political will to prioritise the quality of treatment.

HIV positive people in resource-limited settings should not have to choose between access to life-saving drugs or the risk of debilitating life-long complications - neuropathy and lipoatrophy are largely irreversible - especially when safer alternatives have been used in Western countries for at least the last decade.

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TRIPS extension for least developed countries

EU press statement

On 11 June 2013, the EU issued a press statement on the decision by the World Trade Organisation (WTO) to extend the transitional period for least-developed countries to implement the TRIPS Agreement for a further eight years. [1]

Following a request made by the least-developed countries (LDCs) under the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), the WTO's TRIPS Council agreed today by consensus to grant more time to LDCs to apply the provisions of the TRIPS Agreement. From the outset of discussions, the European Union has recognised the importance of flexibility for the least-developed countries (LDCs) and supported an extension to the transition period.

The agreement sends a strong signal of intent in light of the 2011 United Nations Conference on the Least-Developed Countries in Istanbul, Turkey. The Istanbul Programme of Action seeks to halve (from 48 to 24) the number of LDCs by 2020. It is also a positive result ahead of the ninth WTO Ministerial Conference in Bali in December this year.

The decision does not affect the transition period for patents for pharmaceutical products, which was agreed in 2002; LDCs will not have to protect these patents until 2016. Where least-developed countries voluntarily provide some kinds of intellectual property protection even though they are not required to do so under the TRIPS Agreement, they have committed themselves not to reduce or withdraw the current protection that they give.

The World Trade Organisation's Council on Trade Related Aspects of Intellectual Property Rights (TRIPS) already granted least-developed countries a ten year exemption from complying with the TRIPS Agreement at the time of its inception in 1995. In 2005, a further extension of seven and a half years was given until July 1 2013. With the latest extension, LDCs will not have to provide the intellectual property protection covered by the TRIPS Agreement until 1 July 2021, unless they graduate from LDC status.

C O M M E N T

This small breathing space does nothing to redress the serious threat to global health that is driven by the EU enforcing new and stricter trade agreements on the Indian government that threatens to limit generic access to newer drugs. [2]

This press release from the EU is particularly unhelpful in ignoring this main issue.

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Community request Gilead to study and develop separate formulation of new tenofovir prodrug

Polly Clayden, HIV i-Base

In June of this year close to 300 organisations and individuals signed on to a letter to Gilead Sciences raising the importance of developing a stand-alone formulation of tenofovir alafenamide fumarate (TAF).

TAF is a prodrug of the tenofovir disoproxil fumarate (TDF) and is currently under development by the company. The letter was drafted by HIV i-Base, Treatment Action Group (TAG) and Project Inform who asked organisations and individuals to sign-on to this letter if they agreed. Many did and within a week the letter that went to Gilead included almost 300 signatures.

We are concerned that Gilead's investigation plan will limit TAF to a component of fixed dose combinations (FDCs) only. Based on our communications with senior Gilead staff, and current trial listings on the clinicaltrials.gov registry, we understand that the regulatory plans for TAF are:

- FDC: elvitegravir/cobicistat/FTC/TAF; (10 mg TAF)
- FDC: darunavir/cobicistat/FTC/TAF; (10 mg TAF)
- a dual formulation of FTC/TAF (possibly, but not yet decided).

It seems that a stand-alone formulation of TAF is not part of the plan for the drug. This approach overlooks the importance of a stand-alone TAF for use in combination with a variety of non-Gilead drugs - notably low-cost generic ARVs in low-, middle-, and high-income countries. It also ignores the needs of people who have resistance to tenofovir TDF and other NRTI mutations that the new formulation may be able to overcome.

The authors of the letter met with representatives from Gilead at IAS but we remain disappointed by the company's lack of commitment to developing a stand-alone version of TAF and lack of clarity as to what dose of TAF the combination product with FTC will include.

An interaction with the booster cobicistat means TAF can be used at 10 mg. In order to have enough information to use it in other regimens – including generic FDCs with non-boosted ARVs – TAF also needs to be investigated and approved at a dose of 25 mg.

As we go to press we are once again writing to Gilead and will also issue a public statement with the progress of our discussions.

More information and updates:

http://i-base.info/sign-on-this-week-community-letter-to-gilead-on-new-version-of-tenofovir/

BASIC SCIENCE AND CURE RESEARCH

Sad news regarding attempt to duplicate the cure achieved in Timothy Brown

Richard Jefferys, TAG

In April, doctors at the University of Minnesota announced that they were attempting to reproduce the cure achieved in Timothy Brown in a 12-year old boy with HIV and leukemia who required a stem cell transplant. [1]

Due to the challenges associated with identifying appropriate adult stem cell donors homozygous for CCR5 delta-32 (as was done for Brown), the Minnesota team—led by Dr. John Wagner—obtained cord blood stem cells from the limited available supplies that have been screened for the mutation (the current status of screening efforts is described in a recent review article). [2] Permission was obtained from the Food and Drug Administration (FDA) to conduct the procedure, and it was performed on April 23rd.

On July 12th, the University of Minnesota reported that the boy, Eric Blue, died July 5th from complications associated with transplant. [3] Blue developed severe graft-versus host disease (GVHD), a known risk associated with stem cell transplantation. In the news stories, the doctors express their commitment to honoring Blue's bravery by learning from his case, and highlight the need to expand screening of stored cord blood units for CCR5 delta-32 in order to increase the possibility of identifying sources that are suitably HLA-matched for potential HIV-positive recipients.

Cord blood stem transplantation is an evolving field, but current practice is based on matching 6 HLA antigens (fewer than are required for adult stem cell transplants), with a 6:6 match typically viewed as ideal and 4:6 as the minimum acceptable (although some resource websites cite 3:6 as "unlikely, but possible"). [4]

There are additional complexities related to the direction of the mismatch and the dose of cord blood that is available. Although the issue does not yet seem to be entirely resolved, it has also been reported that limited mismatches may lead to superior anti-cancer effects under some circumstances. One aspect of Eric Blue's procedure that has not been specifically addressed in the news stories or the University of Minnesota's coverage is the extent to which the CCR5 delta-32 homozygous cord blood source was HLA-matched. [5]

In order to provide guidance for future attempts to cure HIV-positive people with cancers using CCR5 delta-32 homozygous cord blood, it will be important for the doctors and researchers that were involved to report the details of the case.

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ART reduces HIV reservoirs in elite controllers: implications for cure research

Matt Sharp, HIV i-Base

Researchers from the US National Institutes of Health have been studying HIV elite controllers for several years. A recent study provides new clues from this population for eradication efforts by learning more about CD4 cells that carry replication competent virus and the dynamics of viral reservoirs when ART is initiated or discontinued.

The study by Tae-Wook Chun and colleagues looked at three elite controllers and one controller and was published online in July 2013 as an ahead of print article for the Journal of Infectious Diseases. [1]

A small proportion of people (controllers) with HIV are able to control HIV replication in the absence of ART. A subset of these individuals (elite controllers) are able to maintain relatively normal CD4 counts and undetectable plasma virus levels. However, there may be low levels of HIV replication due to viral persistence, ongoing inflammation and viral evolution. The precise frequencies of CD4 T-cells carrying replication competent virus and the impact of ART on immunologic and virologic parameters in these patients are unknown.

PMBCs were collected through blood draws and leukapheresis to isolate CD4 cells at baseline, month 6 and 9, and 3 months after discontinuation of the study. Gut biopsies were performed at baseline, after 6 months on ART and 3 months after ART was stopped. Plasma viraemia was measured in quadruplicate with the Cobas Ampliprep/Cobas Taqman HIV-1 Version 2.0 (sensitive to 20 copies/mL). Quantitative co-culture tests were used to determine the frequency of infectious virus in CD4 cells. The half-life of CD4 cells carrying infectious virus was determined at baseline, month 6 and 9. HIV DNA was detected through quantitative real time PCR. Levels of immune activation were looked at in the blood and sigmoid colon. Finally, the frequency of HIV specific CD8 cells was measured.

For this study, the definition of elite controllers (subjects 1, 2 and 3) and controllers (subject 4) were those who had suppressed virus levels at <500 and <50 copies/mL respectively, with no more than one blip above these levels. Throughout the study, CD4 and CD8 percentages remained stable in all participants. In addition, the elite controllers all had undetectable plasma viraemia (<20 copies per mL) throughout the trial, and statistically no difference in residual virus (1-19 copies/mL before, during or after ARV treatment. The baseline viraemia (88.0 +/-25.9; mean +/- SD)

of the controller (subject 4) became undetectable shortly after starting treatment, then returned to detectable (131.5 +/- 24.6; mean +/- SD) following ARV discontinuation.

After no replication competent virus was found in the elite controllers using standard quantitative co-culture assays (sensitive to one per million cell), more sensitive high input quantitative co-culture (37-92 replicates of the 10 x 10(6) per well was performed. After ART initiation (with raltegravir/tenofovir/FTC), replication competent virus decreased by 1 log in two elite controllers and one controller. During ART, the level of replication-competent virus was below the level of detection in all participants. Three months following discontinuation or ART, HIV viral load returned to pre-therapy levels. This showed that ART had an impact on the size of the reservoir of infected CD4 cells that carried replication-competent virus. In the elite controllers, the frequency of CD4 cells in the blood carrying HIV DNA were not detected. This is perhaps because the vast majority of the cells carry replication-defective HIV.

In 3 out of 4 subjects, immune activation markers (CD38 and HLA-DR) decreased in blood and sigmoid colon biopsies during ART and returned to pre-treatment levels after discontinuation. ART was associated with a decrease in the frequency of HIV specific CD8 cells expressing IFN-gamma and MIP-1-beta, and these responses remained low to undetectable after ART was stopped in the three elite controllers.

In this study the researchers looked a little deeper in modifying standard virologic and immunologic parameters to show that ART has a positive impact on reducing replication competent HIV in elite controllers. They suggest that low levels of viral replication in this population can contribute to the size of the reservoir despite detectable plasma viral load.

C O M M E N T

People who have strong individual immune response to HIV are now being given a higher priority in research and may be an ideal population to help answer some of the outstanding questions about HIV reservoir sites and the role and limitations of current ART.

This study also adds to a growing number of studies suggesting that HIV controllers may benefit from ART.

The level of long-term risk from untreated HIV in this population has not yet been quantified.

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PREVENTION AND TRANSMISSION

Bangkok Tenofovir Study: US CDC recommends oral PrEP for injection drug users

Simon Collins, HIV i-Base

On 13 June 2103, the US CDC recommended that Pre-Exposure Prophylaxis (PrEP) should be considered as an option for people who inject drugs in order to prevent HIV transmission. [1]

The recommendation was based on the results of a randomised, double-blind, placebo controlled phase 3 study that was published in the Lancet on the same day. [2]

The Bangkok Tenofovir Study enrolled more than 2,400 HIV negative adults (aged 20-60 years) who inject drugs. Participants were randomised (1:1) to either daily oral tenofovir (300 mg) or placebo. Mean duration of follow-up was 4.6 years (maximum 6.9 years) with approximately 24% loss to follow-up in each arm. Adherence was high (>85% of daily pills taken by patient diaries) and directly observed therapy was an option in the study.

During the study (run from 2005 - 2012), 50 people became HIV positive: 17 in the tenofovir group and 33 in the placebo group, indicating a 48·9% reduction in HIV incidence (95% CI 9·6—72·2; p=0·01). Side effects and complications were similar in each group, although nausea and vomiting were higher in the tenofovir group in the first two months. No tenofovir resistance was detected in participants who became HIV positive in the active arm.

Risk behaviors for injecting drugs decreased significantly over the first year (from 62.7% to 22.7%), sharing needles (18.1% to 2.3%), and reporting multiple sexual partners (21.7% to 11.0%), and these risk behaviors remained below baseline throughout the entire period of the trial (all three comparisons, p<0.001). These rates were similar in the TDF and placebo groups.

Although this study used daily tenofovir, the US CDC recommended that the fixed-dose dual combination of tenofovir/FTC be used as this formulation has FDA approval for use as PrEP.

The CDC press release commented: “Providing PrEP to IDUs at very high risk for HIV acquisition could contribute to the reduction of HIV incidence in the US. In addition, if PrEP delivery is integrated with prevention and clinical care for the additional health concerns faced by IDUs (e.g., hepatitis B and C infection, abscesses, and overdose), substance abuse treatment and behavioral health care, and social services, PrEP will contribute additional benefits...”.

References

1. US CDC Morbidity and Mortality Weekly Report (MMWR). Update to interim guidance for PreExposure Prophylaxis (PrEP) for the prevention of HIV infection: PrEP for injecting drug users (13 June 2013)
   http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6223a2.htm
2. Choopanya K et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet, Volume 381, Issue 9883, Pages 2083 - 2090, 15 June 2013. doi:10.1016/S0140-6736(13)61127-7.
   http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61127-7 abstract

OTHER NEWS

CROI website: vital community and research resource vanishes

Simon Collins, HIV i-Base

It is with a growing frustration that the excellent and unmatched website for the Conference on Retroviruses and Opportunistic Infections has been unavailable for many weeks.

Neither the secretariat responsible for previous meetings (Westover Associates) nor the conference organisers have yet responded to requests for information. Currently the URL returns a "site unavailable" message.

It is somewhat unnerving that the established site (www.retroconference.org) has no information and does not link to (what appears to be) a hastily thrown together holding page for the meeting (www.croi2014.org). This page has no contact details for the organisers, the secretariat or about the disappeance of this essential resource.

CROI is established as the most important HIV scientific meeting and their committment to website is unparalled in the medical field and should be a model for other disease areas. The website is a vital resource not only as a record of previous meetings but as a free open-access research tool.

i-Base, along with many other community organisations, goes to considerable effort to include hyperlinks to abstracts, posters, presentations and webcasts in our reports. The reliability of the original URLs are an essential aspects of the site.

The lack of communication is not helpful. The value of the CROI website is also due to the intellectual and financial investments of many (including public institutions) that have committed to the meeting for over 20 years. It is not acceptable for this to vanish for so long without explanation or commitment that it will return.

FDA guidance for industry HIV development and trials

The US FDA have published new draft Guidance for Industry: Antiretroviral Drugs Using Plasma HIV-RNA Measurements - Clinical Considerations for Accelerated and Traditional Approval.

The new guidance provides recommendations for the development of antiretroviral drugs regulated within the FDA's Center for Drug Evaluation and Research (CDER) for the treatment of HIV. Specifically, this guidance addresses the overall development program and clinical trial designs for antiretroviral drugs to support an indication for the treatment of HIV-1 infection.

Source: FDA list serve. Draft Guidance for Industry: Antiretroviral Drugs Using Plasma HIV-RNA Measurements - Clinical Considerations for Accelerated and Traditional Approval. (10 June 2013).
http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/ucm070968.pdf?source=govdelivery

ON THE WEB

Community publications and reports:

Immune system, HIV, and ageing

Richard Jefferys and Tim Horn, TAG

On 5th June 2013, Treatment Action Group launched a new report on HIV and ageing.

This brief report outlines current scientific knowledge regarding the immunologic connections between HIV and ageing, and provides an introduction to some of the unresolved questions that are being addressed—or need to be addressed—by research.

It includes an assessment of the impact on HIV positive people of illnesses typically associated with ageing. These include cardiovascular, kidney, and liver disease; bone loss and increased fracture risk; frailty; cognitive impairment; and cancer.

As the proportion of older individuals living with HIV grows, there is an urgent need to understand how HIV-related factors including immune inflammation, immune dysregulation, polypharmacy, long-term drug toxicities, and coinfections and comorbidities that are disproportionally prevalent among people with HIV, such as hepatitis B and C, current or former substance-use disorders, stress, and depression, may be contributing to risks for these conditions.

The report emphasises that the elevations in risk for ageing-associated diseases among people with HIV are typically relatively small (compared to their HIV negative counterparts). There are also inconsistencies between studies and as-yet unresolved controversies regarding the extent to which HIV infection is an independent risk factor for specific illnesses.

So while this is an important cause for concern and research, the report highlights that the data do not support a current need to panic: HIV, especially with access to effective treatment, does not appear to have a significantly greater impact on ageing-associated conditions compared to similarly matched HIV negative people.

As a general recommendation, HIV positive individuals should consider the lifestyle factors that are now known or expected to maximise health once a person reaches old age; these include daily exercise, a healthy diet, maintaining low blood pressure and cholesterol, and avoiding substance abuse and excess fat gain.

Download the PDF at:

http://www.treatmentactiongroup.org/hiv/2013/immune-system-hiv-and-aging

RITA! summer issue: HIV and cardiovascular disease

Research Initiative, Treatment Action (RITA!)

This edition of Rita! includes three review articles that focus on cardiovascular risk factors in people with HIV, the role of ART in cardiovascular risk, and screening people with HIV for cardiovascular disease.

Numerous studies have reported that HIV positive adults and children are likely to have a higher risk of cardiovascular disease than the general population. But sorting out the impact of HIV and ART has also produced contradictory results in studies.

Mark Mascolini reviews over 100 studies for these careful reports and also interviews the University of Wisconsin's James Stein, a leading US authority on cardiovascular disease in people with HIV. Stein offers frank and insightful answers to questions on cardiovascular risk, screening adults and children, the Framingham score, lipid targets, aspirin prophylaxis, and smoking.

Available as free PDF download.

http://www.centerforaids.org/publicationsrita.html

http://www.centerforaids.org/pdfs/rita0613.pdf (PDF download)

FUTURE MEETINGS

Conference listing 2013/14

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.

53rd ICAAC

10 - 13 September 2013, Denver, USA.

http://www.icaac.org

8th International Workshop on HIV Transmission Principles of Intervention

4 - 5 October 2013, Barcelona, Spain

http://www.virology-education.com

15th International Workshop on Co-morbidities & Adverse Drug Reactions in HIV

15 -17 October 2013, Belgium

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

14th European AIDS Conference (EACS)

16 - 19 October 2013, Brussels, Belgium.

http://www.europeanaidsclinicalsociety.org

4th International Workshop on HIV & Aging

30 - 31 October 2013, Baltimore

http://www.virology-education.com

20th Conference on Retroviruses and Opportunistic Infections (CROI)

Dates not yet announced (Jan/Feb/Mar)

http://www.croi2014.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

HIV i-BASE

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

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

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

All i-Base publications are available online.
http://www.i-base.info

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

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

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

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

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

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

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

NOTES

HIV i-Base

All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it. However, any donation that your organisation can make towards our costs is greatly appreciated.

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

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

REFUNDS FROM THE TAX MAN

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

However you chose to donate to i-Base,
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