EDITORIAL

CONFERENCE REPORTS
20th International AIDS Conference
- The loss of friends and colleagues from flight MH 17
- Higher ART coverage is associated with lower HIV infection rates in a multi-country analysis
- Pill A, Pill B: simplified second-line treatment for low-income countries
- UNAIDS sets 90-90-90 target for 2020 to end AIDS by 2030
- No difference in overall anaemia rate with reduced dose AZT
- Open label oral PrEP at four doses a week: why zero infections does not equal 100% efficacy
- Cure research at AIDS 2014: TILDA measures the reservoir and romidepsin wakes it up
- Publications launched at AIDS 2014

CONFERENCE REPORTS
6th International Workshop on HIV Paediatrics
- Update on paediatric antiretrovirals
- Is d4T a viable option for children in low-income countries?
- 3TC or FTC monotherapy suboptimal as a bridging strategy for adolescents
- Rationalising the paediatric antiretroviral formulary in Malawi
- Time to first-line failure in the IeDEA cohort
- Influence of early ART on antibody detection in children

CONFERENCE REPORTS
8th International Workshop on HIV Treatment, Pathogenesis and Prevention Research in Resource-Poor Settings (INTEREST)
- Short-term safety of atazanavir/ritonavir-based second line treatment in Zambia
- Pregnancy outcomes in Zambia
- Uptake of ART is influenced by distance to the health facility in rural Zambia
- Genotyping using dried blood spots in rural South African setting

SIDE EFFECTS AND COMPLICATIONS
- Bone mineral density linked to inflammatory markers in HIV positive people who are ART naive

BASIC SCIENCE & CURE RESEARCH
- Effects of long-term ART initiated during primary HIV infection on reservoir size
- Wrestling with the implications of the Mississippi case
- Molecular events in HIV neutralising antibody development

ON THE WEB

FUTURE MEETINGS
- Conference listing 2014/2015

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Editorial

This bumper summer issue of HTB South covers conference reports from AIDS2014 and the Paediatric Workshop held in Melbourne in July. We also report from the INTEREST meeting held in Lusaka in May.

Both Melbourne meetings were overshadowed by the shocking news of the delegates who died on flight MH17 – many presentations included tributes to these colleagues and friends.

Other reports from AIDS 2014 include studies on Treatment as Prevention (TasP); results from open-label oral PrEP and use of lower dose AZT. We include an overview of cure research (see further cure reports later in this issue, including on the Mississippi child).

Summaries of data from the paediatric workshop prior to AIDS 2014 include: an update on paediatric ARV development; use of d4T in children; that 3TC (or FTC) monotherapy is suboptimal as a bridging strategy for adolescents; the advantages of a rationalised paediatric antiretroviral formulary in Malawi; time to first-line failure in the IeDEA cohort and the sometimes confusing influence of early ART on antibody detection in children.

INTEREST reports include reassuring Zambian data both on short-term safety of atazanavir/ritonavir-based second line treatment and on pregnancy outcomes for women receiving ART; unsurprisingly one study showed that uptake of ART is influenced by distance to the health facility in a rural setting; and genotyping using dried blood spots was feasible in a rural South African setting.

New guidelines include those from WHO for key populations: gay men, people who inject drugs, people in prisons, sex workers and transgender people.

Gareth Hardy reports on whether changes in bone mineral density are related to immune activation and with Richard Jefferys covers basic science and vaccine research.

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 member please visit:

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The loss of friends and colleagues from flight MH 17

Polly Clayden and Simon Collins, HIV i-Base

Like so many people at the AIDS 2014 conference and beyond we were jolted with sadness when we heard the appalling news of the six delegates who were killed on flight MH 17.

- Pim de Kuijer, STOP AIDS NOW!
- Joep Lange, co-director of the HIV Netherlands Australia Research Collaboration (HIV-NAT)
- Lucie van Mens, Director, AIDS Action Europe
- Maria Adriana de Schutter, AIDS Action Europe
- Glenn Thomas, World Health Organisation
- Jacqueline van Tongeren, Amsterdam Institute for Global Health and Development

Our thoughts are with their friends, families and colleagues.

Of these people, we were lucky enough to have worked with Joep Lange, an inspiring doctor from the Netherlands, who had supported the community from the early days. He attended a meeting we organised on pharmacokinetics and drug concentrations over 15 years ago and, with David Back and colleagues from Liverpool, encouraged us to learn about this aspect of research and its implications.

Joep was driven by a political response to medicine as an issue of human rights. When global treatment access was making first tentative advances, he was right to challenge the political and economic structures that could get Coca-Cola to every remote village in Africa, and to say this should be just as possible for ARVs. In San Francisco, he noted US inequity by remarking that more people were sleeping on the streets of the host city than he had seen in a recent trip to India. Ever controversial, at a recent meeting on resistance in low-income countries he suggested that funding for the START study should perhaps be spent on a head-to-head comparison of 3TC vs FTC. These ideas and discussions were from a drive to find workable and practical ways to change the world.

An online video on the IAS tribute page - he was president from 2002-2004 - shows many other examples, including supporting drug users when the conference was in Thailand, and negotiating US support after demonstrations in Barcelona. A strong supporter of community activism, he was also happy to challenge community campaigns if he thought they missed the main point - including for an early PrEP campaign that held back research.

One of the many projects developed by Joep, and particularly that of his partner Jacqueline van Tongeren, was the International Workshop on HIV Treatment, Pathogenesis and Prevention Research in Resource-Poor Settings (INTEREST) Workshop. Cate Hankins, Deputy Director of AIGHD - the Amsterdam Institute for Global Health and Development, where they all worked - recently spoke movingly of their lives. At the 2014 INTEREST workshop earlier this year – sitting with two colleagues whose PhDs he had supervised Polly Clayden remarked: “It might be quicker to tell me whose PhD Joep hadn’t supervised.”

With many much-deserved tributes that have marked Joep Lange’s death one thing that stands out is the sheer volume of work that he undertook.
Higher ART coverage is associated with lower HIV infection rates in a multi-country analysis

Polly Clayden, HIV i-Base

If all low- and middle-income countries had achieved the same level of antiretroviral treatment (ART) coverage as Botswana in 2012, 65% of new HIV infections and 70% of HIV-related deaths could have been prevented — according to an analysis presented at AIDS 2014. [1]

A multi-country survey by Andrew Hill and colleagues from the University of Liverpool, St Stephen’s Centre, London, Imperial College, London and World Health Organisation — presented as a late breaker poster — looked at the relationship between the percentage of HIV positive people on ART to HIV incidence and related deaths. The analysis also compared ART coverage rates between low-, middle- and high-income countries.

The researchers used 2012 UNAIDS country-level estimates for 51 low- and middle-income countries; 36 from African and 15 non-African with at least 50,000 people with HIV. Data from published references were used for the seven high-income countries but these were not used in the calculations of the associations between coverage and incidence. Weighted least squares and linear regression models were used in the investigations.

The mean percentage of ART coverage across the low- and middle-income countries was 30% with a wide variation ranging from 0.6% in Madagascar to 62% in Botswana. The mean percentage of new HIV infections was 6.1% and this ranged from 2% in Thailand to 12.5% in Indonesia.

The researchers found a highly significant association between greater ART coverage and both lower percentage incidence and HIV-related deaths (p<0.00001 for both associations). Each 10% increase in ART coverage was associated with a 1.15% reduction in new infections and a 1.13% reduction in HIV-related deaths.

Further analyses suggested that the same level of coverage as Botswana (62%) across all low- and middle-income countries could have prevented 1,243,647 of the 1,901,800 (65%) new HIV infections in 2012. In the same period, under the same conditions, 998,732 out of 1,427,200 (70%) deaths from HIV could have been prevented.

The 51 countries in the analysis plus seven high income ones were ranked according to percentage of HIV positive people receiving ART. Levels of coverage across high-income countries also varied considerably from 67% in the UK to 33% in the US. The US ranked 30th out of 58 countries — between Burundi and Uganda.

The researchers wrote: “The results provide a compelling argument for continuing to improve antiretroviral treatment coverage worldwide.”

Andrew Hill also presented these data in a workshop on trial design for low-income countries. [2] He noted that in the UK the breakpoint in the cascade was between the estimated number of HIV positive people and diagnosis/link to care, respectively 98,400 and 77,610 (79%).

Dr Hill remarked that there are many other differences between countries, which might explain these associations. For example countries with better treatment coverage might also have better HIV prevention programmes.

He also pointed out variability around the association — some countries have high rates of new infections, despite high ART coverage, such as Uganda, or low infection rates despite lower ART coverage, as in Niger.

The analysis is being repeated using the new 2013 UNAIDS database, for validation. The researchers will look in detail at the methods used by UNAIDS to estimate their rates of new HIV infections and deaths, and refine their methods.

References


Pill A, Pill B: simplified second-line treatment for low-income countries

Polly Clayden, HIV i-Base

A one pill, once-daily fixed dose combination (FDC) second-line regimen might be feasible for low-income countries according to a clinical development programme presented at AIDS2014.

Anton Pozniak from the St Stephens Centre at Chelsea and Westminster Hospital, London showed plans for a simplified second-line regimen at a scientific workshop entitled: Research to measure success of antiretroviral use for prevention and treatment at individual and community levels. [1] The workshop was the first public presentation of the proposed second-line development programme.

Currently, the preferred World Health Organisation (WHO) first-line regimen is a once-daily FDC of efavirenz plus tenofovir plus lamivudine or emtricitabine (EFV/TDF/3TC [or FTC]). Low cost, generic versions of this regimen are available and are simple to give in decentralised programmes by nurses and community health workers.

The WHO preferred regimens for second-line antiretroviral treatment (ART) are PI-based (ritonavir-boosted lopinavir [LPV/r] or atazanavir [ATV/r]) with two new NRTIs. These regimens have several shortcomings including overlapping NRTI resistance, comparatively high pill count, twice-daily dosing (LPV/r), NRTI toxicities and high cost compared to first-line treatment.

The new proposal for people who fail first-line treatment with “Pill A” (EFV/TDF/3TC) is to develop “Pill B” – a once-daily heat-stable FDC of dolutegravir (DTG) plus optimised darunavir/ritonavir (DRV/r). Market forecasts suggest that Pill B might be available at low cost: US$250 per patient per year.

Dr Pozniak explained that results from the original dose finding trials of DRV/r, as well as a more recent one with 600/100 mg, suggest that a dose reduction to DRV/r 400/100 mg might be feasible.

The dose ranging (phase 2B) study for the proposed development programme would compare three once daily regimens: TDF/FTC + DRV/r 400/100 mg vs DTG + DRV/r 800/100 mg vs DTG + DRV/r 400/100 mg. This phase would be conducted in treatment naïve participants over 48 weeks.

If 24-week phase 2B data justifies progression of the programme (no obvious safety or efficacy concerns), a 96-week phase 3 pivotal trial with 1050 NNRTI-experienced participants will follow.

Phase 3 – a non-inferiority study conducted in Africa, South East Asia and Eastern Europe – would compare 2NRTI+PI/r (control arm) vs DTG + DRV/r 800/100 mg vs DTG + DRV/r 400/100 mg.

The success of this programme should make switching people who are on current first-line regimens with virologic failure to second-line considerably simpler and more accessible.

The one criticism is that this would lead to recommending DTG second-line when many experts believe it should be the preferred first-line option in the future. It is critical that work is funded to ensure that we have enough information to use DTG first-line in low-income settings but research into first- and second-line DTG-based regimens should not be mutually exclusive. A better second line option is needed for the 5% of nearly 13 million people on first-line (and more as scaling up continues) that need to switch. Dr Pozniak noted that if a DTG/TDF/3TC (or even DTG/ TAF/3TC) becomes the future Pill A, Pill B might be DRV/r plus rilpivirine – which also needs to be investigated.

Research into optimising ART for low-income countries – usually discussed in small closed meetings – stepped out of the shadows at this conference including this presentation and results from a study with reduced dose AZT (see below). [2]

We also summarise work on treatment optimisation in the 2014 Pipeline Report. [3]
for treatment to 34 million. The emphasis on “sustained” ART is to ensure that supply of medicines is no longer vulnerable to stock-outs.

- 90% of those on ART having an undetectable viral load. This highlights both the importance of wider access to viral load monitoring and the importance of viral suppression as a major goal of ART. This also recognises the dramatic reduction in transmission risk once viral load is undetectable.

The targets are ambitious, which is intentional.

In 2002, the “3x5” target to get three million people on treatment by 2005 was seen as dramatically over ambitious by most people in terms of what was achievable in practice and yet woefully inadequate in terms of a global health response. But the target set the momentum for scale up and although is took slightly longer to achieve than 2005, looking back we see the 3 million as something we sailed past years ago.

By December 2013, approximately 12.9 million people were on ART with the target of 15 million people by 2015 roughly on track.

The UNAIDS report highlights additional challenges including the differences between countries in terms of current coverage, for children as well as adults. For example, currently only 41% of babies born to HIV positive mothers have access to early testing and only ten ARVs are available in paediatric formulations.

Although the report focuses almost exclusively on low- and middle-income countries, these targets are likely to be a challenge in all settings, including wealthier countries that have widely different treatment cascades.

References

AIDS 2014: ANTIRETROVIRALS

No difference in overall anaemia rate with reduced dose AZT

Polly Clayden, HIV i-Base

A study looking at reduced dose AZT showed no difference in overall rate of anaemia but demonstrated improved safety and similar efficacy compared to standard dose. These findings were presented as a late breaker poster at AIDS 2014. [1]

If tenofovir remains the preferred NRTI for first-line treatment, as recommended in the 2013 World Health Organisation (WHO) guidelines, people switching to second-line are likely to receive AZT.

According to previous global market forecasts, cost savings from a daily dose reduction of AZT from 600 mg to 400 mg would be US $89 to 60 per patient per year, saving US $282 to 351 million on antiretrovirals over three years. [2]

The MiniZID study – conducted by Matieu Rougemont and colleagues from the National Social Insurance Hospital, Yaounde, Cameroon, University of Geneva, Switzerland and University of Liverpool, UK – compared reduced dose (400 mg) of AZT with standard dose (600 mg) in treatment naive adults. Because reducing the dose might decrease side effects of AZT, the primary outcome of the study was the difference in the proportion of participants with a new grade 1 to 4 anaemia or increased anaemia grade at 24 weeks.

The study was a prospective, randomised, controlled trial conducted at one HIV clinic in Yaoundé, between August 2011 and December 2013. Eligible adults (<350 CD4 cells/mm3) received 3TC plus nevirapine with either 600 mg or 400 mg of AZT.

Participants included in the intention-to-treat (ITT) analysis (n=142) were 59% women and a median of 35 years of age. At baseline, participants were a median: BMI 23.2 kg/m2 (IQR 21-26), hemoglobin 11.6 g/dL (IQR 10.8-12.8), CD4 count 163 cells/mm3 (IQR 99-219) and viral load 5.4 log10 copies/mL (IQR 4.9-5.9).

After 24 weeks of follow up, 50 participants (35%) had a new or worsening anaemia grade overall. The investigators reported no statistically significant difference between the 400 mg and 600 mg AZT arms: 38% vs 33%, p=0.56.

Significantly fewer participants in the 400 mg AZT arm needed to switch to tenofovir because of AZT-related anaemia: 1.4% vs 11.4%, p=0.017. Fewer participants in the lower dose arm required a blood transfusion, but the difference was not statistically significant: 2.8% vs 5.7%, p=0.44.

Of the 50 participants with anaemia, significantly fewer in the 400 mg AZT arm experienced severe anaemia (< 8 g/dL): 11.6% vs 34.8%, p=0.03.

The investigators noted that, participants in the two treatment groups had similar virological response at 24 weeks – although the sample size was not powered to demonstrate non-inferiority. CD4 cell count increase was also similar across the two arms. They recommend a larger phase 3 non-inferiority trial using AZT-based ART second-line in low-income settings.

COMMENT

Although this work seemed a good idea at the time, retrofitting old drugs for low-income countries might not be the best use of resources. We have made the same comment several times about low dose d4T.

The important work at the moment is optimising the dose of darunavir/ritonavir and making sure that there are research programmes to generate data on newly approved and pipeline antiretrovirals – dolutegravir and tenofovir alafenamide (TAF) – to inform the best and simplest future options for low-income countries.

References
AIDS 2014: PREVENTION

Open label oral PrEP at four doses a week: why zero infections does not equal 100% efficacy

Simon Collins, HIV i-Base

One of the most important advances at AIDS 2014 was a late-breaker study on open label use of oral PrEP, presented by Robert Grant from UCSF. [1]

The results were important for two reasons. Firstly, participants knew they were receiving active treatment. Secondly, they knew that PrEP had not only been proven to be highly effective but that efficacy was also dependent on good adherence. A more detailed review of the large and complex dataset were published in Lancet Infectious Diseases to coincide with the conference. [2]

Although participants were predominantly from the extension to the iPrEX study (iPrEX-OLE), two smaller PrEP studies were also included - ATN 082 and the US Safety Study.

The open label study included 72 weeks follow-up and involved monthly clinic visits for the first 3 months and quarterly visits thereafter. Of note, PrEP was not prescribed as continuous treatment: participants were actively encouraged to use PrEP during periods that they thought it was appropriate. This tested a more likely real-world use of PrEP.

The initial iPrEX study was an NIH-funded, international, placebo-controlled randomised trial that enrolled 2470 MSM and 29 transgender women. Intent-to-treat analysis reported a 44% reduction in the primary endpoint of new HIV infections in the active (tenofovir/FTC) arm compared to the placebo group. In a post hoc analysis, the relative risk reduction increased to 73% based on self-reported adherence (defined as taking PrEP 90% doses). The level of efficacy increased to 92% in a sub-study that evaluated adherence based on the presence of active drug levels which nudge up to 95% after adjustment for highest risk behaviour (receptive anal intercourse without a condom) with LLOQ-350, 350-699, 700-1249 and >1250 fmol/punch correlating with adherence levels of <2, 2-3, 4-6 and 7 doses/week, respectively. [3]

Although the iPrEX data contributed to US FDA approval in 2012 of a PrEP indication for daily tenofovir/FTC, uptake was very slow, with use by fewer than 2400 people in the 18 months post-approval (roughly half of whom were women). [4]

Modelling studies in a later pharmacokinetic analysis that included iPrEX data, suggested that either alternate day or daily adherence would provide levels of protection of 96% and 99%, respectively. [5]

This assumed previously reaching steady-state drug levels, which are estimated to take one week of daily dosing. [6]

Uptake and acceptability of PrEP is the first step in the “PrEP cascade”. The first important result from iPrEX-OLE was that 62% of eligible people (1678/2650) enrolled in the open-label study. As the study only recruited from June 2011 (rather than being an immediate roll-over from the end of the initial study), a second important result was that 75 of these people were found to already be HIV positive, suggesting a concern for the time to open label access. However, uptake was similar for the iPrEX (65%: 1526/2336) and ATN 082 (68%: 46/68) studies but lower for the US Safety Study (39%; 106/271). The third notable result was that of the 1603 people eligible for open label PrEP, only 72% (n=1128) chose to start at enrolment, 6% (n=97) started at a later date and 23% (n=378) declined PrEP (but were still followed).

Although this second step reduced overall uptake to about 45% of previous study participants, this could be a positive result. Interpreting the PrEP cascade is dependent on whether each step results in an increasingly higher risk group that is using PrEP. Low risk loss is a good thing. This is fundamentally different to the treatment cascade where every loss is clinically important.

It is helpful that there were some statistically significant differences between people choosing or declining PrEP, and that some of these choices were related to higher background risk for HIV. For example, uptake was 81% vs 75% in people with vs without recent receptive anal sex without a condom (p=0.003) and was 77% vs 75% in those who were HSV positive vs HSV negative (p=0.03). However, although statistically significant, these differences are modest. They also didn’t show a consistent relationship to HIV risk as there were no differences by age, education, use of alcohol (high usage) or recreational drugs (cocaine or methamphetamine, both low usage), gender identity, known HIV positive partner, other STI infections (syphilis or gonorrhoea), or previous trial experience (active vs control), all p >0.05, NS.

Reasons given for declining PrEP (obtained from a computer-assisted self assessment) included a concern for side effects (50%), not wanting to take a daily pill (16%), not liking pills (13%) preference for other options (14%) and concern for stigma about either HIV (7%) or assumed sexuality (3%).

Drug levels were measured for all new cases of HIV infection, and in an additional randomly selected control group who remained HIV negative. Measurements were performed with a newly developed dried blood spot assay for tenofovir diphosphate (TDF–DP) that was able to detect a single dose taken in the previous four weeks. This was considerably more sensitive than the previous plasma test. The long intracellular life time of TDF–DP results in relatively wide target levels of detectable drug: with LLOQ-350, 350-699, 700-1249 and >1250 fmol/punch correlating with adherence levels of <2, 2-3, 4-6 and 7 doses/week, respectively. If no drug was detected adherence was assumed to be zero.

Of the 41 cases of new HIV infections during the study, 13 people were not receiving PrEP (IR 2.6 per 100 PY; 95%CI 1.5-4.5) and 28 were in the PrEP group (IR 1.8; 95%CI 1.3-2.6). In people receiving PrEP, incidence was 36% lower (95%CI: -24 to +67%) in unadjusted analysis and 49% lower (95%CI: -1 to +74%) after adjusting for high sexual risk. As both these ranges cross 1.0, it is important to note that neither of these reach statistical significance - even though this is likely a factor of the limited number of infections and follow-up time.

Most importantly, as with iPrEX, drug level results were highly correlated with incidence of HIV during follow up, with risk reductions (95%CI) of 44% (-31 to 77%), 84% (21 to 99%) and 100% (86-100%) for the <2, 2-3 and >4 doses/week groups.

[2] AIDS 2014, Melbourne
The percentage of follow up time that participants had in each of these three bands (>4 and daily dosing were combined) was 26%, 12% and 33% respectively. A further 25% had no detectable drug levels, interpreted as zero adherence (or perhaps a period off PrEP). Approximately 5% of people did not have drug level results.

Most people started with good adherence (90-100% at week 4) but this dropped over time, with time on study being the major contributing factor. This data categorised adherence as “any detectable drug levels” prior to infection for those who became HIV positive: approximately 80% people had detectable drug at 48 weeks and 60% at 24 weeks prior to infection, but less than 40% at the time of infection. This compared to 70% at week 72 in people who remained HIV negative. When using a cut-off for clinically relevant drug levels, associated with 2 or more doses a week (>350 fmol/punch), only 50% of both cases and controls had this level of adherence at the start of the study, dropping to about 40% in controls after 72 weeks and to less than 5% of cases at the time of infection. Virtually all infections in iPrEX-OLE were in people who had drug levels at the time of diagnosis that indicated a likely adherence level of taking two or fewer doses a week.

This step in the PrEP cascade - ie adherence - lost between a half to two-thirds of participants (depending on how strictly adherence was defined). There is some evidence that this related to risk and that at least some of these losses were leading to PrEP being taken by a higher risk group.

Factors relating to having detectable drug concentrations included higher sexual risk (UAI) (adj OR 1.57, p<0.001) and known positive partner (adj OR 1.40, p<0.03). People older than 30 were twice as likely (aOR 2.02, p=0.002) and older than 40 were three times likely (aOR 3.16, p<0.001) to have detectable drug levels, compared to people younger than 30 years old. Educational level was also significant. No association was seen to alcohol and drug use.

Transgender women were 70% less likely to have detectable drug levels (aOR 0.72, p=0.02) than MSM, although the study rightly concluded that very low numbers of transgender women participants highlighted the need for further studies in this population.

Several assessments looking at risk behaviour during the study, reported no evidence of risk compensation, with risk behaviour appearing to reduce both in cases and in people who remained HIV negative.

### Table 1: Incident HIV infections during iPrEX OLE by dry blood spot drug exposure

<table>
<thead>
<tr>
<th>Drug levels (fmol/punch)</th>
<th>BLQ</th>
<th>LLOQ -350</th>
<th>350-699</th>
<th>700-1249</th>
<th>&gt;1250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated weekly dose</td>
<td>none</td>
<td>&lt;2</td>
<td>2-3</td>
<td>4-6</td>
<td>7</td>
</tr>
<tr>
<td>% of follow-up time</td>
<td>25%</td>
<td>26%</td>
<td>12%</td>
<td>21%</td>
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</tr>
<tr>
<td>Patient years</td>
<td>384</td>
<td>399</td>
<td>179</td>
<td>316</td>
<td>181</td>
</tr>
<tr>
<td>Number of new infections</td>
<td>18</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HIV incidence (95% CI)</td>
<td>4·70</td>
<td>2·25</td>
<td>0·56</td>
<td>0·00</td>
<td>0·00</td>
</tr>
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<td></td>
<td>(2·99–7·76)</td>
<td>(1·19–4·79)</td>
<td>(0·00–2·50)</td>
<td>(0·00–0·61)</td>
<td>(0·00–1·06)</td>
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<td>HR vs previous placebo (95% CI) *</td>
<td>1·55</td>
<td>0·69</td>
<td>0·19</td>
<td>0·00</td>
<td>0·00</td>
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<td></td>
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<td>(0·32–1·32)</td>
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<td>(0·00–0·25)</td>
<td>(0·00–0·50)</td>
</tr>
<tr>
<td>HR vs concurrent off-PrEP (95% CI) †</td>
<td>1·25</td>
<td>0·56</td>
<td>0·16</td>
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<td>(0·60–2·64)</td>
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Key: BLQ: below limit of quantification; LLOQ: lower limit of quantification; HR: Hazard Ration; * Adjusted for study site. † Adjusted for study site, age, number of sexual partners, non-condom receptive anal intercourse, and syphilis. Drug measurements were not available for 5% of visits.

**Comment**

These results are important for quantifying adherence levels and likely efficacy: taking 2-3 tablets a week was associated with a risk reduction 84% (95% CI: 21 to 99%) and taking > 4 tablets a week increased this to 100% (95% CI: 86 to 100%).

However, contrary to headlines in most media reports, the results do not show that PrEP is 100% effective.

Statistically, even with 7 doses a week, the actual level of risk reduction could be as low as 86% and that this could drop to 21% in people only taking four doses a week. The lower margin of the 95%CI is important. Statistically, there is also a 2.5% chance that the real level of protection could be lower still. Although this wide confidence range is a factor of the size of the study, the number of infections, and the duration of follow-up, it might be an important caution before suggesting that alternate dosing is as acceptable.

So while the results do not show that PrEP is 100% effective with good adherence, they show it is likely to get very close. The results also show that even when people know that PrEP works, and they know they are at risk, adherence is a challenge. As with early days of ART, focusing on adherence support may help improve this, as would other formulations and delivery methods. As an option, PrEP has large potential for anyone at high risk, which is a wider population than gay men. It allows anyone who is unable to negotiate safe and consistent condom use to protect this aspect of their health.

iPrEX clearly demonstrated that PrEP works in people who take it. But several thousand participants were enrolled in the original iPrEX study in order to prevent a couple of dozen infections over roughly a year (36 cases in the active arm vs 64 is the placebo...
AIDS 2014: CURE RESEARCH

Cure research at AIDS 2014: TILDA measures the reservoir and romidepsin wakes it up

Simon Collins, HIV i-Base

Cure-related research was one of the leading medical and scientific issues at AIDS 2014, adding new pieces to a puzzle that leading researchers believe is likely to take at least a decade to solve.

Other researchers are more cautious about the timeline for a cure, given the overly optimistic predictions for a vaccine. Françoise Barré-Sinoussi, co-chair for the conference and Nobel laureate for discovering HIV, chose her reply carefully when asked when we could expect this: “We cannot answer this and we shouldn’t give dates, unlike vaccine predictions in the past - first two years, then every ten years - and we still don’t have one after 32 years. There is plenty of evidence saying we can make progress, but we can’t say when.” [1] This caution is important given that many of the 200 leading researchers attending a two-day cure workshop prior to the main conference, believe that an HIV vaccine itself may be an essential component of an eventual cure. [2]

Professor Steven Deeks, co-chair of the International AIDS Society group coordinating global responses to the search for a cure, emphasised the new scientific focus. “It is clear that international community is engaged - researchers, funders and community - but (with a few notable exceptions) - industry is still missing. And we need them to develop new drugs”. [3]

For those who have access, HIV treatment is remarkably effective - normalising life expectancy and linked to few side effects - especially if someone is diagnosed early after infection. Successful treatment sets a high safety bar for a cure. Within a few months of treatment, levels of HIV in blood become undetectable using routine monitoring tests. Residual HIV largely survives in a small reservoir of immune cells that contain HIV but that then enter a dormant or resting as a natural part of their cellular lifecycle, which leaves them out of reach of current HIV meds that only target active immune cells.

Key scientific issues for Deeks include finding out exactly where in the body the reservoir cells reside, noting that a “a single cell in a single reservoir” missed by treatment could have caused the recent report of viral load rebound in the Mississippi baby, who started HIV treatment within 30 hours of birth, and who was hoped to be cured after having remained off-treatment for 27 months. [4] “We need to measure size of reservoir for people on treatment who have very low levels of HIV viral load. We need to develop bigger and better studies to advance the agenda.”

Deborah Persaud from Johns Hopkins University reported that after restarting treatment in this child, CD4% increased from 28% back to 42% and the child is responding well. Although the viral rebound results are disappointing, especially for the child who is now back on treatment, this remains the only case of such a long period off treatment in a child without detectable viral load. The rebound confirms that she was initially infected - some questioned this - and that the effects were due to treatment rather than PEP, providing a rationale for early therapy in trials.
In an overview lecture on cure and vaccine research, Dr Anthony Fauci, head of the US National Institute of Allergy and Infectious Diseases (NIAID) since 1984, highlighted the Mississippi baby as an optimistic case of prolonged virological remission that was just not sustained. “Given the lack of antibody response, we need to know what maintained that suppression for so long and what triggered the rebound?” For a future cure to be effective in a global context, he noted that it “needs to be simple, safe and generally applicable”. [5]

Fauci remains optimistic for a vaccine, following recent discovery of broadly neutralising antibodies and new research into B-cell lineage vaccine design. However, the classic approach to making a vaccine is to mimic human immune responses. With HIV, although the body generates neutralising antibodies, this is commonly only after six months and not sufficient to control infection: too little, too late. Also, broadly neutralising antibodies only develop in 20% of people after about two years and they are not able to protect against HIV reinfection.

Another part of the cure puzzle was reported in a research letter published on 21 July in the journal Nature, which looked at early SIV infection in macaques. This letter suggests that the reservoir seems to be established before HIV is detectable in blood, probably in the lymph nodes where the virus initially establishes infection, and that treatment within three days is not early enough to produce a cure. [6, 7]

The authors tracked viral responses to treatment in 20 monkeys in which combination treatment (with dolutegravir, tenofovir and emtricitabine) was started at 3, 7, 10 and 14 days after infection (four in each group, plus four control animals who received no treatment). HIV viral load was only prevented from becoming detectable in blood in the group treated after three days, but when drugs were stopped six months later, viral load promptly rebounded. Although ART has dramatic benefits, in this group it did not lead to HIV eradication, emphasising the importance of other strategies.

Ole Søgaard from Aarhus University Hospital, Denmark presented the most promising cure research at the conference as a late-breaker oral abstract on Tuesday afternoon. The study investigators used a cancer drug called romidepsin to awaken latent HIV - a first step toward targeting latently infected cells for elimination. [8]

Romidepsin is an HDAC inhibitor that in test tube studies has previously been shown to activate latent HIV. Treatment with romidepsin for 14 days in a group of five men and one woman who had previously been on ART for an average of nine years (who could therefore be expected to have a small reservoir) resulted in significant release of viral particles that were easily detectable with viral load tests. But, no reduction was seen in the reservoir of latently infected cells. These results are seen as a promising step to show that latent HIV can be activated but just not sufficiently to cause the death of latently infected cells and reduce the reservoir. Other more potent interventions might be more successful, but this study is an important proof of principal that sleeping cells can be targeted by treatment. Commenting on these results Deeks noted: “this is the first data to show we can find hidden virus and shock it out of hiding. With research driving viral load even lower so that only a tiny immune response could work”.

The IAS had previously identified developing assays to measure the size of the reservoir as a key scientific priority. So, another highlight was a presentation at the Towards a Cure symposium by Nicholas Chomont from the Vaccine & Gene Therapy Institute of Florida on a new nested PCR-based test called TILDA (Tat/Rev Induced Limiting Dilution Assay). This new test is able to measure the size of the reservoir of latently infected CD4 T cells. More importantly, this is rapid (taking less than two days), sensitive (to 1.4 cells/million), affordable (around $300), and only requires a 10 mL sample of whole blood. Previously, reservoir measurements have been limited to expensive and complex specialised labs. These results also highlighted that the reservoir may be larger than previously assumed (median 24 cells/million), with 90% of cells with inducible virus being latently infected in people on ART (compared to 75% of cells in people who are treatment-naive). TILDA is also able to differentiate between people who started ART during primary compared to chronic infection. [9]

Although designed as an approach to reduce the latent reservoir, the 14-day study using the HDAC inhibitor vorinostat in 20 people on stable ART reported potentially negative immunological changes including an increase in Tregs. TILDA showed no change in inducible virus from the latent reservoir following vorinostat. [10]

Other cases tentatively suggest that early treatment might generate an immune response in a minority of people who are able to start within the first months of infection that could possibly enable significant periods without treatment. Both Barré-Sinoussi and Fauci referenced the 14 people followed in the Visconti cohort. [11] Following treatment for 2-3 years, some of these people have since remained off treatment for over ten years, although different results have been reported in a similar US cohort.

Several attempts to replicate the functional cure reported for the Berlin patient following stem cell transplant form a donor with CCR5 delta32 deletion have so far been unsuccessful. Two cases of allogenic transplantation that were initially reported as successful, notably reported viral rebound. [12, 13]

At AIDS 2014, two further cases were reported in Australian patients after HLA matched allogeneic bone marrow transplantation with reduced intensity conditioning. One patient was treated in 2010 for non-Hodgkin lymphoma and the other in 2011 for acute myeloid leukaemia respectively. Only one patient received a transplant from a CCR5 delta32 heterozygote (so lower CCR5 levels but not CCR5-negative) and the other received a transplant from a donor without the mutation. HIV RNA and DNA are no longer detectable in peripheral blood and CD4 T cell responses to HIV-1 antigen are dramatically reduced in both cases. Crucially, while HIV remains undetectable, both people remain on treatment, so reports that these people are cured are not only premature but also incorrect. [14]

A case study reported undetectable viral load and reduced CD4 HIV responses from a patient in Argentina who has been off treatment for more than seven years, though no intervention was involved. [15]

An oral presentation for another interesting case of possible HIV cure. One patient who started ART during primary compared to chronic infection. [9]

Fauci referenced the 14 people followed in the Visconti cohort. [11]

The final test of any cure research involves asking people to stop treatment in order to see what happens. But, treatment interruptions continue to be controversial and a community discussion paper was published during the conference that outlines safer research approaches. This document is currently posted online for another month for comments. [17]

Thanks to Richard Jefferys for editorial comment.
References
10. Wightman F et al. Multidose vorinostat in HIV-infected individuals on effective ART leads to an increase in regulatory T cells but no change in inducible virus or HIV-specific T cells. Late breaker poster abstract LBEP07. http://pag.aids2014.org/abstracts.aspx?id=11288

Publications launched at AIDS 2014
Simon Collins, HIV i-Base
A selection of publications launched at AIDS 2014 is included below.

i-Base/TAG Pipeline Report
The 264-page 2014 pipeline report was launched on 20 July at the International AIDS Conference in Melbourne.
This annual i-Base/TAG report covers pipeline research into new drugs, diagnostics, prevention, cure and vaccine research for HIV, hepatitis C and TB. It includes a chapter on paediatric ARVs and another on dose optimisation strategies for global health, especially in resource poor settings.
http://i-base.info/htb/26996

UNAIDS: The gap report
This 422-page report sets out a strategy for how to close the gap between the people moving forward and the people being left behind?

Similar to the Global report, the goal of the 422-PAGE Gap report is to provide the best possible data, but, in addition, to give information and analysis on the people being left behind.

The report emphasises the importance of diagnosis and treatment as a foundation strategy to end AIDS by 2030. When people find out their HIV positive status they will seek life-saving treatment. In sub-Saharan Africa, almost 90% of people who tested positive for HIV went on to access antiretroviral therapy (ART). Research shows that in sub-Saharan Africa, 76% of people on ART have achieved viral suppression, so they are unlikely to transmit the virus to their sexual partners. New data analysis demonstrates that for every 10% increase in treatment coverage there is a 1% decline in the percentage of new HIV infections.

The report emphasises the importance of location and population through an in-depth regional analysis of HIV epidemics and through analysis of 12 populations at higher risk of HIV. It analyses the reasons for the widening gap between people gaining access to HIV prevention, treatment, care and support, and people being left behind. It shows how focusing on populations that are underserved and at higher risk of HIV will be key to ending the AIDS epidemic.

References

www.i-Base.info
Vol 7 No 3 July–September 2014
MSF report: Untangling the web of antiretroviral price reductions (17th edition)

Essential reading. This publication from MSF is clearly and concisely written, summarising in less than ten pages of commentary – and this includes photographs – the key factors behind why some people in the world receive HIV treatment and others do not.

Now in its 17th edition, this report has historically compiled information on the global differences in generic prices for all antiretrovirals. For this edition, the information is presented in a new, shorter format focusing on a few key drugs as well as future regimens, along with an analysis of the current opportunities, challenges and threats faced in keeping the price of ARVs down.

http://reliefweb.int/sites/reliefweb.int/files/resources/MSF_UTW_17th_Edition_4_b.pdf  (PDF)

MSF report: Getting to undetectable: usage of HIV viral load monitoring in five countries

This brief report is the fifth in a series called “HIV undetectable” that focuses on one of the key differences between management of HIV in high- compared to low-income countries. Access to viral load testing is a cornerstone of routine care in Western countries, but is taking a long-time to become available in all settings.

While lack of viral load testing should not delay or restrict access to ART, the sensitivity it brings to individualising patient care, especially for those people who do not achieve viral suppression on their first combination, makes it an essential tool, along with adherence support, to help as many people on ART as possible to reach and maintain viral suppression.

In an effort to inform policy makers, people living with HIV, and communities about the rapidly changing viral load testing landscape, MSF has issued a number of reports and issue briefs. The reports cover: product information and profiles (including pricing where available); information on the factors influencing costs and steps that can be taken to make viral load tests more affordable; operational strategies to reduce the complexity of monitoring viral load in resource-limited settings; and the policy landscape across countries that are adopting WHO recommendations to implement routine viral load monitoring for people on ART.

Source: Médecins Sans Frontières (MSF): HIV: Undetectable
http://www.msfaccess.org/undetectable

Issue brief 5: Getting to Undetectable: Usage of HIV Viral Load Monitoring in Five Countries (July 2014)
https://www.msfaccess.org/content/issue-brief-getting-undetectable-usage-hiv-viral-load-monitoring-five-countries

Earlier titles in this series are:
• Issue brief 1: Undetectable: How Viral Load Monitoring Can Improve HIV Treatment in Developing Countries
• Issue brief 2: Putting HIV Treatment to the Test
• Issue brief 3: How low can we go?
• Issue brief 4: HIV status? Undetectable

WHO: Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations

This 170-page report provides evidence-based recommendations for men who have sex with men, people who inject drugs, people in prisons and other closed settings, sex workers and transgender people.

These recommendations aim to:
• increase awareness of the key issues and needs
• improve access, coverage and uptake of effective services; and
• increase national and global commitment to funding and services.

The systematic reviews, literature review, values and preferences, supplementary case studies and technical briefs are available as separate appendices.

The document is also notable for a strong recommendation for the option of oral PrEP for MSM and for harm reduction and opioid substitution therapy for people who inject drugs.

Ref: WHO. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Plus additional policy brief and appendices. (July 2014)
http://www.who.int/hiv/pub/guidelines/keypopulations/en/
http://apps.who.int/iris/bitstream/10665/128048/1/9789241507431_eng.pdf?ua=1&ua=1

Lancet on HIV and Sex Workers

This year, the Lancet special theme issue produced to coincide with AIDS 2014 was HIV and sex workers. [1]

Although this is part of a series of HIV-related global health publications, the full contents are unfortunately only available through subscription access.

However, the publication was also the focus of a symposium sessions in the main conference programme, which included presentations for each of the main chapters, and these are available as free access webcasts from the IAS website. [2]

References
CONFERENCE REPORTS

6th International Workshop on HIV Paediatrics
18-19 July 2014, Melbourne

Introduction

The International Workshop on HIV Paediatrics is now up to number six – an annual fixture before the IAS conference – and goes from strength to strength.

The meeting is an opportunity to show work on a subject that often gets overlooked or lost at the big conferences.

Presentations this year were a mix of plenary talks, abstracts, clinical case studies, debates and discussions. Topics this year included cure, diagnosis and very early treatment of infants, the thorny issue of adolescents, new and older antiretrovirals, rationalising the paediatric formulary, retention in care, long-term complications and TB.

Workshop materials including the programme and abstract book for online viewing are available at http://www.infectiousdiseasesonline.com/6th-hivpediatrics-online-program/

The abstracts of the 5th International Workshop on HIV Paediatrics are published in Reviews in Antiviral Therapy & Infectious Diseases 2014 6:


The slides are online at:

http://www.infectiousdiseasesonline.com/6th-hivpediatrics-presentations

Reports in this issue of HTB include:

• Update on paediatric antiretrovirals
• Is d4T a viable option for children in low-income countries?
• 3TC or FTC monotherapy suboptimal as a bridging strategy for adolescents
• Rationalising the paediatric antiretroviral formulary in Malawi
• Time to first-line failure in the leDEA cohort
• Influence of early ART on antibody detection in children

Update on paediatric antiretrovirals

Polly Clayden, HIV i-Base

Updates on the paediatric development of rilpivirine and the single tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate were shown at the 6th International Workshop on HIV Paediatrics. Presentations at the workshop also included an overview of raltegravir – now approved in the US for infants 4 weeks and above – and tenofovir data for adolescents.

Rilpivirine

Rilpivirine is approved for treatment of adults 18 years old and above with viral load less than 100,000 copies/mL. PAINT (Pediatric study in Adolescents Investigating a New NNRTI TMC278), is an ongoing, open label, 48-week phase 2 trial looking at rilpivirine pharmacokinetics (PK), safety and efficacy in treatment naive adolescents aged 12 to 18 years.

Part 1 of this trial was to find a rilpivirine dose providing comparable exposure to that in adults. Data from part I were shown last year. Based on PK, tolerability and efficacy data up to week 4, 25mg once daily was selected. This dose was effective and generally well tolerated, in combination with 2 NRTIs, over 24 weeks for the treatment of ART-naive adolescents, with viral load <100,000 copies/mL. [1,2]

Safety and efficacy in the 24-week primary analysis of Part 2 were shown. [3]

Participants were recruited from sites in India, Thailand, Uganda, South Africa and the USA. Part 1b and 2 recruited only participants with viral load ≤100,000 copies/mL (following the adult phase 3 results); 8/11 participants from part 1a had viral load ≥100,000 copies/mL.

Participants received 25mg rilpivirine once daily, taken with a meal with two NRTIs: 67% tenofovir disoproxil fumarate/TDF/emtricitabine (FTC), 22% TDF/ lamivudine (3TC) and 11% zidovudine (AZT)/3TC. The primary endpoint was the proportion of participants with viral load <50 copies/mL at 24 weeks.

Of 36 participants in Part 2, 20 (56%) were girls and 32 (89%) black or African American, the majority was from South Africa (56%) and Uganda (31%).

By intent to treat analysis (ITT-TLOVR), 75% (27/36) of participants had viral load <50 copies/mL at week 24. This proportion was 86% (24/28) in those with baseline VL ≤100,000 copies/mL but only 38% (3/8) in participants with viral load >100,000 copies/mL.

At 24 weeks, 9 participants (25%) had discontinued treatment: 7 for virologic failure, 1 due to adverse pulmonary tuberculosis and 1 for other reasons. The median increase in CD4 count from baseline (non completer=failure) was 165 cells/mm3 (range -210 to 530).

Thirteen participants (36%) reported an adverse event (any grade) that the investigators considered could have been related to rilpivirine. Most common were: 5 (14%), somnolence, 2 (6%) rash and 2 (6%) nausea. Most adverse events were grade 1 or 2. Grade 3 or 4 adverse events were: 2 malaria, 1 decreased blood phosphorus, 1 pancreatitis, and 1 depression, suicidal ideation and suicide attempt.

There was 1 serious drug hypersensitivity (with hospitalisation), possibly related to rilpivirine.

Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

The Stribild single-tablet regimen is approved for adults and contains elvitegravir (E/VG) 150 mg, cobicistat (COBI) 150 mg, FTC 200 mg and TDF 300 mg (E/C/F/TDF). Safety, efficacy, and PK of E/C/F/TDF at 24 weeks in adolescents in the initial Part A of a prospective, 48-week, single-arm, open-label trial, were presented. [4]

Thirty-three (Part A n=14/Part B n=17) treatment-naive participants 12 to <18 years of age with viral load >1000 copies/mL, CD4 count >200 cells/mm3 and eGFR >90 mL/min were enrolled and received E/C/F/TDF once daily.
The participants were a median age of 16 years (range 12 to 17), 30% girls, 79% black, 21% Asian and 3% white. At baseline, median CD4 count was 407 cells/mm3 (range 133 to 664), mean viral load 4.71 log10 copies/mL and median eGFR 143 mL/min/1.73m2 (range 102 to 198).

There were no deaths, serious adverse events or adverse events leading to discontinuation of study regimen. Six of 33 (18.2%) participants experienced 11 adverse events the investigators considered to be related to E/C/F/TDF: 6/11 were gastrointestinal (vomiting, nausea, abdominal pain and diarrhoea) and 5/11 were CNS events (headache and dizziness). All were mild and none resulted in change of treatment.

The median change in eGFR from baseline at 24 weeks was -18 mL/min/1.73m2. At 24 weeks 18/21 (85.7%) participants had viral load <50 copies/mL. Two participants had low level viraemia at this time point; 51 and 54 copies/mL and one discontinued due to pregnancy before 24 weeks.

None of the participants had virologic failure with emergent resistance. The antiretroviral steady state exposures of the component agents in E/C/F/TDF were comparable to adults.

**Raltegravir**

In collaboration with the IMPAACT network, the originator company Merck has an ongoing programme for paediatric development of raltegravir, with chewable tablet and granules for oral suspension formulations.

In December 2013 the FDA changed the label to include babies 4 weeks to less than 2 years, weighing at least 3 kg to less than 20 kg receiving the granules – this formulation is expected to be commercially available in the US the third quarter of 2014. [5]

The CHMP of the EMA gave the granule suspension a favourable opinion in June 2014 and approval by the EMA is expected soon.

The company provided a summary of the development programme to date, and ongoing studies in neonates below 4 weeks of age. [6]

IMPAACT P1097 was conducted to establish the washout PK of raltegravir in neonates born to mothers receiving raltegravir in late pregnancy, before starting a direct active dosing study. [7,8] P1097 enrolled 22 mother–infant pairs, confirmed good transplacental transfer (median cord:maternal blood concentration ratio 1.48), and showed variable and prolonged elimination of raltegravir in the first days of life compared with older infants and children: t1/2 26.6 hours (range 9.3-184).

P1097 is now assessing washout PK in a cohort of low birth weight (including preterm) infants.[9]

IMPAACT P1110 is an ongoing two-part PK and safety study of raltegravir in term neonates at high risk of vertical HIV infection, and was informed by P1097 results. [10] Part 1 will collect intensive PK and safety data from two single raltegravir doses (at birth and 7 to 10 days) in approximately 12 neonates to estimate raltegravir clearance in the first two weeks of life.

Modelling and simulation will be used to inform multiple dosing in Part 2 to provide treatment from birth to 6 weeks in 20 additional infants. Raltegravir can be continued beyond 6 weeks if HIV is confirmed.

Completion of this programme should provide data for approval of raltegravir for the entire paediatric age range from birth onwards.

**Tenofovir disoproxil fumarate**

TDF was approved for adolescent use in the US in 2008 and the EU in 2012. The final results of GS-US-104-031 (Study 321) in treatment-experienced adolescents 12 to less than 18 years of age were shown at the workshop.

Study 321 was a 48-week randomised, phase 3, double-blind placebo controlled study with genotype-guided optimised background therapy. Participants received 300 mg TDF or placebo. The primary endpoint was time-weighted mean change in viral load at week 48.

No difference was observed between arms at this timepoint: -1.580 log10 TDF vs -1.549 placebo, p=0.55. Participants with baseline GSS < 1, viral load decrease was -0.57 log10 greater in the TDF vs placebo arm.

TDF open label extension followed the 48-week phase in participants expected to derive benefit from continued TDF up to 336 weeks. To look at efficacy the analysis stratified patients by subgroups: baseline viral load >1000 copies/mL initially randomised to TDF (TDF subgroup); randomised to placebo and failed with viral load >1000 copies/mL and switched to TDF (placebo/TDF >1000 subgroup); and placebo with viral load <1000 copies/mL switched to TDF (placebo/TDF <1000 subgroup).

A total of 81 participants received TDF in the open label extensions (all TDF group): 43.2% male, 53.1% white, 29.6% black, median age 14 years, mean CD4 422 cells/mm3. At TDF baseline, 61 had viral load >1000 c/mL (44 in TDF/TDF, 17 in placebo/TDF >1000) and 18 had HIV-1 RNA <1000 copies/mL (placebo/TDF<1000).

At 288 weeks, only 1/1 participant in the placebo/TDF <1000 subgroup had viral load <50 copies/mL (missing= excluded).

Of 57 participants analysed for resistance, additional mutations from TDF baseline were identified in 20: 1 K65R, TAMS in 11/20 (n=25); p<0.001) – this is consistent with normal changes during adolescence.

There were no deaths. Most frequent adverse events were: sinustitis (32%), cough (30%) and vomiting (26%). Grade 3 or 4 lab abnormalities occurred in 25/81 participants: neutropenia in 15 (14 taking AZT) and hyperbilirubinaemia in 7 (6 taking atazanavir with chronic HCV infection). Median height and weight increased.

Median change in eGFR from baseline in the all TDF group at week 144 was -38.1 mL/min/1.73m2 (n=25; p<0.001) – this is consistent with normal changes during adolescence.

There was 1 acute renal failure during the open label extension after amphotericin B therapy for cryptococcosis; as well as 1 real colic and 2 proteinuria. One participant had signs of phosphoribosyltransferase (decreasing eGFR, hypouricemia, proteinuria, and glycosuria) prior to taking an overdose of TDF as a suicide attempt: eGFR increased following TDF overdose; other abnormalities resolved/improved while TDF maintained. No fractures were reported. Median spine and total body bone mineral density increased over time.

**COMMENTS**

The i-Base/TAG 2014 Pipeline Report includes an update on paediatric antiretroviral drug development:

http://i-base.info/htb/26966
Is d4T a viable option for children in low-income countries?

Polly Clayden, HIV i-Base

Two African studies presented at the 6th International Workshop on HIV Paediatrics looked at whether or not stavudine (d4T) is a viable option for children in low-income countries – with different conclusions.

Victor Musiime from the Joint Clinical Research Centre Kampala presented data from CHAPAS-3 on behalf of researchers from Uganda, Zambia and the Medical Research Council at UCL, London. [1]

In this trial, children aged 1 month to 13 years were randomly assigned (1:1:1) to receive paediatric co-formulated dual NRTI plus single NNRTI or fixed dose combination (FDC) pills in regimens of NNRTI plus lamivudine (3TC) plus either d4T, zidovudine (AZT) or abacavir (ABC). The primary endpoint was clinical grade 2/3 adverse event or laboratory adverse event confirmed grade 3 or any grade 4.

There had been no previous randomised comparisons of the three NRTIs in children. Dr Musiime noted that although d4T-associated lipodystrophy is well documented in adults and adolescents there are few data for younger children receiving lower World Health Organisation (WHO) recommended doses. Of the alternative NRTIs, some cohort data has questioned the efficacy of ABC and AZT-related anaemia is likely in malnourished children in settings where malaria is endemic.

CHAPAS-3 included both treatment-naive (n=365) and experienced (n=113) children. At baseline children were well matched between arms. Overall half were girls; the median age of the naive and experienced children was respectively 2.6 years (IQR 1.6-4.00) and 6.2 years (IQR 5.5-7.2). Just over half (57%) of the treatment-naive children were less than 3 years old. The experienced children had been on d4T for a median of 3.5 years. All the experienced children had viral load <50 copies/mL at baseline, and the naive children had a median of 53,768 copies/mL (IQR 23,060-146,132). Median CD4 percentage was 20% cells/mm3 (IQR 13-25%) and 35% cells/mm3 (30-39%) in the naive and experienced children respectively.

Overall 353 (73%) children received nevirapine (NVP) and the remaining 125 (26%) efavirenz (EFV). All children less than 3 years old received NVP and the proportion receiving this NNRTI was similar within each arm.

The median follow up in the trial was 2.3 years (range 1.8-3.1). Loss to follow up was very low: 91% of children remained at the end of the trial and 98% of follow up visits were completed. There were 19 deaths (all treatment-naive children and 9 within 12 weeks of starting treatment), 17 children were lost to follow up and 8 were withdrawn from the trial.

Only 30 (6%) children substituted their assigned NRTIs: 8 switched from AZT for haematological toxicity; 2 from d4T for lipodystrophy; 9 because of TB treatment. Only 5 (1%) switched to second-line antiretroviral treatment.

The investigators reported that 312 children had 917 primary endpoints with no difference between arms: AZT vs d4T HR 0.99 (0.75-1.29); ABC vs d4T HR 0.88 (0.67-1.15), p=0.63.

Grade 3/4 neutropenia occurred more frequently in children in the AZT arm, p=0.04.

Lipodystrophy occurred in 2 children receiving d4T, p=0.11 – both cases were in experienced children aged 6 and 8 years who had received d4T for 2.5 and 5 years respectively.

Change in sum-of-four skinfold thickness and waist-hip ratio z-scores were similar across all arms: respectively p=0.33 and p=0.49.

At 96 weeks viral load was <100 copies/mL in 76%, 76% and 84% treatment-naive children receiving d4T, AZT and ABC respectively, p=0.32. For experienced children the respective proportions were 97%, 100% and 97%, p=0.51.

Changes in CD4 percentage were similar across arms (p=0.15), increasing from 20% to 36% in naive children, and remaining stable in experienced. There were 14 new WHO 3/4 events: 3, 4 and 7 in the d4T, AZT and ABC arms respectively. Of the 19 naive children that died 7, 3, 9 were in the d4T, AZT and ABC arms respectively, p= 0.5 for progression to WHO stage 3/4 and death.

Dr Musiime concluded: “Priority should be to identify children early and start ART, whichever NNRTI is available”. He suggested that younger children could receive d4T.

In a related presentation, Renate Strehlau showed data from the NEVEREST 3 trial on behalf of colleagues from University of...
Witwatersrand, Johannesburg and Columbia University, New York. NEVEREST-3 was a randomised clinical trial investigating the virological efficacy of an Efavirenz-containing regimen as long-term maintenance treatment in NVP-exposed children, conducted at Rahima Moosa Mother and Child Hospital, Johannesburg. Within the main study, children were randomised to switch to an ABC-containing regimen or remain on one containing d4T.

Dr Strehlau explained that in South Africa 3TC and d4T were used at the start of the ART programme – in 2004 – in first line treatment for children. In 2010 the national guidelines recommended ABC instead of d4T for children starting ART but those already receiving d4T with no adverse events should continue that NRTI. The 2013 guidelines recommended an ABC-containing regimen for children starting treatment and to change d4T to ABC if the viral load is undetectable. At the time that NEVEREST-3 was conducted the guidelines did not yet recommend switching children with no d4T-related adverse events.

The aim of the sub-study was to look at changes in CD4 and viral load; prevalence of lipodystrophy; changes in lipid concentrations and occurrence of ABC-related hypersensitivity reactions.

Of 300 screened, 213 children were randomised to remain on d4T (n=106) or switch to ABC (n=107). The majority of the 87 who were not eligible for randomisation had features that suggested lipodystrophy. Children were similar in both treatment arms: just over half were girls; at treatment initiation they were a mean age of 9.7 months and 8.5 in the d4T and ABC arms respectively and at screening children in both arms were a mean age of 4.2 years. They had been on ART for a mean of 3.4 years and 94% had viral load <50 copies/mL.

Unblinded clinician assessment identified more children in the d4T arm displaying features consistent with lipodystrophy through 48 weeks. But the differences between arms were only significant at 12 weeks (d4T vs ABC, 10.4 vs 2.9%, p=0.03) and 40 weeks (15.7 vs 4.9%, p=0.01) post randomisation.

At screening, fasting lipogram results did not show a significant overall difference in total cholesterol values between the two arms. At 8 weeks after switching to ABC, fasting lipogram results showed mean total cholesterol to be higher in children who had switched to ABC (4.4 vs 4.7 mmol/L, p=0.02). The difference was no longer evident at 48 weeks post randomisation.

The proportion of children with elevated LDL greater than 3.4 mmol/L, or 131 mg/dL, was also higher in children switched to ABC (11 vs 25%, p=0.01) at 8 weeks after the switch. But, at 48 weeks post-randomisation there was no significant difference in the proportion of children with raised LDL levels.

Although the data were not shown in the presentation, Dr Strehlau noted that after 48 weeks of follow-up, the d4T vs ABC groups also did not show significant differences in mean triglyceride levels.

Viral load, CD4, and anthropometric results did not differ between randomisation groups 56 weeks post-randomisation. There were no differences in occurrence of adverse skin manifestations between arms and no cases of ABC hypersensitivity reaction.

Dr Strehlau concluded: “Switching virally suppressed children who are tolerating d4T to ABC, appears to be safe and may provide benefit with respect to reduction in the prevalence of lipodystrophy”.

References

3TC or FTC monotherapy suboptimal as a bridging strategy for adolescents
Polly Clayden, HIV i-BASE

Monotherapy with lamivudine or emtricitabine (3TC or FTC) is suboptimal as a bridging strategy for adolescents compared to failing antiretroviral treatment (ART) regimen according to data presented at the 6th International Workshop on HIV Paediatrics.

Allison Agwu presented results on behalf of researchers from IMPAACT P1094 – a randomised controlled trial that compared the use of 3TC or FTC monotherapy as a short-term bridging regimen vs continuation of non-suppressive ART in non-adherent participants.

Dr Agwu explained that 30-40% of vertically infected adolescents have virological failure with persistent viraemia ≥ 400 copies/mL while on ART. There is no consensus on how best to manage this population.

In the presence of the M184V mutation, 3TC or FTC monotherapy does not suppress viral replication or select for additional drug resistance mutations but reduces viral fitness. The researchers hypothesised that 3TC or FTC monotherapy might prevent immunologic deterioration compared with continuing failing ART.

The primary objective of P1094 was to compare immunologic deterioration over 28 weeks in adolescents receiving the two strategies, with virological failure and documented M184V resistance.

C O M M E N T

It was good to see such recent data from CHAPAS-3 presented as a late breaker and comment from the audience included congratulations to the investigators for such a low rate of loss to follow up.

Another comment was that two years might not be enough time to see d4T side effects in children but no one could disagree with Dr Musiime’s conclusion that priority should be to identify children early and start ART.

The follow up time in the NEVEREST-3 substudy was not long either but this group did observe some feature consistent with lipodystrophy at two time points.

The younger age of some of the children in CHAPAS-3 might account for this.
These adolescents were considered likely to be non-adherent on an optimised ART regimen due to problems with adherence, tolerability or toxicity (and attempts to improve adherence had been unsuccessful). The primary endpoint was ≥ 30% decline in absolute CD4 count.

The study enrolled 33 participants from the US, Brazil, Thailand and Argentina between May 2011 and December 2012; 16 were randomised to continue failing ART and 17 to receive 3TC or FTC monotherapy. The original target for the study was 344 participants but it closed early – in February 2013 – due to slow accrual at US sites and long regulatory processing times that delayed opening in the other countries.

Participants were a median age of 15 years (range 10-24), 33% were male, their median CD4 count was 472 cells/mm3 (156-1078; 70% > 400) and viral load was 4.0 log10/copies/ml (2.2-5.6).

Prior to the study, facilities had attempted the following interventions (participants had a median of 4): counselling (94%), frequent clinic visits (75%), reminders (56%), therapy (56%), ADL triggers (44%), peer support (31%), rewards (31%), regimen modification/simplification (25%), home visits (19%), DOT (8%) and G-tube (6%).

Mechanisms used to determine non-adherence were (participants had a median of 3): participant reported (79%), persistent viraemia (70%), agreement of two health workers (61%), pharmacy refill history (36%), pill count (21%) and other (9%).

Dr Agwu reported that 5 participants in the monotherapy arm reached the primary endpoint for CD4 decline, p=0.03 (log-rank) The Kaplan-Meier estimate of probability of failure at 28 weeks was 0.41 (standard error 0.14). There were no class C CDC events or deaths. There was one grade 4 hyperbilirubinaemia in the continuing ART arm.

She noted that to the investigators knowledge this is the only randomised controlled trial of 3TC or FTC monotherapy in this population and although the sample size was small the findings were highly significant.

**COMMENT**

Retrospective data from a case note review of children with limited options that received 3TC monotherapy as a holding strategy for children in South Africa with limited options was reported last year. [2] The children in the South African Study were younger, 8.02 years (IQR 4.07–11.80) and received monotherapy for a median of 6 months during which time their CD4 count decreased by 23% but did not reach pre-ART levels.

Both studies suggest that this strategy is not ideal and once again highlight the adherence challenges – particularly for adolescents.

**References**


**Rationalising the paediatric antiretroviral formulary in Malawi**

Polly Clayden, HIV i-Base

Rationalising the national paediatric antiretroviral formulary Malawi significantly decreased the cost of paediatric HIV treatment and improved lead times for products, according to data from the Clinton Health Access Initiative (CHAI) presented at the 6th International Workshop on HIV Paediatrics. [1]

There is low demand for paediatric antiretrovirals and multiple, redundant formulations – such as syrups and single drugs – are often used for one regimen when fixed dose combinations (FDCs) are available. With so many formulations, it can be difficult to achieve minimum batch size for procurement, resulting in instability and delays to country level supplies of drugs.

A strategy to overcome this is to limit procurement to a rationalised list of paediatric antiretrovirals. Rationalisation increases volumes – so countries can achieve batch sizes for products – at the same time increasing supply stability and decreasing costs.

In 2010, Malawi procured 23 different formulations, including ddI. In 2011 CHAI held a series of workshops focused on decreasing the number formulations to a limited set of optimal products for Malawi. Opportunities for optimisation included: limiting use of syrups, single tablets and capsules, replacing 50 mg efavirenz (EFV) capsule with 200 mg EFV scored tablet and limiting to one paediatric efavirenz FDC. Malawi reduced the total number of formulations procured between 2010 and 2013 from 23 to eight.

In order to assess the effect of this rationalisation CHAI compared the unit costs and lead times, for the years 2010-2013, of all products used to make up the recommended regimen, AZT + 3TC + nevirapine (NVP) for a 10-14 kg child. Data from the UNITAID-CHAI paediatric programme antiretroviral tracker, which documented all transactions in Malawi during this time period were used.

For each item, costs per patient per year (pppy) were calculated for the following components: product cost, freight cost, procurement fee, handling fee and insurance fee. Lead times were defined as the number of days elapsed between procurement order date and the invoice date.

This investigation revealed a total unit cost savings of over 70% between 2010 and 2013 – mainly driven by the lower cost of FDCs compared to syrups. Other contributions to the reduced costs included shipping-related expenses, which decreased over 95% pppy during the time period.

Lead times declined by 85% from an average of nearly three months to approximately one month for FDCs in 2013. Variation in lead times for individual drugs was included shipping-related expenses, which decreased over 95% pppy during the time period.

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Lead times declined by 85% from an average of nearly three months for syrups, singles, and FDCs in 2010 to approximately one month for FDCs in 2013. Variation in lead times for individual drugs was eliminated by procurement of FDCs, which also reduced the resources needed for stock management and storage of different formulations.

**COMMENT**

The Intragency Task Team for the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children (IATT) has developed an optimal paediatric antiretroviral formulary. [2] Adaptation of the IATT list by countries and rationalised procurement is now recommended.
High rates of death, loss to follow up and first-line failure were observed in the IeDEA paediatric cohort, within five years of starting antiretroviral treatment (ART). Only a third of children meeting criteria for failure were changed to second-line ART and about a quarter died during this period.

World Health Organisation (WHO) 2013 guidelines recommend starting antiretroviral treatment (ART) in all children aged five years old and below. But data are limited on durability of first-line ART in children in resource-limited settings.

A study conducted by the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Consortium looked at the time from starting first-line ART to treatment failure and the time from failure to initiation of second-line ART in children. Findings from the IeDEA study were shown at the 6th International Workshop on HIV and Paediatrics. IeDEA was established in 2005 by the National Institute of Allergy and Infectious Diseases and includes seven geographic regions addressing high priority question about HIV care and treatment. [1]

This study included five regional paediatric cohorts within IeDEA. Children aged 2 to 13 years at ART initiation were eligible.

**Outcomes included: failure after 24 weeks on ART defined by clinical (new or recurrent WHO 3 or 4 event or increase in WHO stage), immunologic (CD4 count <200 cells/mm3 or CD4 percent <10% for children 2 to 5 years; CD4 count <100 cells/mm3 for children >5 years), and virologic (viral load >5,000 copies/mL) criteria; and change to second-line ART; death and loss to follow-up (defined as >6 months without a clinic visit).

The investigators used a cause-specific proportional hazards model to identify factors associated with each outcome.

The presentation included outcomes of 16, 183 children from Asia-Pacific (11.6%), Central Africa (0.3%), East Africa (43.9%), Southern Africa (36.0%) and West Africa (8.2%).

About half were girls, the median age at ART initiation was 6.7 years (IQR 4.4-9.4) years, median CD4 percent for children <5 years was 13% (IQR 8.0-18.0) and CD4 count for children >5 years was 231 cells/mm3 (IQR 73-429).

The majority of children (97.7%) started an NNRTI-based regimen; 1.9% started with a PI and 0.3% triple NRTI-based ART.

Failure was seen in 4,032 children and 2,837 died or were lost to follow up. At 1 year after ART initiation probability of failure or death/loss to follow up were respectively: 12.0% (95%CI 11.5-12.6) and 11.6% (95%CI 11.2-12.2). At 5 years, these rates were respectively: 35.0% (95%CI 34.3-36.2) and 22.1% (95%CI 21.4-23.1).

Factors associated with failure rates were: age at ART initiation, (per year increase) HR 1.03 (95% CI 1.02-1.04); PI based ART (ref NNRTI) HR 0.54 (95% CI 0.04-0.72) and no access or only confirmatory viral load test (ref routine) HR 0.73 (95% CI 0.62-0.87), all p<0.001.

Factors associated with death/loss to follow up were: age at ART initiation (per year increase) HR 0.98 (95% CI 0.07-0.09), p=0.004; PI based ART (higher rates ref NNRTI) HR 2.19 (95% CI 1.38-3.48), p=0.001 and no access or only confirmatory viral load test (ref routine) HR 2.51 (95% CI 2.23-2.82), p<0.001.

At 1 year after failure the probability of death/loss to follow up and change to second-line among 4,032 participants were respectively: 9.6% (95%CI 8.7-10.7) and 11.3% (95%CI 10.4-12.5). At 5 years the rates were respectively: 22.3% (95%CI 21.0-24.6) and 29.3% (95%CI 27.9-32.0).

Factors associated with change to second line were: male sex (ref female) HR 1.33 (95% CI 1.15-1.53), p<0.001; at ART initiation (per year increase) HR 1.09 (95% CI 0.07-0.12), p=0.001; confirmatory viral load test (ref routine) HR 0.54 (95% CI 0.46-0.62), p<0.001; no access to viral load test (ref routine) HR 0.52 (95% CI 0.31-0.85), p=0.001.

No access to viral load test (ref routine) was associated with death/loss to follow up 1 year after failure: HR 0.74 (95% CI 0.63-0.87), p<0.001.

In conclusion, high rates of death/loss to follow up were identified in this study within 5 years of starting ART. Children in facilities without routine viral load testing were less likely to be identified as failing but more likely to be lost to follow up or die. Children without access to any viral load were less likely to switch. Only a third of children who failed were changed to second-line and about a quarter died.

The investigators noted that associations with viral load access might be related to other factors including background mortality.

“Efforts need to be made to determine the reasons for delays in switching antiretroviral regimens in children who have been identified as failing first-line” they wrote.

**References**


2. Wools-Kaloustian K et al. Time to first-line ART failure and switch to second-line ART in the IeDEA pediatric cohort. 6th International Workshop on HIV Paediatrics, 18-19 July 2014, Melbourne, Oral abstract O_03

**Influence of early ART on antibody detection in children**

Polly Clayden, HIV i-Base

Use of standard antibody tests in early treated children can lead to confusion according to data presented at the 6th International Workshop on HIV Paediatrics.

There have been reports of early treated HIV-infected children with suppressed viral load on antiretroviral treatment (ART) having negative antibody tests. It is unclear how frequently this occurs.

Investigators from Empilweni Service and Research Unit, Johannesburg and Columbia University, New York looked at HIV...
antibody in children enrolled in a clinical trial at Rahima Moosa Mother and Child Hospital, Johannesburg. They evaluated 104 samples from HIV-infected children who were under 15 months of age when they started ART and were now 3 to 6 years old and fully suppressed (<50 copies/mL). ELISA (GenescreenTM HIV1/2 version 2; Biorad) was used to perform the tests.

The children were a mean age of 8 months (range 2.2-15) at start of ART and had received ART for a mean of 5 years (range 3.4–6.4). Five of 104 had undetectable antibody (neg) and two had low antibody reactivity (low). Children with neg/low results started ART at a mean age of 3.7 months (range 2.2 to 4.9 months).

Seven of 43 (16%) children who started ART when aged <6 months had neg/low antibody. The investigators reported no association between duration of ART and antibody detection. They found significantly lower optical density (OD) among children starting ART <6 months than those starting >6 months of age: mean 3.6 vs 4.7 OD units, p=0.0002.

When the samples were retested with a more sensitive assay 7/7 children with neg/low antibody tested positive.

An additional 122 samples were included from children under 6 months when they started ART; mean age 3.9 months (range 3 weeks to 6.9 months) currently suppressed for a mean of 5 years. Of 226 children, altogether approximately 30% were antibody negative that started ART at <3 months; this proportion was approximately 5% for those that started ART 4-6 months of age.

The investigators concluded: “Use of standard antibody tests in early treated children can lead to confusion.” They noted that early ART might have several advantages and earlier infant diagnosis than is currently routine might be necessary.

**COMMENT**

The “confusion” referred to in this study is about whether or not early treated children with HIV antibody negative results are HIV positive and need continued treatment, or following the widely reported news of the Mississippi child (now back on treatment) “cured”.

The investigators noted that the prevalence of antibody negativity, even among children initiating ART <6 months of age, was lower than they had expected. All children had detectable antibody on a sensitive, low avidity assay. The investigators suggested that the unusual antibody profiles might mean that early ART could have influenced the ontogeny of antibody responses. They added: “Further investigation of antibody development, early treatment and establishment of viral reservoirs is warranted”.

**Reference**

Pregnancy outcomes in Zambia

Polly Clayden, HIV i-Base

Three presentations at 8th INTEREST were from Zambian studies looking at birth outcomes among women receiving antiretroviral treatment (ART) in pregnancy.

The first study found no significant association between ART duration and risk of low birth weight (LBW) <2500 g.

This was a retrospective review of data from the Zambian Electronic Perinatal Record System (ZEPRS). The investigators looked at the association between timing of ART initiation and LBW in women who were ART-naïve, eligible for treatment (CD4 count <350), and delivered singleton infants at ≥28 weeks at a health facility between 1 January 2009 and 1 September 2013.

They categorised duration on ART as ≤8, 9-20 or 21-36 weeks before delivery and compared these groups to women who were eligible but never started treatment.

To assess the effect of missing data, the investigators looked at predictors of missing ART initiation date and performed multiple imputation for missing dates. They used log-binomial regression to estimate risk ratios (RR) for the association between duration on ART and LBW and adjusted for multiple confounders (preterm delivery was not included as a confounder). Data on World Health Organisation (WHO) clinical stage and viral load were not available.

A total of 9,276 women met the inclusion criteria for the analysis: 5,746 (64%) never initiated ART, 1,432 (16%) received ART for 1-8 weeks, 1,672 (19%) for 9-20 weeks and 1,922 (21%) for 21-36 weeks.

Of women included in the analysis: 5,744 (62%) were missing confounder, exposure or outcome information; a further 2,154 (19%) reported being on ART at delivery, but had no start date.

There were 1,267 (14%) LBW infants – this was greatest in the ART for 1-8 weeks group, 235 (18.6%). In the complete case analysis (reference, never initiated ART and adjusted for: number of ANC visits, age, BMI, CD4 count, education, hemoglobin, malaria prophylaxis, parity, syphilis screening and tuberculosis status) RRs for 21-36 and 9-20 weeks on ART were respectively 0.48 (95% CI 0.21-1.13) and 0.87 (95% CI 0.68-1.12). For 1-8 weeks RR was 1.21 (95% CI 0.97-1.51).

No associations were statistically significant.

In the imputed data analysis, the investigators found that RRs for 21-36 and 9-20 weeks on ART moved closer to the null and the RR for 1-8 weeks on HAART increased and became significant (p-value not reported). They suggested this association might be due to the higher number of preterm births among women on HAART for 1-8 weeks (18.5% vs 12.3% HAART 9-20 weeks and 0.5% HAART 21-36 weeks).

The investigators noted that the limitations of the study included: understanding the impact of preterm birth, whether or not earlier initiation of ART was a marker for better health seeking behaviour and that the data was observational and collected in the previous Option A programme.

The second study also evaluated data from the ZEPRS and used regression discontinuity (a “quasi-experimental approach” that can minimise such confounding with observational data when the probability of being treated is dependent on an arbitrary threshold) to look at CD4 threshold for starting ART in pregnancy ART in pregnancy and possible associations between ART and birth outcomes. This analysis did not find significant associations.

The investigators identified newly diagnosed HIV-positive pregnant women in Lusaka, with CD4 counts 300 to 400 cells/mm³. They modelled the association of ART initiation in pregnancy with birth weight (BW), LBW, and stillbirth. They also conducted sensitivity analyses with wider and narrower CD4 windows around the threshold of 350 cells/mm³; +/-75 and +/-35 cells/mm³.

Between Jan 2009 and May 2013, 3,660 of 31,795 (12%) newly diagnosed pregnant women had CD4 counts of 300-400 cells/mm³, including 1,924 with 301-350 and 1,736 at 351-400 cells/mm³. When the women were stratified according to CD4 category, there was a slightly higher number of preterm births among women on HAART compared to those on ART in pregnancy.
were not statistically different in age, socioeconomic status, parity, gestational age at first ANC, and obstetrical risk factors.

The analysis revealed that women with CD4 300-350 cells/mm3 did not have worse birth outcomes, although they were over twice as likely to start ART vs those with CD4 351-375 cells/mm3: 37% vs 15%, p<0.001. Both the intention to treat and the as-treated analyses suggested that ART initiation is associated slight decrease in probability of LBW (-0.04, 95% CI -0.53 to 0.45 for as-treated) and of stillbirth (-0.13, 95% CI -0.38 to 0.13) and increase in BW (396 grams, 95% CI -345g to 1137g). None were significant and sensitivity analyses using wider and narrower CD4 ranges gave similar results.

The third study looked at a pilot programme that offered universal ART to HIV-positive pregnant and breastfeeding women at the Adult Infectious Disease Centre, University Teaching Hospital, Lusaka from 2008 to 2011. This programme extended beyond the HIV treatment guidelines at the time (ART for those with CD4 count < 350 cells/mm3 or WHO Stage 3 or 4). The data source for the analysis was also the ZEPRS.

This study described the characteristics associated with starting antenatal ART stratified by CD4 count (> or < 350 cells/mm3), and those associated with postnatal ART initiation. It also compared pregnancy and HIV outcomes between women who started antenatal ART and those who did not. Outcomes include: mode of delivery, infant birth weight and newborn vital status, Apgar scores, NICU admission, infant feeding method, and infant HIV status at 6 weeks and 6 months.

In this cohort, CD4 count <350 cells/mm3 was associated with increased ART initiation. Most pregnancy and HIV outcomes did not differ among women on and not on ART stratified by CD4 count. The analysis included 353 women with pregnancy outcomes of which 70 (19.8%) initiated ART before pregnancy. The remaining 283 women were offered ART, 169 (59.7%) had a CD4 count <350 cells/mm3, so were eligible for ART according to Zambian guidelines. Of these, 144 (85.2%) started treatment. A further 114 women with CD4 count > 350 cells/mm3 were also offered ART, and 88 (77.2%) started treatment.

Of the 51 women who declined antenatal ART, 25 (49.0%) started after delivery. For women with CD4 count <350 cells/mm3, higher gravida was the only characteristic associated with starting antenatal ART, p=0.04.

For women with CD4 count > 350 cells/mm3, the median maternal weight was significantly higher in those starting antenatal ART than those who did not: 71.0 vs 63.5 kg, p<0.05. For women who declined antenatal ART, a recent CD4 count <350 cells/mm3 was associated with starting postnatal ART, p<0.05.

Most pregnancy and infant outcomes were similar among women on and not on ART stratified by CD4 count. Most recent CD4 ≤ 350 cells/mm3 preceding post natal initiation was associated with formula feeding, p<0.01. Fewer women who did not initiate antenatal ART formula fed than those who did: 13 vs 33%, p=0.05. Overall, the majority of women chose to breastfeed.

In this cohort women who were not treatment eligible were less likely to initiate ART even when it was offered to them. The investigators noted that messages about Option B+ to pregnant and breastfeeding need to be strengthened and this is a critical role for the community.

The data on outcomes presented here seem reassuring.

References

Uptake of ART is influenced by distance to the health facility in rural Zambia

Polly Clayden, HIV i-Base

A Zambian study at 8th INTEREST showed that the distance between a woman’s home and clinic affects the uptake of ART during pregnancy and breastfeeding.

This finding was from a pilot project to offer Option B+ in four rural clinics in the Kafula District. The programme included household surveys to evaluate the effect on infant HIV-free survival at a population level.

The investigators collected medical data from all women who had delivered a child within the past two years. The women were also tested for HIV.

In the second part of the survey, which provided data for this analysis, geographic coordinates of households were also collected. The analysis included: antenatal care (<4 months gestation, uptake of any PMTCT regimen, and use of ART. The investigators measured the distance between households and clinics (in a straight line not taking into account topographical features) using ArcGIS 10.0 – a computer programme for mapping and spatial analysis.

They used multivariable regression models to measure the association between clinic distance and the outcomes of interest and to explore the relationship between clinic distance and Option B uptake.

They reported that between March and December 2011, 2,448 mother-infant pairs were enrolled, of which 1,708 (70%) had evaluable data. A total of 771 (45%) mothers reported having an antenatal visit before four months gestation, but this had no association with distance from the clinic, p=0.30.

When the analysis was limited to 256 HIV positive women, 168 (66%) of these reported using any antiretroviral drugs during pregnancy and 102 (40%) started ART for PMTCT.

The investigators found that uptake of any PMTCT regimen and ART for PMTCT decreased as the per-km distance to the clinic increased,
AOR respectively: 0.89 (95% CI 0.82 to 0.96) and 0.88 (95% CI 0.80 to 0.96). The probability of starting Option B was highest within 3 km of the clinic, after which the investigators reported a gradual decline. “Programme models that further decentralise care into the community are urgently needed” they wrote.

**Comment**

That every kilometre travelled means loss to follow up might be stating the obvious. Seeing data on decline in uptake associated with distance from the clinic properly evaluated gives weight to the importance of further steps towards decentralised care and treatment.

Reference


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**Genotyping using dried blood spots in rural South African setting**

**Polly Clayden, HIV i-Base**

**Genotyping for HIV drug resistance using dried blood spots (DBS) as a sampling method was successfully implemented in clinical practice in a rural facility in Limpopo, South Africa.** [1]

Investigators from University Medical Center Utrecht (UMCU), the Netherlands and Nditou Care Group, Elandsdoorn, conducted the study. Lucas Hermans presented findings at the 8th INTEREST.

People with virological failure – monitored by yearly viral load test and defined as >3.0 log10 copies/mL after initial suppression <400 copies/mL – were included between 2009 and 2013. The DBS samples were prepared by spotting EDTA whole blood onto filter cards and posted (by standard mail) to the UMCU Netherlands laboratory for genotyping.

The investigators used a magnetic extraction kit to isolate viral nucleic acids, which were amplified and genotyped using a test targeting the protease (PR) and reverse transcriptase (RT) region of HIV-1. Any samples that failed to amplify for PR-RT were analysed using an RT-only test. The resistance analysis was done with HIV-GRADE and the 2011 International AIDS Society guidelines were used to assess the mutations.

In this study, 191 participants with virological failure had DBS resistance testing: 62% were women, median age 35 years, at genotyping their median viral load was 4.2 log10 copies/mL and CD4 count 191 cells/mm3, and they had received ART for a median of 844 days. The majority (83.6%) of the participants were receiving first-line therapy at failure. Genotyping was successful in 181/191 (94%) of cases, of which 79% had resistance.

In this study, 191 participants with virological failure had DBS resistance testing: 62% were women, median age 35 years, at genotyping their median viral load was 4.2 log10 copies/mL and CD4 count 191 cells/mm3, and they had received ART for a median of 844 days. The majority (83.6%) of the participants were receiving first-line therapy at failure. Genotyping was successful in 181/191 (94%) of cases, of which 79% had resistance.

The prevalence of nucleoside reverse transcriptase inhibitor (NNRTI) the prevalence was 77%, and these were most frequently K103N in 40%, Y181C in 25% and V106M in 23% of participants. Protease inhibitor (PI) resistance was seen in 1%.

Dr Lucas noted that resistance testing with DBS in this rural setting was successful, the turnaround time was a median of 16 (IQR 8-33) days and that there was a high success rate in the lower viral load range.

**Comment**

In a related presentation on affordable HIV drug resistance tests, Sue Aitkin from the same group, noted that using RT-only testing offers some advantages over PR-RT as amplification takes three rather than five hours, it has two compared to six sequencing reactions and quick rather than extensive sequence analysis (as short fragment). The majority of people in this setting will have only received first-line treatment. RT-only would result in greater than 75% cost saving compared to a commercial assay and 40% compared to in-house PR-RT.

The low rate of PI resistance in this sample suggests that routine genotyping should be limited to the RT region, thereby reducing costs and processing time.

For the future, it would be ideal if second-line treatment had no overlapping resistance with first-line.

References


2. Aitkin S. Affordable HIV drug resistance tests: options for Africa. 8th International Workshop on HIV Treatment, Pathogenesis and Prevention Research in Resource-Poor Settings (INTEREST). 5-6 May 2014. Lusaka, Zambia. [PDF]
Bone mineral density linked to inflammatory markers in HIV positive people who are ART naive

Gareth Hardy, HIV i-Base

In the July edition of AIDS, Corrilynn Hileman and colleagues at Case Western Reserve University in Cleveland, Ohio investigated changes in bone mineral density (BMD) in treatment-naive subjects who remained off treatment for over 48 weeks and the association of BMD with other factors in order to throw light on the reported higher prevalence of osteoporosis and fracture in HIV positive people. [1]

This was a prospective, matched cohort study performed on ART-naive, HIV positive people and HIV negative controls matched for age (within 3 years), sex and race. The effects of HIV, inflammation and vitamin D concentration were assessed on BMD over 48 weeks. Dual-energy X-ray absorptiometry (DXA) of the spine and left hip was performed at baseline and at 48 weeks. In order to assess their possible relationships with BMD, plasma levels of the following inflammatory markers were also determined: high-sensitivity C-reactive protein (hsCRP); interleukin-6 (IL-6); soluble tumor necrosis factor-alpha receptors-I and -II (sTNFR-I and II); soluble vascular cell adhesion molecule-1 (sVCAM-1); soluble intercellular adhesion molecule-1 (sICAM-1); and 25-hydroxy vitamin D (25(OH)D).

At baseline, no differences were observed between the 40 HIV positive individuals and the 37 HIV negative controls in terms of age, race, sex, BMI, alcohol use or family history of hip fracture. There were more smokers and HCV positive people in the HIV positive group. Mean duration of HIV infection was 4 years (1.1–12.4 years). Median CD4 count was 625 (533 – 844), nadir CD4 was 520 (542 – 618) and median viral load was 4,638 (783 - 20,600). All participants remained treatment naive throughout the study. Higher levels of some inflammatory markers were found in the HIV positive subjects: IL-6; sTNFR-II; sVCAM-1; sICAM-1 (p <0.01 for all). No differences were seen in hsCRP, sTNFR-I or 25(OH)D. There was also no difference in BMD between the groups at baseline, although there was a trend towards lower BMD at the femoral neck in the HIV-infected group (adjusted mean 1.074 vs 1.145 g/square cm for HIV positive participants versus controls; p = 0.054). BMD measured at the total hip, femoral neck, trochanter and spine was not associated with HIV status, inflammatory markers or 25(OH)D at baseline and the proportion of participants with osteopenia or osteoporosis was not different between HIV positive and control groups.

At 48 weeks, there was a significant percentage reduction in BMD at the total hip and trochanter for the HIV positive group (median absolute change in BMD [IQR] at total hip -0.005 (0.026 – 0.008 g/square cm, p = 0.023 within the group; trochanter -0.013 (-0.03 – 0.003), p = 0.002). BMD did not significantly change at any site in the control group. Despite this, the change in BMD did not reach statistical significance between the groups.

However, the HIV positive group was 2.8 times more likely to suffer loss of BMD at the trochanter site (73% vs 49% for HIV positive and control group respectively; OR 2.8, 95% confidence interval 1.1–7.2, p = 0.034). Adjustment for age, race, sex, BMI, smoking and HCV did not affect this risk. However, adjustment for IL-6, sTNFR-II, sVCAM-1 and sICAM-1 reduced the odds ratio for HIV status by 10% with the addition of each marker. With all 4 markers in the model, HIV status no longer independently predicted bone loss at the trochanter, suggesting that inflammation is an important mechanism intermediary in the cause of bone loss in people with HIV.

Progression from normal bone to osteopenia or from osteopenia to osteoporosis occurred in 20.5% of HIV positive individuals compared with 5.6% of controls (p = 0.089). For HIV positive people, higher baseline IL-6 (OR 1.1, 95% confidence interval 1–1.2, p = 0.036) and Caucasian race (OR 17.4, 95% confidence interval 2.1–142, p = 0.008) were independently associated with bone loss. No association was found between reduction in BMD and baseline levels of the other inflammatory markers, 25(OH)D, viral load, CD4 count or CD4 nadir.

This study lends further evidence to the literature reducing the potential for a direct role of low vitamin D levels in loss of BMD in HIV infection, as also suggested by Sherwood et al [2] and El-Maouche et al [3]. Instead, the results indicate that inflammatory markers may play a direct role in bone mineral loss and that IL-6 levels at baseline are associated with progression to osteopenia or osteoporosis in HIV positive people. However, the authors also note that the sample size was not large enough to measure statistically significant differences between HIV positive and control groups for BMD. Furthermore, the 48-week limit of the study may have further hindered the detection of differences in BMD change between groups, although it is not feasible for sufficient study numbers of HIV positive people to remain ART naive for longer periods than this.

References
The estimated frequency of CD4 T cells bearing replication-competent HIV was significantly higher in people who had initiated ART during chronic infection, compared with elite controllers (p = 0.004). There was also a trend to a higher frequency of CD4 cells bearing replication-competent HIV in people who initiated ART during chronic infection, compared with those that initiated ART during primary infection (p = 0.052). The researchers then assessed the decay kinetics of the different forms of HIV DNA in CD4 T cells of the different treatment-initiation groups. Comparing HIV DNA levels at year ten of ART with treatment baseline at year zero, subjects who initiated ART during primary infection experienced a mean log10 decay per year of 0.13+/− 0.04 (p < 0.00001) in total HIV DNA. The mean log10 decay rate of 2-LTR circles was 0.32+/− 0.03 per year (p < 0.00001) and the mean log10 decay rate of integrated HIV DNA 0.07 +/- 0.01 per year (p < 0.00001).

These decay rates were accelerated in a sub-set of 3 people who initiated ART prior to seroconversion, for all three HIV DNA forms. In contrast, the decay rates of 2-LTR and total HIV DNA in CD4 T cells of subjects who initiated ART during chronic HIV infection were slower. Furthermore, the levels of integrated HIV DNA were not significantly different at year ten compared with year zero for people who initiated ART during chronic HIV infection. In all cases, declines in HIV DNA occurred mostly within the first four years of ART. The authors state that their data suggest the decay kinetics of multiple forms of HIV DNA are faster in people who initiate ART during the earliest stages of infection. As a result, rapid initiation of ART could accelerate the decline of the HIV reservoir in CD4 T cells.

As the HIV reservoir is known to persist to different degrees in specific maturational subsets of CD4 T cells, the researchers next assessed the frequency of total HIV DNA in each maturational subset: naive; central memory; effector memory; terminally differentiated memory; and central memory stem T cells. Levels of total HIV DNA were generally lower in all T cell subsets of subjects who initiated ART during primary infection in comparison to those who initiated ART during chronic infection. However, these reduced levels were only significant for effector memory (p = 0.03) and terminally differentiated memory CD4 T cells (p = 0.004). In analysis of the contribution of CD4 T cell subsets to the total reservoir size, effector memory and terminally differentiated CD4 T cells made a greater contribution to the reservoir in subjects who initiated ART during chronic infection than subjects who initiated ART during primary infection. In contrast, the contribution of the less matured, longer-lived T cell subsets, central memory and central memory stem cells, was greater in people who initiated ART during primary infection than in people who initiated ART during chronic infection. Therefore, while initiation of ART early in HIV infection results in a smaller reservoir size, it includes a greater relative proportion of HIV DNA in less matured, longer living central memory and memory stem T cells.

In conclusion, initiation of ART during primary HIV infection seemed to accelerate viral decay and cause a reduced frequency of infected cells. Despite this, central memory and memory stem T cells made a larger relative contribution to the reservoir in subjects who initiated ART in primary infection, compared with during chronic infection. This suggests that seeding of central memory and memory stem T cells occurs within the first six months of infection, during which these people initiated ART and that they “may represent the population of extremely long-lasting and treatment-refractory component of the viral reservoir that were previously hypothesised” [2].

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Wrestling with the implications of the Mississippi case

Richard Jefferys, TAG

Understandably, there has been extensive media coverage of the announcement on 10 July that HIV has rebounded in the “Mississippi Baby” case. [1]

Although a full discussion of the implications will take time, there are some points that may be worth noting now.

The number of individuals considered cured of HIV infection has dwindled back to one: Timothy Ray Brown. It had been hoped that the child in Mississippi was another example, and for a brief time last year two adults from Boston were considered possibly cured. In all three of these cases, the evidence suggests that HIV reservoirs were reduced to extremely low levels but eventually a dormant, latently infected cell became activated and sparked a renewal of viral replication.

Earlier this year it was reported that a second baby from Long Beach in California shows no detectable HIV after very early treatment, [2] and some media outlets erroneously portrayed this case as potentially another example of a cure, but the infant remains on antiretroviral therapy. The sobering outcome in Mississippi further emphasises that the absence of detectable HIV cannot be assumed to mean the virus has been cleared.

As highlighted by amfAR in their statement, the case underscores the challenges associated with attempting to measure the vanishingly small amounts of HIV that can persist, particularly in body tissues. [3]

The fate of the clinical trial based on the Mississippi baby, IMPAACT P1115, may become a matter of controversy. A variety of opinions are reported in the current media coverage. Some scientists note that two years without the need for treatment is not trivial and represents a benchmark to try and build upon; based on this view, it is perhaps possible that the IMPAACT trial could attempt to establish how frequently such remissions occur, and whether they might last longer in some cases (close monitoring would certainly be required during interruptions to ensure treatment could be restarted as soon as any HIV rebound was detected). But other scientists argue that interrupting treatment would now be unethical (NPR quotes an ethicist making this argument). [4] Further dialogue is clearly needed to reach agreement on how (or if) the trial should proceed.

Although the news has dealt a severe blow to hopes that very early HIV treatment alone might be curative, the evidence remains clear that swift initiation of antiretroviral therapy after infection is associated with a significant reduction in the size of the HIV reservoir. For this reason, there is still broad consensus that early-treated individuals are ideal candidates for trials of interventions that aim to further reduce the reservoir or induce containment of any residual HIV. Such trials are already being planned in a cohort of early-treated adults in Thailand, using interventions such as therapeutic vaccination and infusions of broadly neutralising antibodies (the design of the latter trial, RV397, was presented and discussed at the Regulatory Pathway for HIV Cure Research meeting). [5]

The return of the Mississippi child to the media spotlight is also a reminder that the case arose from a bad situation, in that the mother had an undiagnosed infection and did not receive necessary prenatal healthcare. Ideally, all HIV positive mothers should be able to access high quality, appropriate care to minimise the risk of perinatal transmission, and this remains a vital priority. Jim Merrell from the Prevention Justice Alliance wrote a commentary on this issue last year that is still relevant. [6]

Source: TAG basic Science Blog (11 Jul 2014)
http://tagbasicscienceproject.typepad.com/

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Molecular events in HIV neutralising antibody development

Gareth Hardy, HIV i-Base

In the May edition of Nature, Nicole Doria-Rose and colleagues, at the Vaccine Research Center, National Institutes of Health, Bethesda, USA, investigated the molecular evolution of an HIV-specific unmutated ancestor antibody through its affinity maturation to an antibody with broadly neutralising capability [1]. These steps may be important guides for the development of a successful HIV vaccine.

Neutralising antibodies against the V1/V2 region of HIV gp120 are the most common cross-reactive neutralising antibodies in natural HIV infection.

They are characterised by long heavy chain complementarity determining region-3 loops (CDR-H3) that protrude, are anionic and are often tyrosine-sulphated. This extended antibody structure is able to penetrate the glycan shield of the HIV envelope protein in order to access its epitope.

Using antibody isolation, B-cell next generation sequencing, structural characterisation and viral single genome amplification Doria-Rose et al delineated longitudinal interactions between the developing antibody and autologous virus in one donor, CAP256, who demonstrated broad virus neutralisation one year after infection. In this individual, superinfection with a second virus was detected 15 weeks after infection with the initial primary virus.

B-cells were isolated from the donor at weeks 59, 119 and 206 after initial infection and used to isolate 12 somatically related monoclonal antibodies, denoted VRC26.01 through to VRC26.12. The same level of virus neutralisation achieved with the donor’s unfracti...
plasma was also achieved by use of all 12 mAbs in combination, suggesting this antibody lineage was responsible for the broad and deep neutralising capability of the donor's plasma.

Using a combination of negative stain electron microscopy, gp120-binding assays and neutralisation fingerprints, the researchers found that the epitope recognised by VRC26 antibodies was similar to that of the PG9 class of neutralising antibodies. This epitope is located at the membrane-distal apex of the gp120 trimer, the specificity of which is dependent on the trimer's quaternary structure.

Longitudinal sampling of B-cell immunoglobulin sequences with phylogenetic analysis revealed that the VRC26 lineage bifurcates from an unmutated common ancestor at about week 38 following infection, giving rise to one branch containing VRC26.01 and one branch containing VRC26.02-12. Thus this data identified the unmutated common ancestor, defined the product of gene recombination in the ancestor B cell and provided a genetic record of the lineage development over the following four years.

Analysis of crystal structures of the antibody Fab fragments of the unmutated common ancestor and six of the other antibodies revealed that the VRC-256 lineage began with an anionic protruding CDR H3, that has structural features similar to other V1V2-specific broadly neutralising antibodies. Over the course of four years almost 20 light chain and more than 30 heavy chain mutations were introduced, including a disulphide bond and the loss of the CDR H3 orientation and its negative charge, although tyrosine sulphation was maintained.

The development of the VRC-256 antibody lineage, together with the selective pressure exerted on viral evolution, were followed by viral single genome amplification (SGA) sequencing over 3 years. Distinct sequences were observed in the V2 region of gp120, which distinguished the primary infecting virus from the superinfecting virus, while substantial recombination between the two viruses had occurred. Before the VRC-26 lineage emerged, most V1V2 sequences in this donor were representative of the primary virus and were neutralisation resistant. While all 12 antibodies effectively neutralised the superinfecting virus, only one, VRC-26.06, neutralised the primary infecting virus. This suggests that the naive B cell that gave rise to the VRC-26 lineage was first engaged by the superinfecting virus.

As the VRC-256 antibody lineage emerged at week 38, a rare K169I mutation occurred in the superinfecting viral sequence that rendered it resistant only to the earliest antibody, VRC-26.01. Therefore VRC-26.01 effectively neutralised the superinfecting virus and drove the selection of mutations that enabled viral escape from this antibody. Once resistance to VRC-26.01 had been achieved, the viral population became predominantly composed of sequences represented by the superinfecting virus. Subsequent somatic mutation of the VRC-26.01 clone gave rise to the development of antibodies (VRC-26.02-12) that neutralised the superinfecting virus. These antibodies corresponded with consistent V1V2 sequences until further viral escape occurred that resulted in a net charge change in the V2 epitope while the VRC-26 CDR-H3s become less acidic. Together the data reveal the co-evolution of viral epitope and antibody specificity, in which the superinfecting virus epitope drove expansion of the VRC-26 lineage.

An effective HIV vaccine should elicit broadly neutralising antibodies. As many neutralising antibodies target the V1V2 region of env, the physical characteristics of the VRC-26 lineage that enable broad neutralisation should be a feature of vaccine-induced V1V2 antibodies: The ability to penetrate the glycan shield and access the V1V2 epitope because they have long CDR H3 regions. Such long CDR H3s only occur in the immunoglobulin VDJ gene rearrangements of an estimated 3.5 - 0.4% of naive B cells, and many of those are auto-reactive and therefore deleted, leaving an even smaller precursor population. This study found that the unmutated common ancestor of the VRC-26 lineage did have a long CDR H3, and that this feature itself did not arise as a result of somatic mutation. Importantly strongly neutralising breadth was achieved from the common ancestor relatively quickly, over a period of months rather than years, resulting from somatic mutation driven by antibody-virus interactions. The authors argue that the crucial factor in developing these antibodies are the engagement of B cells with uncommon receptors that have protruding, anionic, tyrosine-sulphated CDR H3s and that vaccine antigens should be screened that select such B cells.

References

Community reports and briefings

Migrant access to the NHS: implications of proposed changes

A briefing paper (March 2014) from the African Health Policy Network (AHPN) looks at the implications of the proposed NHS changes and whether this is justified by current evidence.

For example, redefining the eligibility criteria of “ordinary resident” to mean “indefinite leave to remain” unfairly targets many long-term migrants who work, study and pay taxes that contribute to the running of NHS services as well as other public services.

http://www.ahpn.org/
http://www.ahpn.org/Upload/page/155_Policy_Brief___Migrant_access_to_the_NHS_5.pdf (PDF)

Online journals

A selection of important HIV journals articles with free online access.

Early HIV infection in the United States: a virus’s eye view

Hallett TM
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001569

Tim Hallett reflects on the practical significance of new research by Erik Volz and colleagues on the influence of early HIV infection on disease epidemic dynamics.

HIV-1 transmission during early infection in men who have sex with men: a phylodynamic analysis

Volz EM et al.
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001568

Erik Volz and colleagues use HIV genetic information from a cohort of men who have sex with men in Detroit, USA to dissect the timing of onward transmission during HIV infection.

Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis

Drake AL et al.
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001608

Alison Drake and colleagues conduct a systematic review and meta-analysis to estimate maternal HIV incidence during pregnancy and the postpartum period and to compare mother-to-child HIV transmission risk among women with incident versus chronic infection.

Provider-initiated HIV testing and counselling for children

Davies MA, Kalk E
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001650

Mary-Ann Davies and Emma Kalk reflect on recent research by Rashida Ferrand and colleagues into barriers to provider-initiated HIV testing for older children in Zimbabwe.

Safety of pediatric HIV elimination: the growing population of HIV- and antiretroviral-exposed but uninfected infants

Mofenson LM, Watts DH
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001636

Lynne Mofenson and Heather Watts discuss the context and implications of the study by J. Sibuide and colleagues, which provides a detailed analysis of birth defects in infants with in utero antiretroviral drug exposure in the French Perinatal Cohort.

Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11)

Sibiude J et al.
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001635

Jeanne Sibiude and colleagues use the French Perinatal Cohort to estimate the prevalence of birth defects in children born to HIV-infected women receiving antiretroviral therapy during pregnancy.

HIV monoclonal antibodies: a new opportunity to further reduce mother-to-child HIV transmission

Voronin Y et al.
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001616

Yegor Voronin and colleagues explore how monoclonal antibodies against HIV could provide a new opportunity to further reduce mother-to-child transmission of HIV and propose that new interventions should consider issues related to implementation, feasibility, and access.

Changes in HIV incidence among people who inject drugs in Taiwan following introduction of a harm reduction program: a study of two cohorts

Huang Y-F et al.
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001625

Kenrad Nelson and colleagues report on the association between HIV incidence and exposure to a national harm-reduction program among people who inject drugs in Taiwan.
FUTURE MEETINGS

Conference listing 2014/2015
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.

18th Annual Resistance and Antiviral Therapy Meeting
18 September 2014, London
http://www.mediscript.ltd.uk

16th International Workshop on Comorbidities and Adverse Drug Reactions in HIV
6-8 October 2014, Philadelphia, USA
http://www.intmedpress.com

BHIVA Autumn Conference, 2014
9-10 October, London
http://www.bhiva.org

5th International Workshop on HIV & Aging
20-21 October 2014, Baltimore, USA
http://www.virology-education.com

9th International Workshop on HIV Transmission Principles of Intervention
25 26 October 2014, Cape Town, South Africa
http://www.virology-education.com

12th International Congress on Drug Therapy in HIV Infection
2-6 November 2014, Glasgow
http://www.hiv11.com

Five Nations Conference on HIV and Hepatitis
8-9 December 2014, London
http://www.bhiva.org

7th International Workshop on HIV Persistence during Therapy
8-11 December 2015, Miami
http://www.hiv-persistence.com

5th International Workshop on HIV & Women, from Adolescence through Menopause
21-22 February 2015, Seattle
http://www.virology-education.com

22nd Conference on Retroviruses and Opportunistic Infections (CROI 2015)
23-26 February 2015, Seattle
http://www.croi2014.org

HIV i-BASE

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

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http://www.i-base.info

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

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

The site also includes a web-based Q&A section for people to ask questions about treatment.
http://www.i-base.info/questions

We have also posted online a set of generic clinic forms, developed with the Royal Free Centre for HIV Medicine, which may be a useful resource for other hospitals.
http://www.i-base.info/clinicforms
**HIV i-Base**

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