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EDITORIAL

This bumper summer issue of HTB 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) and review studies related to transgender issues and HIV.

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.

Other news questions UK access to dolutegravir and the soon-to-follow single-tablet regimen. Have you commented yet?

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

New ARV prescribing guidelines for London are now released - and, so far, only apparently available on the i-Base website.

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.

And finally we report on a US Senate investigation of Gilead for the sofosbuvir price that has the potential to bankrupt Federal healthcare and add $300 annually to every American insurance premium for the next five years.

HTB supplement

The July 2014 edition of the i-Base Introduction to Combination Therapy is now available:

This is already online and additional print copies are available free, including in bulk to UK clinics. Please order online in the regular way.

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

CONFERENCE REPORTS

20th International AIDS Conference

20-25 July 2014, Melbourne

Introduction

This year the IAS conference was held under somber remembrance for the six delegates who were travelling to the meeting as passengers on flight MH17. This loss and their lives was included in many of the conference sessions and events.

In an early statement, the IAS confirmed that the meeting would continue in recognition of these individuals work and the broad goals that brought delegates, many of them travelling long distances, to focus on ending HIV.

Although the location this year is likely to have affected attendance - with approximately 14,000 delegates, compared to close to double this figure for the Washington meeting in 2012, this made the meeting easier to navigate.

As with previous meetings, the programme for the meeting is accessible online using the programme at a glance link from the conference website.

http://www.aids2014.org/

http://pag.aids2014.org/

Some programme sessions include the option to download PowerPoint slides for some of the slides (use the link underneath the full session listing), and some have links to webcasts.

Other webcasts are linked to the IAS YouTube channel:

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

Articles in this issue of HTB are:

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.

For this and many, many reasons, he will be hugely missed.

The follow links are are to just a few of the many tributes.

IAS. In remembrance: Professor Joep Lange.

http://www.iasociety.org/Joep_Lange.aspx

Hankins C. Remarks on the lives of Jacqueline van Tongeren and Joep Lange. AIGHD AMC Information Session, AMC Amsterdam, 24 July, 2014. Internationale AIDS Conferentie, EYE Amsterdam, 25 July, 2014.

http://aighd.org/media/medialibrary/2014/07/Remarks_on_the_lives_of_Jacqueline_van_Tongeren_and_Joep_Lange_by_Cate_Hankins.pdf

Mascolini Mark. HIV world loses Joep Lange, early outspoken proponent of triple ART. IAS. 18 July 2014.

http://www.iasociety.org/Default.aspx?pageId=5&elementId=15920

Piot P. Joep Lange obituary. The Guardian, 21 July 2014.

http://www.theguardian.com/society/2014/jul/21/joep-lange

Maurice J. Joep Lange obituary. The Lancet, Volume 384, Issue 9940, Page 302, 26 July 2014. doi:10.1016/S0140-6736(14)61052-7.

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61052-7/fulltext

Economist. Joseph Marie Albert Lange, AIDS researcher, died on July 17th, aged 59.

http://www.economist.com/news/obituary/21608567-joseph-marie-albert-lange-aids-researcher-died-july-17th-aged-59-joep-lange

AIDS 2014: TREATMENT AS PREVENTION

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 Stephens 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 Burandi and Uganda.

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

C O M M E N T S

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.

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1. Hill A et al. Higher antiretroviral treatment coverage is associated with lower adult HIV infection rates: analysis of 51 low and middle-income countries. 20th International AIDS Conference. Melbourne. 20-25 July 2014. Late breaker poster abstract LBPE29.
http://pag.aids2014.org/abstracts.aspx?aid=11070
2. Hill A. Is higher antiretroviral treatment coverage associated with lower HIV infection rates? 20th International AIDS Conference. Melbourne. 20-25 July, 2014. Workshop presentation TUWS1103.
http://pag.aids2014.org/abstracts.aspx?s=1967

AIDS 2014: TREATMENT ACCESS

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 sites 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.

C O M M E N T

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]

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1. Pozniak A. How can we evaluate simple sequences of first and second-line treatment in low-income countries? 20th International AIDS Conference. Melbourne. 20-25 July 2014. Workshop presentation TUWS1105.

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http://pag.aids2014.org/PAGMaterial/PPT/1486_1326/melbourne_trials_pozniak_july14.pptx (Slides)
2. Rougemont M et al. The MiniZID study: a randomized controlled trial on safety of reduced dose (400 mg) of zidovudine compared with standard dose (600 mg) in HIV-infected patients starting antiretroviral therapy. 20th International AIDS Conference. Melbourne. 20-25 July 2014. Poster abstract LBPE16. http://pag.aids2014.org/abstracts.aspx?aid=11206
3. Clayden P. Fit for purpose: treatment optimisation. i-Base/TAG. 19 July 2014. http://i-base.info/htb/26960

UNAIDS sets 90-90-90 target for 2020 to end AIDS by 2030

Simon Collins, HIV i-Base

The AIDS 2014 conference was notable for the launch by UNAIDS of a strategy with a target of eliminating AIDS by 2030. [1]

This included a 90-90-90 campaign outlined in report detailing new targets for testing and treatment. [2]

The target refers to three key steps that are essential to both better health and care for HIV positive people and to limiting new infections and the further spread of the HIV pandemic.

- 90% of all people living with HIV should know their status. Currently, 19 million people globally are estimated to be HIV positive and are not aware of their HIV status. [3]
- 90% of all those who are diagnosed HIV positive to be on sustained antiretroviral treatment (ART). While global access has advanced tremendously, with over 14 million people on treatment, double this numbers should be eligible for treatment in low- and middle income countries based on WHO 2013 guidelines that recommend a CD4 threshold of 500 cells/mm3 to initiate treatment. Using a "test and treat" model, increases the number of people eligible 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 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.

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1. UNAIDS. Press statement. Global leaders commit to ending the AIDS epidemic in cities by 2030. (20 July 2014). http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2014/july/20140720cities
2. UNAIDS. Ambitious treatment targets: writing the final chapter on the AIDS epidemic. (July 2014). http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2014/JC2670_UNAIDS_Treatment_Targets_en.pdf (PDF)

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 naïve 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): 11/1% 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.

C O M M E N T

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.

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1. Rougemont M et al. The MiniZID study: a randomized controlled trial on safety of reduced dose (400 mg) of zidovudine compared with standard dose (600 mg) in HIV-infected patients starting antiretroviral therapy. 20th International AIDS Conference. Melbourne. 20-25 July 2014. Poster abstract LBPE16. http://pag.aids2014.org/abstracts.aspx?aid=11206
2. Crawford KW et al. Optimising the manufacture, formulation, and dose of antiretroviral drugs for more cost-efficient delivery in resource-limited settings: a consensus statement. Lancet Infect Dis 2012 Jul;12(7):550-60. http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(12)70134-2/abstract

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 nudged up to 95% after adjustment for highest risk behaviour (receptive anal intercourse without a condom [UAI]). [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 (1678/2680) 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 showed 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 half life 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.

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

Drug levels (fmol/punch)	BLQ	LLOQ -350	350-699	700-1249	>1250
Estimated weekly dose	none	<2	2-3	4-6	7
% of follow-up time	25%	26%	12%	21%	12%
Patient years	384	399	179	316	181
Number of new infections	18	9	1	0	0
HIV incidence (95% CI)	4·70 (2·99–7·76)	2·25 (1·19–4·79)	0·56 (0·00–2·50)	0·00 (0·00–0·61)	0·00 (0·00–1·06)
HR vs previous placebo (95% CI) *	1·55 (0·88–2·56)	0·69 (0·32–1·32)	0·19 (0·01–0·88)	0·00 (0·00–0·25)	0·00 (0·00–0·50)
HR vs concurrent off-PrEP (95% CI) †	1·25 (0·60–2·64)	0·56 (0·23–1·31)	0·16 (0·01–0·79)	0·00 (0·00–0·21)	0·00 (0·00–0·43)

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.

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 level" 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 1.69, p < 0.0001), having five or more partners in previous three months (adj OR 1.57, p < 0.0001) and known positive partner (adj OR 1.40, p < 0.03). People older than 30 were twice as likely (aOR 2.02, p = 0.0002) and older than 40 were three times likely (aOR 3.16, p<0.0001) 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.

C O M M E N T

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 group). In iPrEX OLE, much of the potential protection was lost because of suboptimal adherence. Some level of consistent adherence is needed, preferably more than four doses a week, though missing occasional doses in a daily schedule has little impact on efficacy.

Irrespective of how effective PrEP is, and contrary to the conclusions in the AIDS 2014 presentation, it may be problematic to claim that 43% uptake is "high" especially when drug was provided free and from experienced PrEP providers. Public health officials who are worried about costs can perhaps breathe a little easier: daily oral PrEP will not be for everyone. Several community surveys have also reported that only about half of sexually active HIV negative gay men would be interested in using PrEP. [7]

The "PrEP cascade" as a concept is likely to get an increasing focus but needs to be interpreted carefully. Unlike the treatment cascade, where every loss has a clinical implication, each step for PrEP could be a positive outcome if it is selecting out those as lowest risk and focusing the intervention on those who need it most.

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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 co-ordinating 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 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 T-regs. 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 delta-32 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 clearance from an HIV positive long-term non-progressor, who was infected 33 years ago through transfusion and has been off treatment with no detectable viral load, perhaps due to infection with a poorly replication competent virus. [16]

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]

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AIDS 2014: TRANSGENDER RESEARCH

HIV and transgender issues at AIDS 2014

Simon Collins, HIV i-Base

Where available – and information is scare even from resource-rich countries – data increasingly report very high rates of HIV in transgender people, especially those who have sex with men. The lack of data is itself a key priority for trans activists, as "without data we remain invisible to services and providers". [1]

It is therefore appropriate that transgender people are one of the five groups that are the focus of the WHO consolidated HIV guidelines for key populations. The other four are: men who have sex with men, people who inject drugs, people in prisons and other closed settings and sex workers. [2]

In this article, the term trans* is used to refer to someone who identifies as a sex or gender that is different to the one they were assigned at birth.

At the launch of the WHO guidelines, Kate Montecarlo Cordova from the Association of Transgender People in the Phillipines, talked about the high vulnerability and specific health needs of transgender people. In many countries, the prevalence of HIV among transgender women is as high as or higher, than among men who have sex with men.

For example, in a meta-analysis published in 2013 of 11,066 transgender women from 14 countries - the US, Asia-Pacific (6), Latin America (5) and Europe (3) - the pooled HIV prevalence was 19·1% (95% CI 17·4–20·7). This proportion was similar independent of setting: 17.7% in ten low- and middle-income countries and 21·6% in five high-income countries. This data produced an odds ratio for being HIV positive in transgender women (compared with all adults of reproductive age) of 48·8 (95% CI 21·2–76·3). [4]

Although data and research are still limited, this trend appears to be slowly changing. A global search for "transgender AND HIV" on PubMed presented at the IAS conference in 2012 reported finding 98 results for 2010-2012, compared to only 65 results from 2007-1009 and 18 results from 2002-2006. [5]

This article briefly reviews the studies presented at the conference and includes interviews with two delegates who are working to ensure even greater presence of trans issues at the meeting in Durban in 2016.

To inform the new guidelines and as a result of its Civil Society Reference Group, WHO worked with trans people on a small qualitative survey (34 people, 14 in-depth interviews). The result stressed that transgender people's needs should be seen as separate from those of other populations (particularly independent of MSM with whom they are usually grouped). Guidelines should include a specific review of evidence and values and preferences, and a specific brief on young transgender people.

The new WHO recommendations are an important first step - but they are also dependent on supportive legislation (especially to tackle violence), decriminalisation, community empowerment and health services that are available, acceptable and accessible.

Criminalisation and the very real threat of violence were common themes in many of the sessions discussing transgender issues, including a symposium in the main programme on criminalisation, which is also available as a webcast. [6] The criminalisation session included legal case examples from the US, India, Nepal and Uganda.

Manisha Dhakal from Nepal focused on examples from the Nepalese legal system, which has a 100-year old code against "unnatural sex" (undefined in terms of specific activity) that is often misapplied and misused against transgender people, especially if they are sex workers. Trans* men are threatened with human trafficking charges if they have relationships with women. Both the police and judiciary lack understanding and transgender people who are the victims of crime are often punished rather than supported. More positively, in 2007 the government granted rights to transgender people including passport recognition for "other" gender status. There is some movement towards a same-sex relationship law and issues surrounding sexual orientation and gender identity policies are addressed in schools and universities. [7]

The issue of funding to enable adequate and sustainable development of trans* communities - directly related to the capacity to sustain this critical work - was the focus of another satellite (co-sponsored by amfAR, the American Jewish World Service (AJWS), and the Global Action for Trans* Equality (GATE). [8]

Although limited material from the meeting is available - a missed opportunity that is frustrating for many of these sessions - the presentation by Joe Wong, Asia Pacific Trans Network (APTN) is available online. [9] This talk summarised the findings from an extensive survey of 340 trans* and intersex groups globally, most of which work locally (only 22 work regionally and 6 work globally). Of these groups, 313 were mostly, or exclusively, comprised of HIV positive people.

The resulting 32-page report covers human rights violations against trans* and intersex people, key milestones for organising including the importance of being trans*-led (reported by 198 groups), current and future funding, and recommendations. Although the greatest number of groups came from the US (n=100), 54 organisations were based in Sub-Saharan Africa and 51 were from the Caribbean, Central America and South America. Median annual budgets (91 organisations) were less than US $5,000 (including 66 unfunded groups), and were lower for trans*-led groups. Only seven organisations have a budget higher than $1 million. [10]

Other notable sessions covering transgender issues in the AIDS 2014 programme include:

- An oral abstract session (abstracts, slides and webcasts all available) with presentations covering HIV risk in transgender communities, disclosure and persecution, ART support and housing. [11] This session included a webcast on the positive effect of progressive Argentinian legislation that supported transgender identity and rights that within one year and directly lead to greater empowerment through schools, education, work and civil society. The webcast is essential viewing and a model for the future. [12]
- A peer-led workshop on trans* men who have sex with men – a group that are rarely considered in HIV-related and LGBT-produced health resources. [13]
- A presentation on trans* women and drug use by Nyah Harwood from the Centre for Social Research in Health at the University of New South Wales and the International Network of Women who use Drugs. The lack of scientific data in this talk was directly related to transgender people not historically having an assigned epidemiological category: "The norms of sex and gender that underpin most existing research methodologies constitute trans people as invisible and therefore erase them, characterising the lives of trans women with extraordinary physical and structural violence". [14]
- A focus on sex work among transgender women as part of the Lancet special issue on HIV and sex work. [15] Despite higher HIV risk, there are almost no interventions focused on this population and changes need to be grounded in empowerment and led by communities. This presentation pointed out the lack of data on the risk related to gender-related surgery.
- On a policy level, at another satellite meeting on sexual and reproductive health and rights, organised by the International Planned Parenthood Federation (IPPF), Leigh Ann van der Merwe, a transgender woman from South Africa, stressed the importance of including sexual and gender minorities in the post-2015 Millennium Development Goals, as part of a platform that also included young people living with HIV, sex workers, and people who had experienced gender-based violence. [16]

A quick search of the AIDS 2014 online programme found 28 sessions and 105 abstracts with the word transgender. This compared to 19 sessions and 135 abstracts from the Washington conference in 2012.

But, although this year the IAS conference included transgender issues throughout the programme and in more sessions, the presentations were overwhelmingly in the community-based satellite meetings rather than the main conference, or in the Global Village - the community counterpart to the more sober scientific and policy sessions. Very few sessions were webcast.

Sometimes the IAS World AIDS Conference can be seen as two separate meetings. It is not unusual - and always disappointing - to hear that someone has been so busy with one venue that they hardly left it to interact with the other. The crossover should be the point of the conference. If not, the benefit from community networking is unlikely to affect the research and policy agenda and, conversely, researchers will remain too removed from the people whose lives they hope to change with their work.

C O M M E N T

Perhaps the most positive presentation was the results of legal changes in Argentina, which dramatically affected the quality of life for transgender people and showed the importance of policy changes.

Similar changes should be easy in the UK, yet many NHS services including HIV clinics do not cater appropriately for transgender people. Trans* people are invisible in sexual health and HIV data collection and do not receive appropriate informed services.

For example, we have no real statistics in the UK for how many trans* women and trans* men are HIV positive. At present the only dedicated community-led sexual health, HIV and holistic well being service for transgender people is a weekly clinic at at 56 Dean Street in Soho called cliniQ. [16]

Michelle Ross, co-founder of cliniQ commented that: "We are proud of our achievements, but we are not proud to be the only such service. There needs to be a European, UK response on HIV in trans* communities that has parity to the excellent work being done in the US by Centre of Excellence and people like JoAnne Keatley".

"Some of the very real barriers as to why many trans* people do not access mainstream sexual health service; are issues of being mispronounced, misgendered, and lack of awareness of trans* health needs. Sexual health services in the UK are gradually and slowly becoming aware of how much this is a concern. This is mainly through the activism of some trans* people who are committed to bringing an awareness of the issues of HIV and holistic sexual health by providing community led, culturally appropriate services for trans* people, partners, and families. Trans* people's issues on HIV are global issues of human rights and equality."

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Transgender services and clinics: interviews at AIDS 2014 with JoAnne Keatley and Beatriz Grinsztejn

Simon Collins, HIV i-Base

The following two short interviews are included to complement the review article on transgender issues at the AIDS 2014 conference. JoAnne Keatley is a leading transgender activist and Dr Beatriz Grinsztejn developed the first transgender HIV clinic in Rio de Janiero.

The first interview is with JoAnne Keatley, director of the Centre of Excellence for Transgender Health at University of California, San Francisco; and co-chair of the International Reference Group on Transgender People and HIV (IRGT).

Q: Hi JoAnne, we are at AIDS 2014 and one of the slides used in many of the transgender sessions shows global rates of HIV in transgender people and also highlights the lack of data from many countries. I wondered whether you could talk about how you captured data in California and why this is important.

A: It is essential to get a better idea of how many of us exist and then also look at the health issues that are impacting our communities. As trans people, if we are not counted we just don't count.

So as an advocacy point we came up with a standardised way to capture gender variance and trans identities universally across governments and through organisation such as WHO. We are often collapsed with other groups, and we sometimes overlap with other communities, but we have our own specific issues.

HIV impacts transgender communities differently due to the social determinants of health. The stigma and discrimination that trans people are exposed to on a daily basis are the main drivers of the HIV epidemic among trans people.

Q - It sounds tough. You describe life as being vulnerable.

A - It is very tough, especially when your very existence is criminalised. In many countries, a trans person can be arrested or be a victim of violence, just because of who they are. Many in the trans community are victims of violence from the authorities and from the police. The people who are charged with protecting civil society from harm are often perpetuating the violence against us. We have a lot of work to do.

Q - My impression from AIDS 2014 is that there is more transgender awareness in the programme than at previous meetings.

A - I agree there are lots of sessions with papers that include references to trans people. The reason for increased participation is because there has been a lot of advocacy from the trans community, to assure we were adequately, or at least better represented, than for example, in Washington DC when there were zero sessions that were specific to trans populations in terms of scientific papers being presented.

Although the International Reference Group for Transgender People organised the trans networking zone in the Global Village – where we have had many activities – we have not been as prevalent or as visible in the decision making and policy work that happens inside the scientific sessions.

Sometimes you see sessions about "MSM and transgender people" or "key populations" and they break down the key populations. But although the research may have had some trans involvement, this is not always the case. It is one thing to say a study or trial or even a service programme is inclusive of trans people, but I always want to see the numbers and the level of involvement. I want to know whether transgender issues are just an afterthought, and if so, this is not good enough.

Q - So it sounds like a good goal for future meetings is for transgender issues to be included in more of the scientific and policy sessions?

A - Yes, and it is time that we consider a trans plenary that has trans people on the panels. It seems crazy that it is not already here after more than thirty years of the epidemic.

Q - What has been your highlight from this meeting?

A - As always, it has been networking with my own community and being able to move policy makers so we can continue to strive for change. The highlight is always engagement with my and other communities that share in the struggle and supporting each other works, even when these are sometimes baby steps.

Q - Could you talk a little about the service you set up in California. Is it an HIV-specific clinic, or is sexual health and well being?

A - The Centre of Excellence for Transgender Health is a capacity building assistance and technical assistance provider in the US and beyond. It develops treatment advocacy and educational materials for transgender populations (http://www.transhealth.ucsf.edu). We document and disseminate best practices for linking and providing services to transgender communities.

We have a clinic and a medical doctor is part of our team, providing primary care services, but her practice is not specific to HIV.

The Centre is also a collaborative effort between the Centre for AIDS Prevention Studies at UCSF and the Pacific AIDS Education and Training Centre. We put together training materials and educate health providers about services for trans people. We also run one of the largest domestic funded programmes from the US government focused on trans populations, called the Trans Women of Colour Initiative for which we are the evaluation and technical assistance centre.

There are nine sites around the US that are delivering care for HIV positive transgender women, including cross sex hormone therapy, as part of the treatment model and ARVs. There are two clinics in each of NYC, Chicago and Los Angeles and three in the Bay Area, San Francisco.

The clinics are tasked with finding new cases of HIV in the trans community, testing and engaging with these women, linking them to care and supporting them to stay in care, and then tracking the outcomes over time. We are 18 months into a five-year project designed to find the best practice. It is very exciting.

Q - Roughly how many people are involved?

A - We currently have about 180 women enrolled into care but we only started enrolment seven months ago. I always feel very fortunate to have the opportunity to do this work and to give back to my community.

Q - Thank you, you are doing fantastic work.

The second interview was with Dr Beatriz Grinsztejn, the director of the STD/AIDS Clinical Research Laboratory at the Clinical Research Institute Evandro Chagas (IPEC/FIOCRUZ), Brazil.

Q - Hi Beatriz, I was impressed that your presentation at AIDS 2014 included transgender services and I remember you were just setting up a trans clinic for HIV positive people in 2005.

A - Yes, one of difficult things we had to deal with was stigma. When setting up the clinic we knew we needed to train staff so that clients would feel welcomed and would want to come. Our HIV clinic is based in a large hospital and is on the main campus of a large research foundation.

Now, as we are getting more trans people coming we put together a training curriculum to make sure everyone in the hospital is trained. This includes administrators and porters, so they know how to provide services that are inclusive. The clients are coming to get services and if they feel stigmatised they won't come.

Q - Can you talk about who uses the services, how they know about the clinic and the main issues you face?

A - The main clinic sees 3,300 HIV positive people, about 45% of whom are MSM. The transgender clinic now includes about 120-150 people,

mainly trans women. It took a time to build this up with people coming because they heard about us from friends and peers. It is a strong community with a lot of connections. One of the main problems is late diagnosis.

Sometimes people are very sick and have very low CD4 counts - they only come because their peers bring them. I might get a call asking: "Can bring a friend who is not doing well". These cases will nearly always be HIV-related.

In Brazil, across all groups, about 30% of people have a CD4 count that is already below 200 when they are diagnosed, even though ARVs are free. This is probably even lower for the transgender clinic. Unfortunately, whatever the guidelines say about starting treatment, a lot of people still don't get tested. It is slowly getting better because testing is being expanded to community organisations and we hope this will help things improve.

Q - Did the transgender clinic integrate easily in the general HIV services or was this run at different times?

A - No, definitely not, we did not want the services to be separated - if you separate people within the clinic you create ghettos. Some people took a while to get used to the bathrooms as we made sure that these were not gender specific. We took down the signs for men and women and this has worked better for everyone.

Q - Can you say something about services for trans women? Is transition surgery available at the same clinic?

A - Our team includes an endocrinologist to provide support about drug interactions with hormones and ARVs. It is very important to have someone who knows about this. We also have a trans peer support group. Transition surgery is now available as part of public health system but it takes a lot of steps. This takes place at a different hospital and although our clinics do not formally connect, we know the referral services. HIV testing is part of pre-surgery evaluation and HIV positive people are still able to have surgery.

Q - In London we have been asked about people who are using hormones from the Internet, especially if they are not registered with a clinic or if their residency status was difficult. Does this happen with your clients too?

A - You definitely need a doctor to do this prescription, especially if you are on ARVs. Drug interactions are serious and can affect your HIV treatment. Another issue we have comes from complications of self-injecting fillers. Many of our clients are poor and deep tissue infections and abscesses can be a common complication if they have injected bad quality silicon.

Q - Are you involved in sexual health service for HIV negative trans women?

A - Yes, we offer all HIV prevention services. We are planning a PrEP demonstration study for high risk MSM and trans women. We are advertising but not yet recruiting - this is not a clinical trial. It is difficult to get people to the clinic without providing the drugs yet. I love the chance that we may be able to offer PrEP.

Q - Finally, we are at AIDS 2014 and lots of activists are hoping for transgender issues to be included in the main conference programme for the next meeting. Do you have any influence in the IAS to help to include transgender people on the panels?

A - Yes, I am co-chairing Track C, so I will do it!

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AIDS 2014: PUBLICATIONS & REPORTS

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 pipleine 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.

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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 other 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 is 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

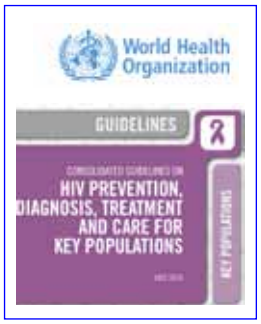
Issue brief 5: Getting to Undetectable: Usage of HIV Viral Load Monitoring in Five Countries (July 2014)

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 recommend-ations 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]

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CONFERENCE REPORTS

6th International Workshop on HIV Paediatrics

18-19 July 2014, Melbourne

Introduction

The International Workshop on HIV Pediatrics 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 Pediatrics are published in Reviews in Antiviral Therapy & Infectious Diseases 2014_6:

http://regist2.virology-education.com/abstractbook/2014_6.pdf

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 IeDEA 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 1 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 (EVG) 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 diarrheoa) 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 participants 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 and M184V in 5/20.

There were no deaths. Most frequent adverse events were: sinusitis (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/1.73 m^2 (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.

C O M M E N T

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

http://i-base.info/htb/26966

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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 NRTI 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 EFV-containing regimen as long-term maintenance therapy 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 Stehlau 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 3.4mmol/L, or 131mg/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 Strelau 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".

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.

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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. 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 (6%) 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.

C O M M E N T

Retrospective data from a case note review of children with limited options that received 3TC montherapy 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.

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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 d4T 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 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.

C O M M E N T

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.

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Time to first-line failure in the IeDEA cohort

Polly Clayden, HIV i-Base

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 73-423).

The majority of children (97.7%) started with 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; triple NRTI 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; age 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

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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.

C O M M E N T

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".

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CONFERENCE REPORTS

8th International Workshop on HIV Treatment, Pathogenesis and Prevention Research in Resource-Poor Settings (INTEREST)

5-6 May 2014. Lusaka, Zambia.

Introduction

The 8th International Workshop on HIV Treatment, Pathogenesis and Prevention Research in Resource-Poor Settings (INTEREST) was held in Lusaka this year.

The workshop includes presentations from and for participants mainly from African countries. This years meeting included a number of studies by Zambian researchers.

Presentations this year included plenary talks, abstracts, overviews and discussions. Topics included WHO guidelines, antiretrovirals, cure, hormonal contraception, resistance in Africa, pregnancy and PMTCT and PrEP.

Workshop materials including the programme and abstracts are online.

http://www.infectiousdiseasesonline.com/event/workshop/8th-interest-2.

The abstracts of the 8th INTEREST are published in Reviews in Antiviral Therapy & Infectious Diseases 2014_3, and are available in PDF format online.

http://regist2.virology-education.com/abstractbook/2014_3.pdf (PDF)

The slides are online at:

http://www.infectiousdiseasesonline.com/8th-interest

Articles in this issue of HTB are:

- 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

Short-term safety of atazanavir/ritonavir-based second line treatment in Zambia

Polly Clayden, HIV i-Base

Atazanavir/ritonavir (ATV/r) was well tolerated in a Zambian cohort according to data presented at 8th INTEREST.

The Zambian HIV treatment programme introduced ATV/r as an alternative second-line protease inhibitor to lopinavir/ritonavir (LPV/r) in 2013. There are currently limited data describing the use of ATV/r-based regimens in sub-Saharan Africa.

Mpande Mukumbwa-Mwenechanya from the Centre for Infectious Disease Research in Zambia showed findings from an evaluation of adults who started ATV/r-based second-line ART at the University Teaching Hospital in Lusaka between November 2012 and February 2014. The investigators used multivariable logistic regression to assess potential risk factors – age, sex and transaminases – for hyperbilirubinaemia.

The investigators found, of 103 patients receiving an ATV/r-based regimen with evaluable data, 44 (43%) had no prior exposure to LPV/r and 59 (57%) were switched to ATV/r because of suspected LPV/r-related side effects (gastrointestinal intolerance and hyperlipidaemia).

The participants were similar in both treatment groups: median of 42.5 years old and had been taking ATV/r for a median of 7.5 months (IQR 6-11) and just over a third were men.

The majority reported no side effects (n=90, 87%). The participants most commonly reported yellow eyes (n= 8, 8%). Hyperbilirubinaemia was the most common adverse event overall (n= 19, 18%). The range was 27.5 to 141 umol/L and it was not associated with age, sex or elevated transaminases: HR 1.02 (95% CI 0.98-1.06), HR 0.82 (95% C: 0.31-2.14), HR 0.92 (95% CI 0.41-1.87) respectively. Only one participant stopped his ATV/r-based regimen due to severe abdominal pain.

C O M M E N T

Although a small and short-term study these data are reassuring. The LPV/r monopoly is quite entrenched for second-line in low-income settings, despite generic co-formulated ATV/r being available and generally considered to be a more tolerable protease inhibitor.

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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-naive, 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, 1432 (16%) received ART for 1-8 weeks, 1672 (19%) for 9-20 weeks and 192 (2%) 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 were no not statistically differences 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 gravidity 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.

C O M M E N T

The data on outcomes presented here seem reassuring.

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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 Kafue 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.

C O M M E N T

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.

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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 Ndlovu 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.

The prevalence of nucleoside reverse transcriptase inhibitor (NRTI) mutations was 69%, the most common were M184V in 63% and K65R in 28%. For non-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.

C O M M E N T

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.

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ANTIRETROVIRALS

Dolutegravir-based single-tablet regimen set for EU approval

Simon Collins, HIV i-Base

On 27 June 2014, ViiV Healthcare issues a press statement noting a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for approval of a single tablet regimen (STR) of dolutegravir/lamivudine/abacavir. [1]

A positive opinion from this European Medicines Agency (EMA) advisory committee, usually predicts successful approval in Europe within two months.

The indication is for the treatment of HIV infection in adults and adolescents aged 12 years and older and weighing at least 40kg.

C O M M E N T

The EU approved dolutegravir in January 2014 but broad UK access is still dependent on the final outcome of the Medicines Optimisation Clinical Reference Group (CRG) recommendations. [2]

This has been put out for a three month comment period that will delay UK access to dolutegravir until at least mid October. Public engagement in this process may be essential to minimise further bureaucratic delays by the NHS - and this may become increasingly important for future drugs.

Comments on the proposed commissioning policy should be made online by 17th September 2014. [3]

Hopefully the same process with not need to be repeated for the STR, although access will also be connected to the price set by ViiV.

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GUIDELINES

WHO guidelines for key populations: gay men, people who inject drugs, people in prisons, sex workers, transgender people

Launched at AIDS 2014, 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.

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/

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EASL update guidelines for hepatitis C (April 2014)

Responding promptly to the approval of new drugs in the EU, this update is notable no longer requiring separate management guidelines for HIV positive people who are coinfected with hepatitis C, based on efficacy and safety of DAAs, though this is dependent on access to DAAs.

Treatment options using sofosbuvir, simeprevir and declatasvir - now all approved or available in the EU - are given by HCV genotype.

http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-C.pdf (PDF)

New ARV prescribing guidelines for London (April 2014)

Simon Collins, HIV i-Base

New guidelines for prescribing HIV drugs in London are now available.

These guidelines are effective from April 2014 and although not yet posted online by the NHS, the summary slides are available in PDF format. [1]

The guidelines are the result of a therapeutic tender that encourages drug manufacturers to offer volume discounts for use at different stages of the treatment pathway, for example, for preferred use in first-line, second-line and multiple resistant treatment.

Procurement on a London-wide basis aims for equity of ARV access across the capital by ensuring all hospitals pay the same prices for these medicines. This process has been driven by government-imposed budget constraints across the NHS, that since 2011 has made no annual increase for inflation. Since April 2011, the HIV tender have saved more than £10 million from the drug budget. [2]

This is the first major update to the initial 2011 guidelines and proposals this year should save a further £4.8 million. This is approximately 2.5% of the total drug budget.

Irrespective of drug costs, the primary focus for the guidelines is to outline the best standard of clinically appropriate care. This aspect of the recommendations is guided by a sub-committee which includes key consultants, pharmacists and community advocates.

Key recommendations

Informed patient choice should be central to all treatment decisions.

Preferred first-line treatment remains abacavir/3TC plus efavirenz, when clinically appropriate (as previous guidelines).

Tenofovir/FTC is the preferred alternative to abacavir/3TC (as previous guidelines).

The preferred alternative to efavirenz is now raltegravir (as this is a twice-daily drug, this a significant change).

Access to further options is based on clinical decisions (rather than patient preference). These include atazanavir/r, darunavir/r, Eviplera or Stribild and require referral to a virtual clinic.

The virtual clinic (at least for PI/r use) can be retrospective and appears primarily as part of an auditing process.

There is no requirement to switch for people currently already on treatment. However, people currently stable on PI/r-based therapy or the FDC Eviplera (rilpivirine/tenofovir/FTC) should be offered the option to switch to raltegravir.

Generic formulations are recommended for some drugs when like-for-like formulations are available.

In line with current national policy, Atripla and Kivexa do not need to be split to use separate generic options and there is no recommendation to switch from nevirapine PR 400 mg once daily to generic nevirapine.

First-line therapy

The 2014 recommendations are predominantly focused on first-line treatment. Budget targets can be met from the management of drug choices for people starting treatment, rather than from changing treatment for people who are already receiving it.

As in 2011, the preferred Initial treatment is abacavir/3TC plus efavirenz. If abacavir/3TC is not clinically appropriate (due to drug resistance, HLA B*5701 positive, viral load >100,000 copies/mL or high cardiovascular risk), then tenofovir/FTC is recommended. If efavirenz is not clinically appropriate (due to drug resistance, CNS toxicity, anxiety/depression, shift work etc), then the integrase inhibitor raltegravir is recommended.

The exclusive recommendation for raltegravir as an alternative to efavirenz is the most significant new change. It is also problematic, as raltegravir is a twice-daily drug, and national and regional guidelines (since efavirenz was first approved in 1998) have consistently recognised the benefit from once-daily treatment.

Twice-daily combinations can be very effective for some people. In some studies few differences are seen compared to once-daily combinations. However, people taking part in these studies have all consented to multiple dose combinations. In real-life settings, the frequency of daily dosing complicates adherence and is one of the key factors for HIV positive people when deciding on choice of treatment.

In 2014, access to alternatives to efavirenz now requires an additional level of bureaucracy through referral to a virtual clinic or other multidisciplinary team. This includes the option to use a once-daily boosted protease inhibitor (PI/r) - atazanavir/r or darunavir/r - both of which are already prescribed very widely. A late amendment to the guidelines, noted that this review clinic could be retrospective, making this an auditing process rather than one based on patient care.

There is also a concern that the reasons given to use alternatives to efavirenz or raltegravir are baseline drug resistance or concerns about adherence.

This is a point in the guidelines where patient choice should have been emphasised, and its omission here is not helpful. HIV positive people should be able to simply prefer a once daily to a twice daily combination, if this is important for them, because of how it fits with their life. In 2014, this should not need to be described as a “concern for adherence”. It should be a preference.

But, at the launch meeting for the guidelines on 4th June it was clarified that the guidelines are not designed to restrict access to boosted atazanavir or darunavir, both of which are still expected to be widely used. [3]

Higher cost single tablet regimens (STRs)

The STRs Eviplera (rilpivirine/tenofovir/FTC) and Stribild (elvitegravir/cobicistat/tenofovir/FTC) can still be prescribed when clinically appropriate, but only after review by a virtual clinic. The guidelines are unclear about whether this review can also be retrospective. Although details of prices from the tender outcome are not published, this implies that Eviplera and Stribild in London remain significantly more expensive than other recommended combinations.

Eviplera is included as an option when efavirenz, raltegravir, atazanavir/r or darunavir/r are not suitable, but only if baseline viral load is <100,000 copies/mL.

Stribild can be prescribed if Eviplera is not suitable, in line with NHS England commissioning policy. [4]

People on stable treatment

The guidelines do not include recommendations to change people who are currently stable on existing treatment. There is no indication to switch between atazanavir and darunavir unless clinically indicated.

However, the guidelines recommend that raltegravir should be "offered" to people who are currently stable on either protease inhibitor based combinations or on Eviplera. Although the guidelines note that raltegravir may have clinical benefits of fewer drug interactions and a reduced impact on lipids than boosted PIs, this offer is likely to be driven by a new lower price for raltegravir.

People who are happy with a twice-daily combination might prefer raltegravir, so broader access to an integrase inhibitor in first-line combinations is welcomed.

Fixed dose combinations and generics

Fixed-dose combinations are not specifically recommended for any intrinsic benefits of requiring fewer pills, but they can be used when the individual drug components would be appropriate. The guidelines use this indirect wording to say that Atripla can be prescribed when it falls within the guidelines, but that this is not based on data showing particular benefit from having three drugs in a single pill.

There is no indication to switch treatment for people currently on Atripla to generic efavirenz plus Truvada, or to switch people on Kivexa to abacavir plus generic lamivudine.

Similarly, there is no requirement to switch people who are currently on once-daily prolonged release (PR) nevirapine 400 mg tablet to the generic immediate release (200 mg twice-daily) formulation.

Boosted-PI monotherapy

It is notable that boosted PI monotherapy is not recommended, as this has been used as a cost saving strategy for several years in other countries, including Spain. [5]

Boosted PI-monotherapy is only recommended when the decision not to use either Kivexa and Truvada is clinically driven. In these cases, boosted darunavir is recommended and boosted atazanavir monotherapy is specifically not recommended.

Dolutegravir

Although dolutegravir was approved in Europe in January 2014, NHS England has not yet made a funding decision. The initial stakeholder consultation was recently completed and a further three- month open consultation has just started. [6]

This makes broad access to dolutegravir unlikely in the UK until at least mid-October.

The London guidelines note that they are only going to consider dolutegravir after the NHS publishes this decision.

Audit

A prospective audit is planned for all patients who start HIV treatment and then switch within six months.

An additional audit will be carried out for clinics using higher proportions of non-efavirenz containing combinations, although details for how this is defined is not included in the document.

Patient choice and quality of life

The guidelines include a principal that patient choice should be central to all treatment decisions and that "patients should be given the opportunity to be involved in decisions about their treatment".

This aspect is especially important given the differences between drugs that have broadly similar efficacy and costs but that have very different lifestyle-related factors, including dietary restrictions, numbers of daily doses, psychological factors including anxiety and depression and shift work.

Community input was allowed at many stages of this process. However, including community representatives in the final decision-making group is essential, and unlike 2011, this did not happen this year. It is not acceptable for HIV positive people to be seen as just another stakeholder in this process. We are the patient focus for these recommendations.

Evidence base

At the time of HTB going to print, the evidence base for the guidelines had still not been published.

C O M M E N T

The guidelines continue to outline a high standard of care that should remain broadly similar across London. As long as all individual drugs remain available, this should also minimise the difference in prescribing practice in other parts of the country.

But, in 2014, anyone starting treatment in the UK should have the option of a once-daily alternative to efavirenz. As cost savings are not given for the recommendation to use raltegravir, the option to use once-daily treatment should be a personal choice. This is a preference related to quality of life that should not be reduced to a medicalised "concern over adherence" in patient notes.

It is significant that there is no requirement to split Atripla or Kivexa - to use generic efavirenz and lamivudine, respectively, or to move back to off-label use of twice-daily generic nevirapine. Also, that boosted-PI monotherapy is not recommended. Although the PIVOT study recently reported that this could be a potential strategy that does not compromise long-term treatment options, approximately 35% of patients experienced low-level viral rebound that required restarting NRTIs. [7]

Although the final guidelines were circulated following a launch meeting on 4th June, the document has not yet been posted online, so are linked below. [1]

Simon Collins is one of the community representatives on the London Drugs Sub-Committee. However, it is not acceptable that community representatives were not included this year in the decision-making meetings responsible for producing the final guidelines.

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SIDE EFFECTS AND COMPLICATIONS

Bone mineral density linked to inflammatory markers in HIV positive people who are ART naïve

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 mechanistic 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.

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BASIC SCIENCE & CURE RESEARCH

Effects of long-term ART initiated during primary HIV infection on reservoir size

Gareth Hardy, HIV i-Base

A study conducted by Maria Buzon and colleagues at Massachusetts General Hospital and Harvard University, sought to determine whether intiation of ART during primary HIV infection could limit the seeding of viral reservoirs. [1]

The research group focused on a group of nine HIV positive people who had begun ART during primary HIV infection, defined as within 6 months of infection. A cohort of 26 people who had initiated ART during chronic infection were used as controls. Both groups had maintained uninterrupted ART for at least ten years. In addition, a cohort of 37 elite controllers who had maintained undetectable viral loads for eight years in the absence of ART were recruited as a reference population. In terms of age, sex, baseline viral load or CD4 counts, or the time to achieve undetectable viral load after ART initiation, there were no differences between the groups that started ART during primary or chronic infection. Despite this, increases in both CD4 T cell counts and the CD4/CD8 T cell ratio were more substantive in the group that initiated ART during primary infection.

Cross-sectional analysis of CD4 T cell HIV DNA levels was performed after ten years ART for the primary and chronic treatment initiation groups and eight years for elite controllers. As expected, elite controllers demonstrated significant reductions in all forms of HIV DNA compared with people who had initiated ART during chronic infection: total HIV DNA (p < 0.0001), 2-LTR HIV DNA (p = 0.015) and integrated HIV DNA (p < 0.0001). Of interest was the contrasting observation that levels of HIV DNA in subjects who initiated ART during primary infection were comparable to those of elite controllers and much lower than those of subjects who initiated ART during chronic infection.

Levels of replication-competent HIV were also determined in the ART-treated cohorts at this time using a previously described viral out-growth assay. Replication-competent HIV was recovered from 3/8 elite controllers, 5/8 people who initiated ART during primary infection, and 9/11 people who initiated ART during chronic infection. 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 HIV 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+/-0.01 (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 month 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)
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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 unfractionated 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 phylogenic 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.

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HEPATITIS C

US Senate investigate Gilead for sofosbuvir price: potential to bankrupt Federal healthcare and add $300 annually to every American insurance premium for the next five years

Simon Collins, HIV i-Base

On 11 July 2014, the Committee of Finance of the US Senate – which has jurisdiction over social security funded health programmes (including Medicare and Medicaid) – wrote to Gilead Sciences CEO John Martin. The letter contained a comprehensive list of demands for disclosure of documents relating to the development, pricing and marketing costs for sofosbuvir, including all papers relating to Gilead's acquisition of Pharmasset (who led early development of this drug) and is available online. [1]

The investigation is into Gilead's decision to charge $1000 for each sofosbuvir pill. A 12-week course of treatment costs $84,000 for the sofosbuvir component (additional meds are required) but for people requiring 24 or 48 weeks of treatment this increases to $168,000 and $336,000, respectively.

An estimated 3.2 million Americans are living with hepatitis C, more than half of who are incarcerated. Even if Medicare only treated 75,000 people in the next year, this would increase programme costs by $6.5 billion and increase premium costs for all enrollees by 8%.

Given such an impact on federal health programmes, the Committee is now investigating whether the price the Gilead set is "competitive, fair and transparent". The letter raises this issue in the context of development costs for sofosbuvir at Pharmasset which for the three years from 2009-2011 was less than $180 million, with only $62 million directly attributed to sofosbuvir. It also notes the significant difference between the 44% discount offered to treat US prisoners with the 99% discount arranged with the Egyptian government.

The Committee also raises the "substantial risk of a conflict of interest" between individual panel members of the three main professional associations responsible for producing treatment guidelines - the American Association of the Study of Liver Disease (AASLD), the Infectious Diseases Society of America (ISDA) and the International Antiviral Society-USA (IAS-USA) - with 17 out of 27 members disclosing either direct or indirect financial relationship with Gilead.

The letter demands breakdowns of marketing costs and patient assistance programmes (through which, 30,000 people have received sofosbuvir in the US).

Gilead has 14 days to start producing information and 60 days to produce the complete dossier.

The price of sofosbuvir is also estimated to have a dramatic impact on private healthcare in the US.

In a letter to the Journal of American Medicine, CVS Caremark, one of the largest US pharmacies has estimated that the current price of sofosbuvir could add $200-$300 a year to every American insurance premium for the next five years. It also notes that universal treatment in the US alone would generate more than $250 billion for Gilead, and this would be inappropriately high at more than a 20-fold return on the acquisition cost of Pharmasset. [2]

C O M M E N T

The scope of this Senate committee investigation into corporate greed is interesting for several reasons. And this PR disaster for both Gilead and its shareholders is not going away.

Firstly, it reconnects drug pricing to the actual cost of development, including marketing - which in this case appears well under the $1 billion commonly quoted - and which has already been recouped many times over during the first months of licensing (Gilead earned over $3 billion in the first quarter of 2014). Gilead have so far tried to justify the price based on a model of potential lifetime savings compared to current treatment. [3]

The acquisition costs of $11 billion for a compound that had cost well under $200 million to develop, makes Pharmasset equally responsible for this low point in healthcare research.

Secondly, it raises issues of ethical pricing in the context of population need and the overall ability for any health system to be able to adequately provide treatment for the majority of people who need it. Gilead's price, by definition, limits access to less than 1% of people with hepatitis C, even in rich countries. The investigation challenges the ethics of allowing a company absolute freedom in setting a price for a medicine.

Most shamefully, Gilead could easily have recouped the same level of profits by setting a significantly lower price – given the numbers of people needing treatment – and treating far more people. Setting a price that excludes more than 99% of people who could benefit from treatment is difficult to interpret as anything but greed.

Thirdly, it highlights the very low production costs that enable a 99% discount to Egypt to still be financially viable and profitable for the company. Independent analyses of manufacturing costs are estimated at less than $200 for a three-month course of treatment. [4] Importantly, this work has driven a community demand for total cost of HCV treatment to become US$500 or less for low- and middle-income countries. [5]

Whether this Senate committee has the resolve to change things or this is simply window-dressing in preparation for the next US elections, also remains to be seen.

In the UK, where more than 200,000 people are estimated to be living with hepatitis C, the price of sofosbuvir has forced the NHS to only commit to using it to treat 500 people with the most advanced liver disease. It also forced NICE to examine cost effectiveness for each combination of HCV genotype and stage of infection together with each permutation of prior HCV treatment history. [6]

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ON THE WEB

Community reports and briefings

Report: 1st Hepatitis C Virus World CAB

This report is from the First Hepatitis C virus (HCV) World Community Advisory Board (CAB), held in Bangkok, Thailand, 22–25 February 2014.

The objectives of the meeting were to:

- Provide a forum for leading activists to learn about developments in HCV treatment and access barriers
- Find common advocacy strategies
- Meet with pharmaceutical companies about their plans for low- and middle-income countries (LMICs).

The HCV World CAB included a broad range of 38 activists from 22 countires, including people with HCV, people who inject drugs, HIV positive people, representatives from non-governmental organisations and regional and global advocacy networks, and clinicians and researchers.

This was the first global meeting focused on HCV treatment access in low- and middle-income countires (LMIC) with pharmaceutical companies that produce HCV treatment.

The meeting was organised by Treatment Action Group and the Asia Pacific Network of People Living with HIV/AIDS. The HCV World CAB was supported by AIDS Fonds, the Global Network of People Living with HIV, Médecins du Monde, Open Society Foundations, and the World Health Organisation.

The report is available in PDF format from Treatment Actiong Group website:

http://www.treatmentactiongroup.org/hcv/publications/wcab-report-2014

RITA on HCV/HIV coinfection: What HIV clinicians should know (and do) about HCV coinfection

http://centerforaids.org/pdfs/0614ritafinal.pdf (PDF)

This issue of *Research Initiative, Treatment Action* (RI*TA*) examines how direct-acting antivirals (DAAs) have already transformed treatment of HCV infection and considers how they may continue to do so. An interview with Douglas Dieterich offers nuts-and-bolts advice on prescribing DAAs for people with coinfection and encourages more involvement by HIV clinicians in HCV management.

A second review article dissects the most controversial question about HCV/HIV coinfection: does HCV make HIV infection worse? Scores of studies addressing different aspects of this question are almost evenly split in their conclusions.

A final review analyses sexual HCV transmission among gay and bisexual men. Early research rated sexual HCV transmission a rare event. But that thinking – still echoed in some online US CDC material –stands starkly at odds with an explosive HCV epidemic documented in gay and bisexual people who do not inject drugs.

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

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website: updates for PDA access

The i-Base website is designed to meet access standards for PDA, iPad, tablet, Windows 8 and touch screen access.

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

http://www.i-Base.info

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

Publications and regular subscriptions can be ordered online.

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

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

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

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

Non-technical treatment guides

i-Base treatment guides

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

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

- NEW: Introduction to combination therapy (July 2014)
- HIV testing and risks of sexual transmission (February 2013)
- HIV and quality of life: side effects & complications (July 2012)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (November 2013)

Publications and reports

HIV Treatment Bulletin (HTB)

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

HTB South

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

HTB Turkey

HIV Tedavi Bülteni Türkiye (HTB Turkey) is a Turkish-language publication based on HTB.

HTB West Balkans

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

Why we must provide HIV treatment information

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

Translations of i-Base publications

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

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

Advocacy resources

Online treatment training for advocates

http://i-base.info/ttfa

Entry-level curriculum relating to HIV and treatment.

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

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community advocates from across the UK that has been meeting since 2002. It now includes over 580 members from over 120 organisations.

http://www.ukcab.net

Phoneline and information services

Online Q&A service

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

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

Order publications and subscribe by post, fax or online

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

http://i-base.info/order

htb(e)

HIV TREATMENT BULLETIN (e)

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

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

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

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http://www.i-Base.info

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

HIV i-Base

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

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REFUNDS FROM THE TAX MAN

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

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- **HIV Treatment 'Passports' - Booklets for patients to record their own medical history**
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- **HIV and your Quality of Life: Side Effects and other Complications** *(July 2012)*
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Treatment guides in other languages are available as PDF files on the website

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