ISSN 1472-4863

hiv treatment bulletin (e)

htb(e): volume 16 number 5/6

may–june 2015

CONTENTS

Published by HIV i-Base

EDITORIAL

The issue of HTB is led by the news of the unexpected death of Professor Martin Fisher. His extraordinary contribution to HIV care and the enthusiasm and buoyancy that he brought to all aspects of the field will be greatly missed.

Thoughts about Martin dominated the BHIVA conference where most people first heard the news, but the meeting still went ahead and several reports are included here.

Together with BHIVA, we include news from two other meetings. These are the 5th Workshop on HIV & Women and continued news from CROI 2015 - covering paediatric and maternal care and, thanks to natap.org, an excellent overview of cardiovascular studies by Priscilla Hsue (who give a leading plenary talk at BHIVA on vasculitis and HIV).

The news that the DSMB for the international START study found that benefits of earlier ART significantly outweighed the risks - and reporting at least 18 months earlier than expected - is leading news not just for HTB but for media globally. i-Base reports technical results in this issue of HTB with additional non-technical community articles and a Q&A resource on the i-Base website.

The investigators and participants should be acknowledged for providing the evidence gap that everyone wanted - but that no-one quite predicted. Finding that early ART reduced AIDS events at very high CD4 counts will change guidelines nationally and globally.

Other news in this issue includes the FDA submission for tentative approval for the integrase inhibitor dolutegravir - less than two years after US approval for the originator formulation. This also has the potential to change treatment prescribing globally. The rapid route for a new generic is thanks to a collaboration between originator and generic manufacturers with support from the Clinton Health Access Initiative (CHAI).

Basic science articles related to cure research cover new data from a Thai study looking at the impact on mucosal dysfunction of ART started during very early Fiebig stages, plus reviews of research on broad CD4 responses and neutralising antibodies.

We report a new study for extremly drug resistant TB is just starting in South Africa - and the urgency for broader access to recently approved TB drugs is highlighted in a report from MSF.

We include news of legal actions that are challenging Gilead's patent on sofosbuvir - driven by the unaffordably high cost - and note that UK access is both extremely slow and extremely limited.

The WHO have strengthend their call for tranparency in publishing trial results - now supported with maximum timelines for publications.

And finally, we include a resource for health workers - drafted by 56 Dean Street and i-Base - to clarify that ChemSex does not refer just to using recreational drugs for sex, but is specific to three drugs: meth, meph and G.

BHIVA members – print copies of HTB

Please note that BHIVA members who are reading HTB electronically who want to continue to receive the print edition, need to subscribe online at:

http://i-base.info/forms/postsub.php

Or send your name, position, organisation and full postal address details to:

subscriptions@i-Base.org.uk

IN MEMORY

Remembering Professor Martin Fisher

Simon Collins and Polly Clayden, HIV i-Base

It was with immense sadness that as delegates arrived for the Annual BHIVA Conference they learned that Professor Martin Fisher had died unexpectedly on the eve of the meeting.

This was particularly difficult because Martin was so strongly associated with developing the HIV and care services in Brighton where the conference was being held and because he was one of the most active members of BHIVA with a key role in organising the meeting.

As a doctor and researcher, Martin's career was rooted in the importance of healthcare coming from the community and a belief that patient care should be individualised. His frustration with services that were anything other than the best, meant that he was always one of the first people to understand when new advances needed an active response.

Martin had always supported community activist projects, including i-Base, and it is difficult to think or an aspect of HIV care that he was willing to ignore.

Just of few of these strongly community-driven challenges included the importance of adherence, access to New-fill, of lifestyle changes for HIV positive people, responding to HCV epidemic in HIV positive gay men, including patient advocates in NHS clinics and in pressing access to PrEP for HIV prevention. He was the only doctor we knew who stopped smoking in order to be able to look his patients in the eye when telling them that quitting was important for their health.

It was unlikely that most of Martin's patients knew of his critical role for years as an active member of UK professional organisations BHIVA and BASHH, where he was active on guidelines panels for at least the last 15 years, helping to ensure national standards of care, and leading HIV trainings for new doctors in the UK and Europe.

It was more likely that his patients had insight into Martin's spirited sense of fun. The hundreds of pictures projected on three screens in the main conference hall for the tribute held at the BHIVA conference, played to Bowie's "Heroes" - showed just a glimpse of a man who new the importance of finding time to enjoy friendships and life.

The loss felt by those at the conference was palpable, and personal and moving – and it was something everyone would have wanted for him to know.

Martin's impact was extraordinary and he is deeply missed.

A foundation is being established to celebrate and take forward the legacy of his work to treat HIV positive people with dignity, compassion and respect and focus on the development of new strategies for effective treatment and prevention.

http://www.martinfisherfoundation.org

TREATMENT ALERT

Early START results recommend ART for all study participants: starting HIV meds when the CD4 count is above 500 reduces AIDS-related events

Simon Collins, HIV i-Base

On 27 May 2015, early results from the international Strategic Timing of AntiRetroviral Treatment (START) study were announced by Dr Anthony Fauci, head of the US National Institute of Allergy and Immune Diseases (NIAID). The findings are expected to change HIV treatment guidelines globally. [1]

The results were not anticipated and will have implications for everyone: doctors, researchers, guidelines committees, policy makers and funders - and HIV positive people, whether or not they are yet on treatment.

Timeline for DSMB recommendations

Although only limited findings have been released from START, they show surprises that nobody predicted.

The top-line results are based on data collected up to 13 March 2015. A more detailed analysis will be available in time for the International AIDS Conference being held in Vancouver in July, and will include data to the end of May 2015.

The first surprise is that the results are at least 18 months earlier than expected. This is due to a recommendation from the independent Data and Safety Monitoring Board (DSMB) for the study, who were tracking unblinded results. On 15 May 2015, this small group of experts decided that the primary research question had been definitively answered. Although the overall rate of serious events was low, and involved fewer endpoints than expected, the difference between the two arms of the study was highly significant. Based on pre-defined rules for changing the study, the DSMB recommended that all participants be offered treatment and that follow-up should continue as planned. The continued follow up is important: the START study is therefore still ongoing.

START is a large randomised international study and the size, randomisation and global network involved are all key to the importance of the results. The primary research question was whether the benefits and risks of starting antiretroviral treatment (ART) at high CD4 counts outweighed the benefits and risks of waiting until later. The definition of 'early' vs 'late' was having a CD4 count above 500 cells/mm^3 vs waiting until 350 cells/mm^3. Until now, observational cohort studies had reported conflicting results on whether there were clinical advantages of starting earlier and randomised studies had deferring treatment until even lower CD4 cut-offs.

The two groups in START were compared based on the different rates of serious clinical events. These events included important AIDS-related and non-AIDS related illnesses together with deaths from all causes. Numerous sub-studies were included to look at the impact of both HIV and ART on other key areas of health in early infection – including on bone heath, neurological function, cardiovascular risks, lung function and quality of life. Although information about the sub studies has not been released, these unblinded results were available to the DSMB when making their recommendations.

Enrolment and patient characteristics

From April 2009 to December 2013, START enrolled 4685 HIV positive people at 211 sites in 35 countries. By the time of the data cut in March for the 2015 DSMB review, the mean follow up time was about 3 years, contributing to 7000 patient years of follow-up.

Baseline characteristics for the main study and related sub-studies have been well described in the annual DSMB open reports and in a recent open access supplement to *HIV Medicine*. [2. 3]

Age ranged from 18-81 years, with a median age of 36 (IQR: 29 to 41). Just over half of participants were gay men and more than a quarter were women. Most people were enrolled within a year of their HIV diagnosis (median estimated time 1.0 (IQR: 0.4 to 3.0) years).

START is a global study: with 33% of participants in Europe, 25% in South America or Mexico, 21% in Africa, 11% in the US, 8% in Asia and 2% in Australia.

Given that entry criteria included having a CD4 count >500 cells/mm^3, the study enrolled many people at CD4 counts that were significantly higher than expected, with 20% off participants starting above 800 cells/mm^3. The median CD4 count was 651 cells/mm^3 (IQR: 584-765; range 503 to 2296). Viral load at baseline also showed that this was a group in early infection. Median viral load was about 12,000 copies/mL (IQR: 3,000 to 40,000) and 8% had viral load <400 copies/mL.

The number of other medical complications within this diverse group is important. At baseline, almost one-third were current smokers, half had at least one cardiovascular risk based on the Framingham calculator, almost one in five either

had hypertension or were on hypertensive treatment and 8% either had high blood lipids or were on lipid-lowering drugs. Just over 3% had diabetes, were using diabetes treatment or had high fasting glucose. Prevalence of viral hepatitis was 2.9% and 3.7% for coinfection with hepatitis B and C, respectively. Other important health issues included about that 3% had documented alcohol or substance use issues and 6% had a psychiatric diagnosis (including depression, bipolar and other conditions).

These baseline data suggested that cardiovascular disease (CVD) and non-AIDS cancers would be the most common serious events. START was designed as an endpoint-driven study and modeling projected that 213 serious events would be needed to show that earlier treatment would reduce the risk of events by about one third. The study was expected to run until the end of 2016.

Top line results: ART has greatest impact on HIV-related events

In the press conference, results were released for three separate endpoints, see Table 1 below. The number of events for each endpoint and the relative differences between the early and late treatment groups were also provided. These figures are based on data from March 2015 and so will change slightly when the final dataset become available.

The differences were highly significant for endpoints 1 and 2, but not for endpoint 3.

- The combined endpoint of AIDS, serious non-AIDS or death was reduced by 53% in the early treatment group (HR 0.47; 95%CI 0.32 to 0.68). This was based on 41 vs 86 events in the early vs deferred groups, with rates of 0.60 vs 1.25 per 100 person years (PY).
- The combined endpoint of AIDS or death was reduced by 70%, (HR 0.30; 95%CI 0.17 to 0.55). This was based on 14 vs 46 events in the early vs deferred group, with rates of 0.20 vs 0.66 per 100 PY.
- The combined endpoint of serious non-AIDS events or non-AIDS related deaths was reduced by 33% (HR 0.67; 95%CI 0.42 to 1.09). This was based on 28 vs 41 events in the early vs deferred groups with rates of 0.41 vs 0.59 per 100 PY. This difference is not statistically significant because the 95% confidence intervals cross 1.0.

These preliminary results were not expected. They show that early treatment had a greater impact on HIV-related illnesses than on non-AIDS events. To understand the importance of this finding, the clinical concern behind some treatment guidelines already recommending ART at CD4 counts above 500 cells/mm^3 was driven by risk of non-AIDS illnesses. Non-AIDS events include serious heart, liver, kidney disease and non-AIDS cancers.

Table 1. Primary endpoint and its components in open DSMB report (15 May 2015)

	Early ART (arm A)		Deferred ART (arm B)		Hazard Ratio
	N	rate/100 PY	N	rate/100 PY	Arm A/B (95% CI)
AIDS, serious non-AIDS, or death (primary)	41	0.60	86	1.25	0.47 (0.32 to 0.68)
AIDS or AIDS death	14	0.20	46	0.66	0.30 (0.17 to 0.55)
Serious non-AIDS or non-AIDS death	28	0.41	41	0.59	0.67 0.42 to 1.09) NS**

* PY = patient years, ** NS = non significant

How much better was early and how much worse was late?

It is important that the interim results in Table 1 included information both on relative rates and the absolute number of events. While the relative rates were so highly significant in answering the study question, the absolute number of serious illnesses was low. Less than 3% of participants experienced these problems. More the 97% of participants did not have serious complications over the average three years of follow-up.

This means that fewer participants had to undergo serious event than was initially planned in order to see a difference between early and late ART. Back in 2009, it was thought that 370 endpoint events would be needed. Then in 2013, the study team recalculated that only 213 events would be needed, because the enrolment of people with very high CD4 counts widened the difference of risk in the two groups. [4]

In May 2015, the DSMB announcement showed that the number of endpoints was reduced further, with the study question answered based on only 127 events. This is good for the study and good for participants.

These results highlight that for people who have high CD4 counts but are not on treatment, that the absolute risk of events is still low. START results mean that a discussion about starting ART at the routine visit will be important but that the timeline for starting treatment can be paced.

The most common AIDS-related events were pulmonary tuberculosis (TB), Kaposi's Sarcoma (KS) and non-Hodgkins Lymphoma (NHL). The most common non-AIDS events were cancer, cardiovascular events and other causes (including traffic accidents, assault, suicide and overdose).

Earlier treatment therefore had a greater impact on reducing the risk of HIV-related events than on reducing non-AIDS events.

The combined results also imply that earlier treatment was not associated with significant harm. This is important for HIV positive people who already started treatment at high CD4 counts. However, results from important secondary endpoints, including virological efficacy, side effects and drug resistance, together with important substudies, will be essential.

Although the results have not been released for each geographical region, it is notable that the overall benefit of earlier ART were found for both high and low/middle-income countries.

Implications and impact of the START results

The START results are likely to have a significant impact for anyone interested in HIV treatment.

- For HIV positive people who are not yet on treatment, the results should make it easier to be treated. The results should reduce the reliance on any CD4 threshold in order to access treatment.
- For HIV positive currently on treatment, the findings should be reassuring in terms of low risk of serious complications.
- Now that both treatment benefits have the highest grade of evidence supporting earlier treatment, this should also make Treatment as Prevention (TasP) easier to access. The default will be that treatment becomes the routine next step after an HIV diagnosis. It is already common for newly diagnosed individuals to want ART in order to reduce the risk of transmission to sexual partners: this data is reassuring that ART also benefits their health.
- HIV activists have long-demanded evidence for earlier treatment, so it a major achievement from START is to establish such a strong and robust dataset for this evidence. Different national guidelines are likely to become more similar.
- For health professionals, it is difficult to overestimate the importance of the START results given how keenly the study was being followed. Even when the US DHHS treatment guidelines recommended ART at CD4 counts above 500 cells/mm^3 in February 2013, this was based on the lowest evidence rating of expert opinion. These guidelines included an important caveat for this recommendation – that definitive evidence would only come from randomised studies such as START. [5]
- Similarly, in July 2013, when the WHO consolidated guidelines (produced for low- and middle-income countries) increased the threshold for ART from a CD4 count of 350 to 500 cells/mm^3, this was based on the hoped for merger of clinical, prevention and operational benefits of earlier treatment. [6] The 2015 review of the WHO guidelines is therefore likely to benefit from strong data supporting both clinical and prevention benefits from starting ART at higher CD4 counts. It is important that these finding also come at a time when first-line treatment globally has shifted to wider use of effective and tolerable drugs.
- The clinical benefits from START are similarly likely to change national HIV guidelines that until now have retained CD4 thresholds of 350 cells/mm^3 (for the UK) or 500 cells/mm^3 (for South Africa, Australia and some European countries including France and Spain).
- Finally, researchers and scientists now have a rich and complex dataset to further explain the pathogenesis of early infection, including hypotheses on risks of immune activation and activation and that challenge earlier assumptions that HIV-related illnesses were not an appreciable risk at very high CD4 counts.

The NIAID press conference is accompanied by a press statement and related Q&A document, both of which are online. [1]

A non-technical i-Base article about the START study and a community Q&A is also online. [7, 8]

Simon Collins is a member of the START Community Advisory Board and was involved as a community advocate from the planning stages of the study.

C O M M E N T

Overnight, these results are likely to overturn the 30-year dependence on a CD4 threshold for initiating HIV treatment. They are the crucial missing evidence that will unify the benefits of ART for both treatment and prevention.

This is positive news, with findings similar in low- and high-income country settings, and with the study question answered so much earlier than expected.

It was believed that early ART would be better, as this was a key assumption in the study. The surprise was that (i) the benefits were so significant and that (ii) ART reduced AIDS-related at high CD4 counts, rather than non-ADS events such heart, liver, kidney disease and some cancers.

Even people who were vocal in not supporting the START study – and there were a few – did not predict the results. START was driven by a demand for data. One of the most important results is therefore realigning the

importance of evidence-based medicine. This outcome is probably as important as finding benefits of early ART.

Follow-up will now continue for all participants. Extending this beyond 2016 might also be warranted, given the unique nature of this cohort.

START is likely to be a source for many further surprises. Further results will be headline news when presented in Vancouver in July.

References

1. NIAID press announcement and statement. Starting antiretroviral treatment early improves outcomes for HIV-infected individuals, study finds: trial results will likely impact global treatment guidelines, (27 May 2015).
   http://www.niaid.nih.gov/news/newsreleases/topics/Pages/aidsReleases.aspx
2. START Study. DSMB Open reports, 2009-2014.
   http://insight.ccbr.umn.edu/start/index.php?study=start&page=&menu=safety&submenu=DSMB
3. The START Trial Characteristics at Study Entry, HIV Medicine, April 2015, Volume 16, Special Issue: Supplement S1 Pages 1–146.
   http://onlinelibrary.wiley.com/doi/10.1111/hiv.2015.16.issue-s1/issuetoc
4. START study DSMB 10th open report. (15 May 2015).
   http://insight.ccbr.umn.edu/official_documents/START/open_DSMB/START_OpenDSMB_30May2014.pdf (PDF)
5. US Department of Health and Human Sciences (DHHS). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. February 2013.
   http://www.aidsinfo.nih.gov/guidelines
6. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. June 2013.
   http://www.who.int/hiv/pub/guidelines/arv2013/en/
7. Collins S. Breaking news: what do the START results mean for HIV positive people.
   http://i-base.info/breaking-news-what-do-the-start-results-mean-for-hiv-positive-people
8. i-Base Q&A on the START study results.
   http://i-base.info/i-base-qa-on-the-start-study-results

CONFERENCE REPORTS

21st Annual BHIVA Conference

21 - 24 April 2015, Brighton

Introduction

This year, as always, BHIVA included an important and diverse programme that included 30 oral presentations and over 200 posters from submitted studies.

A selection of these are briefly summarised below.

For full details, and for other studies, please see the webcasts for oral session and online abstract book for posters.

Abstract book

http://www.bhiva.org/documents/Conferences/2015Brighton/AbstractBook2015.pdf (PDF)

Articles in this issue include:

- BHIVA pregnancy audit 2013 to 2014.
- Transmitted drug resistance in HIV positive pregnant women.
- Primary HIV infection and early use of ART.
- Rectal STIs and viral load in HIV positive men on and off ART.
- Impact of age and HIV on use of non-HIV meds: early results on health care use in the POPPY study.
- Other short reports from BHIVA.
  - HIV and transgender care.
  - Tacrolimus-based immunosuppression for HIV-positive kidney transplant recipients.
  - Exclusion of HIV positive people from experimental studies for lymphoma research.

- Meta-analysis of randomised studies finds no higher risk of viral failure in fixed-dose combinations compared to separate drugs.
- Phenomenon of seroreversion in UK children started on early ART after birth.
- Informed consent and patient information are too difficult for most people to easily understand.

BHIVA pregnancy audit 2013 to 2014

Polly Clayden, HIV i-Base

The BHIVA pregnancy audit, presented at the spring 2014 BHIVA Conference, revealed:

- Most initial ART regimens were compliant with BHIVA guidelines.
- ART was started in nearly 80% of cases.
- Only 29% of newly diagnosed women with CD4 <350 cells/mm^3 started ART within 2 weeks.
- Many women started ART late and this was mostly not explained by late booking.
- More than half of deliveries were by caesarean section.
- 27% of women with viral load <50 copies/mL at ≥36 weeks planned for caesarean section.

The audit uses confidential data collected for the National Survey on HIV in Pregnancy and Childhood (NSHPC). Reporting to the NSHPC is voluntary and currently receives data from approximately 225 centres.

Pregnancies with an estimated delivery date between 1 January 2013 and 30 June 2014 were included. BHIVA audited data against outcomes described in its 2012 guidelines. Sonia Raffe from Royal Sussex County Hospital, Brighton presented these findings.

During the 18 month period there were 1483 pregnancies in 1469 HIV positive women. The majority (73.7%) were black African; 17% white; 3.1% black Caribbean; and 6.1% other or undocumented. Almost two thirds (64.8%) of women were aged 30 to 39 years at their estimated delivery date; 23% were 20 to 29; 11% were 40 or more; and only 0.8% were 16 to 19. Most women (85.2%) acquired HIV through heterosexual sex.

Of the total pregnancies, 1263/1483 (85.2%) women were diagnosed with HIV before they became pregnant: 920 conceived on ART; 332 off ART; and ART status for the remaining 11 were unclear. The 217 (14.6%) women who were diagnosed in pregnancy included 6 known seroconverters. The time of diagnosis was unclear for 3 women.

Of the diagnoses in pregnancy, 140/217 (65%) were made between 0 and 15 weeks; 53 (24%) were between 16 and 23 weeks; 17 (8%) between 24 and 35 weeks; and 7 (3%) were diagnosed at 36 weeks or later.

ART in pregnancy

The audit found management of women who had conceived off ART but were indicated for treatment for HIV to be 94% compliant with BHIVA guidelines; 3% of women received different antiretrovirals to the recommended ones (including one who was given AZT monotherapy); and management of 3% was unknown or not reported.

For women who conceive off ART and are not indicated for treatment for their own health, the BHIVA recommendations are stratified by viral load. The audit found excellent compliance among this group (n=338): 98%, 99% and 100% for viral loads <10,000, 10,000 to 100,000 and >100,000 copies/mL respectively. Only 8 women (5%) in the <10,000 copies/mL group received AZT monotherapy.

Management of 2 late presenters with very high viral loads (booked after 28 weeks, viral load unknown or >100,000 copies/mL) was 100% compliant with the guidelines, which recommend intensive regimens containing raltegravir.

Dr Raffe included a few extra observations:

- 9 women had started NVP with a reported CD4 count of >250 cells/mm^3.
- Raltegravir was included in first line regimens in 5.1% of all pregnancies and in 15.3% with viral load >30,000 copies/mL
- 73 women started darunavir in pregnancy (despite it not being a preferred antiretroviral).

In 12 pregnancies no ART was reported; 8 were ongoing at the time of the audit. The remaining 4 resulted in live births: 2 women declined ART but had elective Caesarean sections; 1 was diagnosed in labour and delivered vaginally; and 1 was known to be HIV positive but not booked for antenatal care and delivered vaginally.

Timing of ART

The results for starting ART were disappointing.

The guidelines recommend that women who need treatment (CD4 <350 cells/mm^3 or otherwise indicated) start ART as soon as possible. The audit looked at a start date within 2 weeks of diagnosis.

Of the 105 women diagnosed during pregnancy with CD4 <350 cells/mm^3, only 29% started ART within the target time of 2 weeks. Almost half (n=43) started 29 days or more after diagnosis.

Of 108 women who were diagnosed before conception with <350 cells/mm^3, 33 started within 2 weeks of booking and 44 started ART more than 29 days after diagnosis.

The recommendation for women with viral load <30,000 copies/mL is to start ART by the beginning of week 24 of gestation and >30,000 copies/mL by the beginning of week 16.

Starting ART for women with <30,000 copies/mL was 76% compliant with guidelines but only 38% compliant for those in the >30,000 copies/mL group.

Sexual health screening

BHIVA recommend that all women diagnosed with HIV have a sexual health screening. There was a marked increase in sexual health screening over the audit period. For women diagnosed with HIV during pregnancy the rate rose from <10% in the first quarter of 2013 to nearly 80% in the second quarter of 2014. The overall rate was lower, about 50% by the second quarter of 2014 across all pregnancies.

Viral load reporting

Of a total of 1354 pregnancies resulting in live births, 613 (45%) had viral load results from between 36 weeks gestation and delivery as recommended; 21% and 29% had viral load data from 34 to 35 weeks gestation or earlier in pregnancy respectively; and 4% had none.

Mode of delivery

The guidelines recommend a planned vaginal delivery for women with viral load ≤50 copies/mL at ≥36 weeks gestation. It is recommended that women with an intermediate viral load between 50 and 399 copies/mL consider caesarean section taking into account individual factors. Women with viral load ≥400 copies/mL are recommended a planned caesarean section.

A total of 1134 women had ≤50 copies/mL at some point during their pregnancy. Of this group, 786/1134 (69%) planned a vaginal delivery. Out of the women that met the audit target with viral load results from ≥36 weeks, 391/540 (72%) planned a vaginal delivery ie were compliant with the guidelines. Dr Raffe noted that 27% of women in the latter group planned for a caesarean section.

There were 50 women with a viral load in the intermediate range at ≥36 weeks: 24 planned for a vaginal delivery and 26 for caesarean section. A further 21 women with last reported viral load 50 to 399 copies/mL at 0 to 35 weeks planned for vaginal delivery. Dr Raffe suggested that this might reflect under-reporting of viral load measurements.

Fewer women (n=24) had a viral load of ≥400 at >36 weeks: 19 planned for a caesarean section of which 18 did so and 1 had an unplanned delivery; 3 planned for a vaginal delivery but all went on to have a caesarean section; 1 woman was diagnosed in labour; and 1 woman did not book antenatally.

As viral load data were incomplete it was unclear how many women delivered with a viral load >400 copies/mL but Dr Raffe said this could have been as many as 29. At least 3 women did so at ≥37 weeks: 1 planning a caesarean section on ART had an unplanned birth at 37 weeks with 16,402 copies/mL; 1 diagnosed during labour with 18,924 copies/mL; and 1 known HIV positive but unbooked for antenatal care with viral load after delivery of 57,000 copies/mL. Two of the infants were confirmed uninfected and 1 had a negative test at birth but no later test results.

Overall 719 (53%) women delivered by caesarean and 630 (47%) delivered vaginally. Types of caesarean were: 50% emergency; 35% elective; and 15% for MTCT.

The audit compared planned and actual mode of delivery. Of the 889 women who planned a vaginal delivery, 69% achieved this; 28% had an emergency caesarean; 20% and elective one; and 0.8% had a caesarean for MTCT.

Only 2% of women who planned an elective caesarean section delivered vaginally; 21% had an emergency caesarean; 23% had one for MTCT; but over half (54%) had an elective one as planned.

A large group (61%) of women with no reported plan had an emergency caesarean; 26% had an elective one; 7% for MTCT; and mode of delivery was unknown for 7%. Dr Raffe said that 18 women in this group delivered before 36 weeks – including 16 by emergency caesarean section – and it is likely that some women delivered before making a plan.

C O M M E N T

The presentation concluded with some recommendations. The first that maternity and HIV services should review and agree pathways to ensure rapid assessment and prompt start of ART. In the discussion after the presentation it was noted that this group of women can be very difficult to reach and vital support is being cut by draconian government policies.

Secondly, clinicians should encourage women to plan vaginal delivery unless obstetric factors or insufficient virological control means a woman is indicated for caesarean section. The rate of caesarean section in England is about 25% but only 11% are elective – so the rate in HIV positive women who are virologically suppressed seems high.

Of note the National Survey of Management of Pregnancy in Women Living with HIV presented at the autumn 2014 BHIVA conference found that some centres have a policy of maternal choice rather than recommending vaginal delivery for eligible women – which should be reviewed. If a woman has an undetectable viral load and is not otherwise indicated for a caesarean, having one is not necessarily safer.

Finally, that use of ART should be consistently reported to the Antiretroviral Registry (APR) – although this was not directly discussed in the audit, it is a recommendation that we have also made for years.

Reference

Raffe S et al. Audit of management of pregnancy in HIV. 21st Annual Conference of the British HIV Association (BHIVA), 21–24 April 2015, Brighton.

http://www.bhiva.org/150423SoniaRaffe.aspx

Transmitted drug resistance in HIV positive pregnant women

Polly Clayden, HIV i-Base

Preliminary data using linkage between three National HIV surveillance databases showed genetic diversity among HIV positive pregnant women in England and Wales. The women had low prevalence of transmitted antiretroviral drug resistance – consistent with other UK and European studies.

Laura Byrne from UCL Institute of Child Health presented these findings at the spring BHIVA Conference 2015.

BHIVA guidelines recommend resistance testing for most pregnant women starting ART. But the prevalence of resistance in pregnant women in the UK had not been investigated before. The study looked at HIV subtype in pregnant women matched to at least one resistance test and transmitted drug resistance in newly diagnosed ART-naive women.

The investigators linked data from three databases: the National Study of HIV in Pregnancy and Childhood (NSHPC) collects data on pregnancies in HIV positive women and their infants; the UK HIV Drug Resistance Database (UKHDRD) collects all results from resistance tests conducted within routine HIV care; and the Survey of Prevalent HIV Infections Diagnosed (SOPHID) is a cross-sectional survey of all diagnosed people receiving HIV care at NHS sites.

Women who had at least one reported pregnancy between 2000 and 2013, delivered of due to deliver by September 2014 in England and Wales were included. Women were matched to resistance test results in UKHDRD via their SOPHID unique identifier. The investigators used the REGA HIV-1 subtyping tool v3 to identify their subtype. They used the IAS 2013 surveillance list to determine major mutations.

There were 14,416 pregnancies during the study period. The median age at conception was 30 years (IQR 26 to 34); 78% of women were black African and only 1.3% likely infected by IDU. The median year of HIV diagnosis was 2004 (range 1982 to 2013). Of the women, 49.9% were matched to $\geq$1 resistance test, with year of first resistance test 1996 to 2013. This proportion rose to 58.2% in women diagnosed after 2005. Overall, 63.5% women were classified as naive on their first test.

Factors associated with being matched to $\geq$1 resistance test were: having >1 reported pregnancy, aOR 1.65 if 2 pregnancies and aOR 1.98 if $\geq$ 3 pregnancies; year diagnosed 1985 to 1995 aOR 0.75, 1996 to 2000 aOR 0.56, 2001 to 2005 aOR 0.63 vs 2010 to 2013; woman born in Africa aOR 0.75, woman born elsewhere aOR 0.80 vs London; first pregnancy elsewhere aOR 0.66 vs London; first pregnancy 2000 to 2005 aOR 0.55 and 2004 to 2008 aOR (all comparisons $p<0.001$).

Of 4929 matched women: 46.6% had subtype C; 13.1% CRF02_AG; 10.6% A: 10.1% B; 8.3% other recombinant forms; 5.3% G; 4.1% D, 0.7% other pure; and 0.7% unclassified.

Overall 5.2% of 1302 women with a resistance test had transmitted drug resistance: 2.8% NNRTI; 1.9% NRTI and 1.2% PI. This rate is similar to that previously observed in the heterosexual population in the UK.

Reference

Byrne L et al. Antiretroviral drug resistance in pregnant women living with HIV in England and Wales: Preliminary results from the matching of three national HIV surveillance databases. 21st Annual Conference of the British HIV Association (BHIVA), 21–24 April 2015, Brighton. Oral abstract O27.
http://www.bhiva.org/150424LauraByrne.aspx

Primary HIV infection and early use of ART

Simon Collins, HIV i-Base

Several studies at BHIVA added to the growing evidence from using ART in earlier HIV infection.

This includes specifics reasons linked to treatment during primary HIV infection (PHI) for the diagnosed in this earliest window and also for earlier use in chronic infection.

Definition of timing is essential when looking at these studies.

Immunological benefit from very early treatment persist after ten years ART

A study looking at immune responses in people treated in primary HIV infection (PHI, n=37) compared to starting ART in chronic infection (CHI, n=115) was presented by Colette Smith and from the Royal Free Hospital. [1]

This analysis was conducted after all patients had used ART for at least five years and the results were notably for showing that significant differences persisted even after ten years of ART.

The PHI group started ART within 3 months of infection (median 3 weeks, range 0 to 3 months) compared to the CHI group who started >12 months after diagnosis (median 3 years, range 1 to 14 years). All patients in the CHI started at a CD4 count above 350 cells/mm^3.

In the PHI vs CHI groups, median age at diagnosis was 34 vs 32 years; 95% vs 87% were male and 87% vs 73% were MSM.

Median pre-ART viral load was higher for the PHI group: 511,000 (range 3,400 to >10 million) vs 278,000 (range 2500 to >750,000). This would be expected given the earlier samples likely for people diagnosed in early infection. However, median pre-ART nadir CD4 count, CD4% and CD4:CD8 ratio were all similar at ART initiation in each group.

Immune responses to these three markers were significantly better for the PHI vs CHI groups after one, five and ten years of ART. After ten years, median CD4 count was 966 vs 874 cells/mm^3 (p=0.02), CD4% was 33% vs 39% (p=0.01) and CD4:CD8 ratio was 1.09 vs 0.85 (p=0.04).

When defining optimal immune reconstitution as achieving one or more criteria of CD4 >800, CD4% >40% or CD4:CD8 ratio >1.0, this was reached after ten years ART by 85% of those treated in PHI vs 53% in CHI (p=0.003).

Some doctors reluctant to discuss early treatment in primary HIV infection

Results from an online survey of more than 200 UK HIV doctors about approaches to ART in primary HIV infection (PHI, <6 months since infection) were presented by Vicki Parsons from UCL.

Although 81% of these doctors had offered ART to at least one PHI patient in the past year (median 2 patients; IQR: 1, 4.5; range 0 to 50), 43% of doctors would not recommend starting ART in PHI for asymptomatic patients when CD4 was <350.and 16% would still not treat if CD4 was confirmed <350 cells/mm^3.

Another concern at variance to BHIVA guidelines was that although nearly all doctors (98%) would discuss TasP if their patient was sexually active, only 81% would do this if the patient did not reported sexual partner(s).

Both these later points show aspects of the guidelines that are not being followed consistently.

HIV positive people's interest in early treatment in PHI

A similar survey from the same group at UCL, this time in HIV positive people, was similarly interesting for highlighting the importance of their doctors advice in using early ART - and therefore the importance of early treatment being discussed.

From July to December 2013, this cross-sectional survey recruited 102 men diagnosed in PHI (half in London) who were enrolled in the UK HIV seroconverters register.

Acceptability of starting ART at diagnosis was high: 69% would have done so if offered, 8 would not and 23 were unsure. Of the 68 who would have started at diagnosis, only 42 (62%) started ART. In contrast, of the 31 who either would not have started or were unsure, 6 (19%) started ART based on their doctor's advice.

Of the 52 not on ART, 21 (45%) reported their doctor had advised starting ART and 26 (52%) expected to start in the next month. Also, 40 men (83%) would be happy to initiate ART to reduce the chance of transmitting HIV, even if there was no proven individual health benefit.

References

Unless stated otherwise, all references are to the programme and abstracts from the 21st Annual Conference of the British HIV Association (BHIVA) Brighton, 21–24 April 2015.

1. Kinloch S. Enhanced immune reconstitution with initiation of ART at HIV-1 seroconversion (PHI). 21st BHIVA, 21–24 April 2015, Brighton. Oral abstract O7.

2. Parsons V et al. UK clinicians' approach to ART in primary HIV infection; comparison with the BHIVA guidelines. 21st BHIVA, 21–24 April 2015, Brighton. Oral abstract O13.
3. Parsons V et al. Attitudes, beliefs and acceptability towards early ART amongst men who have sex with men (MSM) recruited to a UK cohort of HIV seroconverters. 21st BHIVA, 21–24 April 2015, Brighton. Poster abstract P33.

Rectal STIs and viral load in HIV positive men on and off ART

Simon Collins, HIV i-Base

A study by O Davies and colleagues from Guy's and St Thomas' looked at the impact of rectal gonorrhoea (GC) and chlamydia (CT) on HIV viral load in plasma and rectal tissue. [1]

The study enrolled 42 HIV positive gay men half of who were on treatment and half were still treatment naive. In each group, 7 men had a rectal STI (either GC or CT) and 14 did not. The group also looked at biomarkers of inflammation in rectal tissue.

The men were recruited during routine sexual health screening. In addition to comparisons by HIV treatment and STI status, men with an STI were their own control, pre- and post- STI treatment.

In the 21 men on ART, there were no significant differences in HIV viral load between men with or without and rectal STI, with all plasma and rectal levels at <100 copies/mL. Inflammatory markers were also not significantly different between the those with and without an STI: IL-6 (p=0.41), IFN-gamma (p=0.42), and TNF-alpha (p=0.26).

Of the 21 HIV positive men not on ART, there were also no differences in viral load (p=0.50) or cytokines for those with compared to without and STI. However, there was a non-significant drop in HIV viral load in rectal tissue in this group two weeks after GC/CT treatment (median 0.6 log copies/mL; range: 0.3 to 1.4). There was also significant change in plasma (p=0.37).

The concern that STIs could increase HIV transmission risk through higher viraemia was not found in this study and perhaps helps explain the lack of transmission in the PARTNER study when STIs were present. [2]

C O M M E N T

While other STIs are often believed to increase the risk of HIV transmission there are limited data for many specific questions.

This is especially important given the impact of HIV treatment on reducing HIV transmission, and the data from the PARTNER study finding no transmissions even in the presence of other STIs. [2]

References
1. Davies O et al. Impact of rectal gonorrhoea and Chlamydia on HIV viral load and inflammatory markers in the rectum: potential significance for onward transmission. 21st Annual Conference of the British HIV Association (BHIVA), 21–24 April 2015, Brighton. Oral abstract O19.
2. Rodger A et al. HIV transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER Study. 21st CROI, 3-6 March 2014, Boston. Oral late breaker abstract 153LB.
http://www.croiwebcasts.org/console/player/22072

Impact of age and HIV on use of non-HIV meds: early results on health care use in the POPPY study

Simon Collins, HIV i-Base

Early data from the UK POPPY study reported on use of health service and non-HIV drugs in HIV positive people older than 50 compared to two control groups: HIV positive people younger than 50 and HIV negative people older than 50, both matched by race, gender, sexuality and region. [1]

The UK POPPY study is an ongoing longitudinal observational cohort study looking at the impact of HIV on ageing. Notable in the design is the aim of establishing an HIV negative cohort that is well matched for the confounding lifestyle factors that complicate many other studies looking at HIV and ageing.

Alan Winston from Imperial College, presented early results for 540 people: n= 306 HIV+ >50 years; 136 HIV+ <50 years and 98 HIV negative >50 years. The full study plans to enroll 2000 participants.

The older HIV positive group had highest use of non-HIV medication (38% vs 21% vs 24%; p=0.0003) and higher use of analgesics (8.8% vs 5.9% vs 2.0%; p=0.06) compared to the younger HIV positive and older HIV negative groups, respectively.

Use of health services was high in all groups, with more 70% in all groups seeing their GP in the previous year (p=0.32, NS). Other significant differences included that older HIV positive people were significantly more likely to have had a

hospital procedure (28% vs 13% vs 12%; p=0.0001), and younger HIV positive people to have seen a psychiatrist (16% vs 24% vs 11%; p=0.03).

C O M M E N T

The significance of some of the differences highlights the importance of supporting the full study.

POPPY is also collaborating in the European COBRA study that is looking at impact of HIV on ageing. [2]

References
1. Healthcare utilization and non-antiretroviral medication use in people living with HIV over and under 50 years of age compared to matched controls: the Pharmacokinetics and Clinical Observations in People over Fifty (POPPY) study. 21st Annual Conference of the British HIV Association (BHIVA), 21–24 April 2015, Brighton. Oral abstract O6.
2. COBRA study: Co-morbidity in Relation to AIDS. http://fp7-cobra.eu

Other short reports from BHIVA

Simon Collins, HIV i-Base

Short summaries of other studies are included below.

HIV and transgender care

For the first time at a BHIVA conference the programme included a lecture, now online as a webcast, that addressed the management needs of HIV positive transgender patients. [1]

The presentation by Asa Radix from the Callen-Lorde community Centre in New York was especially well timed as in 2015 the NHS is at last starting to adopt a non-binary gender approach that might finally end the exclusion of transgender people from public health statistics.

Ref: Radix A. HIV and vulnerable populations: transgender medicine. Invited lecture. 21st Annual Conference of the British HIV Association (BHIVA), 21–24 April 2015, Brighton.

http://www.bhiva.org/150424AsaRadix.aspx

Tacrolimus-based immunosuppression for HIV positive kidney transplant recipients

A UK study of HIV positive kidney transplant recipients reported significantly better outcomes when tacrolimus (Tac)-based immunosuppression was used compared to ciclosporin (CsA).

Data on allograft rejection (AR) was available for 79/85 renal transplants in HIV positive people carried out between 2005 and 2013, with 32/79 using CsA) and 45/79 using Tac).

Demographics included mean age 44.8 years, 75% black ethnicity, median CD4 cell count 277 cells/mm^3 and that 97% had viral load <200 copies/mL.

Using logrank tests to compare survival and Cox proportional hazard models for AR, cumulative incidence of AR at 1 year was 57% and 20% among patients who started CsA and Tac respectively (p=0.002), with choice of immunosuppressant being the only significantly associated factor (HR 0.30: 95% CI: 0.13 to 0.67, p=0.003).

Overall one-year patient and graft survival were 97.3% and 94.6% respectively. AR was observed in 28 patients (36%), with a median time from transplant of 2.6 months (IQR: 0.5, 5.9 months).

The researchers commented that not using protease-based combinations enabled the safer use of Tac.

Ref: Gathogo E et al. Risk factors for acute allograft rejection in HIV-positive kidney transplant recipients. 21st Annual Conference of the British HIV Association (BHIVA), 21–24 April 2015, Brighton. Oral abstract O23.

Exclusion of HIV positive people from experimental studies for lymphoma research

Although HIV does not affect the prognosis for Hodgkin lymphoma or non-Hodgkin lymphoma, this incidence of both cancers in significantly higher in HIV positive people compared to general population.

This makes the opportunity to enrol in studies for new treatments especially important. Although historically HIV was an exclusion criterion in the pre-ART era, there is now little rationale for excluding HIV positive people from clinical research studies that are not exclusively designed for HIV. Most HIV positive people are able to achieve undetectable viral load and the choice of ART enables combinations that minimise the risk of interactions with chemotherapy for lymphoma.

A review of current UK studies found that only 14/46 interventional studies with eight classes of compounds were open to HIV positive people. In no cases was the exclusion justified in the protocol. Requests to see complete protocols were only provided for 8/32 studies although researchers from a further four studies responded to questions.

In no case was the exclusion of PLWH explicitly justified in the protocol. Following review of the trial protocols or published data on novel agents, there was a biologically valid reason for excluding PLWH for 1 trial and a possible valid reason for one further study. Choice of ART would be able to overcome potential for drug interactions in the 28/32 where this might be a theoretical concern.

Ref: Venturelli S et al. The exclusion of people living with HIV (PLWH) from clinical trials in lymphoma: prejudice or justified? 21st Annual Conference of the British HIV Association (BHIVA), 21–24 April 2015, Brighton. Oral abstract O21.

Meta-analysis of randomised studies finds no higher risk of viral failure in fixed-dose combinations compared to separate drugs

A new meta-analysis from Andrew Hill and colleagues of nine open-label randomised studies in over 2500 patients reported few significant differences between use of fixed-dose combination (FDCs) and separately dosed combinations. Most of these studies (7/9) were switch studies in people who were virally suppressed.

However, FDCs had small but significant benefits for two endpoints. For the switch equals failure endpoint FDC had a 3% lower risk of failure (95% C.I. 0 to -5%, p=0.05) and for the 95% adherence endpoint FDCs had a 5% higher rate of success (95% C.I. 1% to 9%, p=0.007).

Ref: Hill A et al. No difference in risk of virological failure between antiretroviral treatments using co-formulated versus individual drugs: Meta-analysis of 9 randomised trials in 2,568 patients. 21st Annual Conference of the British HIV Association (BHIVA), 21–24 April 2015, Brighton. Oral abstract O10.

Phenomenon of seroreversion in UK children started on early ART after birth

A retrospective analysis from five paediatric centres in the UK reported that seroreversion was identified in 10/398 (2.5%) children: 6 male and 4 female.

Median age at HIV diagnosis was 0.2 years (range 0 to 0.3) and ART was started at median age of 0.3 years (range 0 to 0.4).

All were still alive and on ART at last follow-up. Median age was 9.4 years (range 2.0 to 14.3]. Median CD4 count was 1112 cells/mm^3 (429 to 1501). Importantly, 9 children had viral load suppressed to <50 copies/mL and one had a low level viral load of 230 copies/mL.

In this first study of seroreversion in children in the UK, and the researcher were unable to comment on whether this phenomenon relates to differences in HIV reservoirs or genetic factors.

Patel A et al. To determine the prevalence of HIV seroreversion across 5 collaborating paediatric HIV centres in the UK. 21st Annual Conference of the British HIV Association (BHIVA), 21–24 April 2015, Brighton. Oral abstract O26.

Informed consent and patient information are too difficult for most people to easily understand

Activists at HIV i-Base analysed a range of patient information leaflets (PiLs) used as part of the informed consent process for nine ongoing studies. They reported that all document were written to a higher level of literacy to that recommended in NHS guidelines.

The study explained how readability results are easy to calculate and included information on how to produce information that would be easily read by a larger percentage of people. Results were compared to community produced PiLs for documents of similar length and complexity.

Ref: Collins S et al. Patient information leaflets (PILs) currently require graduate-level reading skills equivalent to The Guardian or The Telegraph. 21st Annual Conference of the British HIV Association (BHIVA), 21–24 April 2015, Brighton. Oral abstract O4.

CONFERENCE REPORTS

2015 Conference on Retroviruses and Opportunistic Infections (CROI)

23-26 February 2015, Seattle

Introduction

The 2015 Conference on Retroviruses and Opportunistic Infections (CROI) was held from 23-26 February in Seattle, Washington.

CROI is the most important scientific and medical HIV conference and this year, the conference opened with important news on oral PrEP (including the PROUD and IPERGAY studies), topical PrEP and other HIV prevention options, including research to reduce mother to child transmission. Other key sessions included HIV-related complications, studies of new drugs in the pipeline and HIV pathogenesis - especially in the context of cure research.

Abstracts for each study are available in a searchable online database and some posters are available to download as PDF files.

http://www.croiconference.org/abstracts/search-abstracts

Webcasts of all plenary lectures and oral research presentations are as webcasts.

http://www.croiwebcasts.org

Coverage from CROI 2015 will be included in the next two issues of HTB. Articles included in this issue of HTB are:

- Elvitegravir in children and adolescents
- PK of ARVs in pregnancy: rilpivirine, etravirine and raltegravir
- HIV and cardiovascular disease

CROI 2015: PAEDIATRIC CARE

Elvitegravir in children and adolescents

Polly Clayden, HIV i-Base

Three posters at CROI 2015 showed new paediatric elvitegravir (EVG) data. The posters described preliminary safety in the 6 to 12 year old age group, and safety, efficacy, pharmacokinetics (PK) and resistance in 12 to 18 year olds receiving EVG in fixed dose combinations (FDCs). [1, 2, 3]

EVG 150 mg is approved for adults as a component of the once-daily FDC containing cobicistat (COBI, C), emtricitabine (F) and tenofovir disoproxil fumarate (TDF), or when co-administered with a ritonavir-boosted protease inhibitor.

EVG has also been co-formulated with tenofovir alafenamide fumarate (TAF) in E/C/F/TAF, the FDC that is currently under regulatory review in the US and EU.

EVG 85 mg is used in combination with ritonavir-boosted atazanavir or lopinavir because of increased EVG plasma concentrations due to UGT enzyme inhibition. Previous studies have confirmed use of the ritonavir or COBI-boosted adult dose in 12 to 18 year olds. [4]

Elvitegravir in children aged six to less than 12 years

GS-US-183-0160 is an ongoing, phase 2/3 open label, study with an age de-escalation design (oldest to youngest) evaluating the safety and PK of EVG in treatment experienced infants, children and adolescents 4 weeks to <18 years of age.

PK and preliminary safety data from 6 to <12 year olds (Cohort 2) were presented.

Sixteen participants were enrolled: median age 9 years (range 6 – 11); 14 had viral load <50 copies and 2 >1000 copies mL and baseline, their mean CD4 count was 811 cells/mm^3.

Participants received EVG (adult or paediatric formulation) once daily added to their background regimen including either lopinavir/r or atazanavir/r. Data were available for 14 (57% male, 14% Asian, 71% black and 14% white).

Participants weighing ≥30 kg received the adult EVG 85 mg dose (n=6) and those weighing 17 to <30 kg received 50 mg (n=8).

The investigators compared PK parameters to exposures in adults from EVG plus boosted protease inhibitor phase 3 trials.

This comparison revealed geometric mean ratios (GMR) of 136%, 147%, and 129% vs adult exposure for AUCtau, Cmax and Ctrough respectively.

Mean EVG Ctrough was approximately 11-fold above the in vitro protein-binding adjusted IC95 (44.5 ng/mL); all participants' Ctroughs were above the IC95.

These data are consistent with the range of exposures seen in the 12 to <18 years age group.

The investigators suggested that EVG appeared to be safe and well tolerated, based on limited data in a small number of participants.

E/C/F/TAF PK in adolescents

Treatment-naive 12 to 18 year olds (n=50), with viral load >1000 copies/mL, CD4 >100 cells/mm^3 and eGFR ≥90 mL/min/1.73m^2 received E/C/F/TAF once daily, in a phase 2/3, single arm, open label, two part trial.

Steady-state PK parameters of EVG, COBI, FTC, TAF and tenofovir (TFV) were compared to adult exposures by GMR with equivalence boundary of 70% to 143% for the 90% confidence interval. The trial evaluated adverse events, laboratory tests, and the proportion of subjects with viral load <400 and <50 copies/mL.

There were 48 participants (24 Part A/24 Part B) with a median age of 15 years (range 12 – 17), median weight of 52 kg, 58% female, 88% Black and 12% Asian; 21% with viral load >100,000 copies/mL, median CD4 count 452 cells/mm^3, and median eGFR 158 mL/min/1.73m^2.

The investigators found TAF, TFV, EVG, COBI, and FTC PK parameters in adolescents consistent with those associated with safety and efficacy in adults. TFV exposure by AUCtau was >90% lower from E/C/F/TAF than E/C/F/TDF as is seen in adult PK. All participants had EVG Ctau above the protein binding adjusted IC95 of 44.5 ng/mL.

Lack of resistance in adolescents on EVG-based FDCs at 24 week

Data from week 24 interim analyses that included 21 treatment-naive adolescents on E/C/F/TDF and 23 on E/C/F/TAF – from two ongoing single-arm studies of these FDCs, conducted in the US, Thailand, Uganda and South Africa – was also shown.

Most participants receiving the TDF FDC had HIV subtype C (47.6%, 10/21) or B (38.1%, 8/21) and the remainder had subtype AE (14.3%, 3/21). Most of the group receiving the TAF FDC had subtype A1 (56.5%, 13/23) and smaller proportions had subtype AE (17.4%, 4/23), B (17.4%, 4/23), D (4.3%, 1/23), or complex mixtures (4.3%, 1/23). The investigators noted that distribution of subtypes reflected geography: A1, Uganda; AE, Thailand; B, USA; C, South Africa.

The majority of adolescents receiving both FDCs had viral load <50 copies at 24 weeks: 85.7% (18/21) on E/C/F/TDF and 91.3% (21/23) on E/C/F/TAF.

Genotyping was performed at baseline in all participants at study entry to confirm sensitivity to FTC and tenofovir; screening genotyping to confirm sensitivity to EVG was only done in those receiving the TAF.

At baseline 14.3% of the participants receiving the TDF FDC had NNRTI-associated resistance mutations and 95.2% had secondary PI-associated mutations. Of those receiving the TAF FDC, 17.4% had NRTI-associated, 21.7% had secondary INSTI-associated, 8.7% had NNRTI-associated, and 100% had secondary PI-associated resistance mutations.

There was no correlation between pre-existing NNRTI, NRTI, secondary PI and secondary INSTI resistance mutations and virologic success at 24 weeks. No emergent resistance was detected in participants receiving E/C/F/TDF of E/C/F/TAF in these interim analyses.

References

Unless otherwise stated, all references to the programme and abstracts to the 22nd Conference on Retroviruses and Opportunistic Infections, 23-26 February 2015, Seattle.

1. Custodio JM et al. Safety and pharmacokinetics of elvitegravir in HIV-1 infected pediatric subjects. Poster abstract 951. http://www.croiconference.org/sessions/safety-and-pharmacokinetics-elvitegravir-hiv-1-infected-pediatric-subjects
2. Kizito H et al. Week-24 data from a phase 3 clinical trial of E/C/F/TAF in HIV-infected adolescents. **Poster abstract 953.** http://www.croiconference.org/sessions/week-24-data-phase-3-clinical-trial-ecftaf-hiv-infected-adolescents
3. Porter DP et al. Lack of emergent resistance in HIV-1-infected adolescents on elvitegravir-based STRs. Poster abstract 952. http://www.croiconference.org/sessions/lack-emergent-resistance-hiv-1-infected-adolescents-elvitegravir-based-strs

CROI 2015: PREGNANCY and PMTCT

PK of ARVs in pregnancy: rilpivirine, etravirine and raltegravir

Polly Clayden, HIV i-Base

Three posters at CROI 2015 described pharmacokinetics (PK) of antiretrovirals in pregnancy: rilpivirine, etravirine and raltegravir. [1,2 3] None of the studies suggested that dose adjustment is required.

Rilpivirine

Data from IMPAACT P1026s showed extensive variability in rilpivirine (RPV) exposure during pregnancy and post partum. But no dose adjustment is needed for pregnant women as AUC and Cmin remained above targets with the standard RPV dose.

IMPAACT Protocol P1026s is an ongoing, multicentre, non-blinded prospective phase 4 study, supported by the US National Institute of Health. The study investigates the PK of antiretrovirals in pregnant HIV positive women receiving ART as part of clinical care and includes a RPV arm.

Thirty-two women receiving ART regimens including 25mg RPV once daily were enrolled at IMPAACT sites in the US. The women underwent intensive steady-state 24 hour PK profiles during the 2nd trimester (20 to 26 weeks gestation), 3rd trimester (30 to 38 weeks) and postpartum (6 to 12 weeks after delivery). Maternal and cord blood samples were taken at delivery.

Plasma RPV concentrations were measured using liquid chromatography-mass spectrometry (lower limit of quantification 0.010 mcg/mL). Target AUC24 was at least 0.88 mcg*hr/mL, which is the 10th percentile AUC for non-pregnant adults. The median AUC in non-pregnant adults is 2.1 mcg*hr/mL.

At the time of analysis results were available for: 19 women in 2nd trimester, 31 in 3rd trimester and 30 women postpartum. All women received concomitant TDF/FTC, five also received AZT and one received darunavir/ritonavir during pregnancy.

The evaluation revealed high variability in RPV PK parameters. C24 and AUC24 were reduced during the 3rd trimester. C24 was reduced during the second trimester. When the investigators compared the 2nd and 3rd trimesters, C0 and Cmin were increased, while Vd/F and T1/2 were reduced during 2nd trimester. All comparisons $p<0.05$. See Table 1.

Table 1: PK parameters RPV in pregnancy and postpartum

Parameter	2nd trimester	3rd trimester	Postpartum
AUC24 (mcg*hr/mL)	1.97 (0.87 to 12.4)	1.70 (0.56 to 4.31)	2.39 (0.19 to 6.74)
C0 (ng/mL)	101 (31 to 550)	61 (<10 to 210)	66 (<10 to 285)
Cmax (ng/mL)	146 (43 to 669)	146 (49 to 267)	134 (48 to 407)
Tmax (hr)	4 (0 to 6)	4 (0 to 6)	4 (0 to 8)
C24 (ng/mL)	65 (37 to 517)	56 (<10 to 181)	81 (<10 to 299)
Cmin (ng/mL)	68 (29 to 416)	52 (<10 to 136)	58 (<10 to 200)
Tmin (hr)	24 (0 to 24)	1 (0 to 24)	5 (0 to 24)
Vd/F (L)	750 (148 to 12035)	1210 (155 to 30626)	695 (74 to 23571)
CL/F (L/hr)	13 (2 to 29)	15 (6 to 45)	10 (4 to 133)
T1/2 (hr)	37 (5 to 552)	63 (7 to 836)	35 (6 to 1375)

Median (range)

The investigators reported that the AUC target was met in 15/16 (94%) 2nd trimester women, 27/29 (93%) of 3rd trimester women and 23/26 (88%) of post partum women with available data.

For 9 women where maternal plasma and umbilical cord samples were available: cord blood RPV was 53.8 ng/mL (range <10.1 to 219.7) and maternal delivery plasma RPV was 103 ng/mL (<10.0 to 273.4), giving a cord blood/maternal plasma ratio of 0.55 (0.38 to 0.83).

Despite the reduced RPV exposure at some time points, AUC and Cmin remain well above targets in pregnant women receiving standard adult doses. The investigators recommended that no dosing adjustment is needed for RPV during pregnancy.

Etravirine

Data from the etravirine (ETV) arm of P1026s combined with that from the European PANNA study (with a similar design) were presented. This evaluation found that although 2nd trimester and postpartum ETV PK were similar to non-pregnant adult PK, 3rd trimester ETV exposure was significantly higher than postpartum and historical controls. No ETV dose adjustment is needed during pregnancy.

Median ETV trough concentration in non-pregnant adult studies was 275 ng/mL, and median AUC was 4.4 mcg*hr/mL.

Results were available for: 5 women in 2nd trimester, 13 in 3rd trimester and 9 women postpartum. One woman took 400 mg once daily and the remainder took 200 mg twice daily. For the once daily dosed woman only Cl/F, Vd/F, t1/2, and AUC12 were presented.

The results showed higher ETV maximum and 12-hour concentrations and lower clearance in the 3rd trimester of pregnancy compared to postpartum, $p<0.05$. See table 2. 3rd trimester AUC trended towards a significant increase compared to postpartum. All other parameters were similar at all time points.

Sixty per cent of women in the 2nd trimester, 100% in the 3rd trimester, 89% postpartum had AUCs above the 10th percentile in non-pregnant historical controls.

The investigators noted that there was no difference in exposure between women taking or not taking boosted protease inhibitors.

Table 2: PK parameters ETV in pregnancy and postpartum

Parameter	2nd trimester	3rd trimester	Postpartum
AUC24 (mcg*hr/mL)	4.5 (3.4 to 10.7)	8.3 (2.7 to 31.0)	5.7 (2.1 to 16.4)
C0 (ng/mL)	261 (69 to 1053)	635 (<5 to 2640)	430(<5 to 1210)
Cmax (ng/mL)	696 (442 to 1053)	1023 (264 to 3470)	631(301 to 1600)
Tmax (hr)	2 (0 to 8)	4 (2 to 6)	4 (1 to 4)
C12 (ng/mL)	356 (80 to 750)	540 (77 to 1940)	378 (67 to 1140)
Cmin (ng/mL)	253 (69 to 750)	473 (<5 to 1940)	378 (<5 to 1140)
Tmin (hr)	12 (0 to 12)	1.5 (0 to 12)	6 (0 to 12)
Vd/F (L)	44 (19 to 59)	432 (154 to 3563)	657 (225 to 1758)
CL/F (L/hr)	13 (2 to 29)	24 (7 to 75)	35 (12 to 95)
T1/2 (hr)	45 (5 to 45)	10 (6 to 82)	23 (5 to 37)

Median (range)

For 6 women where maternal plasma and umbilical cord samples were available: cord blood ETV was 222 ng/mL (range 68 to 2890) and maternal delivery plasma ETV was 339 ng/mL (188 to 680), giving a cord blood/maternal plasma ratio of 0.76 (0.19 to 4.25).

The investigators explained that the metabolism of ETV is complex: unlike other cytochrome P450 (CYP) 3A4 substrates, ETV exposure trends towards being higher in the 3rd trimester compared to postpartum. But 2nd trimester and postpartum exposure are similar to non-pregnant historical controls.

ETV is metabolised by CYP 3A4, 2C9 and 2C19, which have increased (3A4, 2C9) or decreased (2C19) activities in pregnancy. The investigators suggested that the decreases in CYP2C19 activity or altered absorption might be associated with the increase in 3rd trimester exposure. “More data are needed on etravirine in pregnancy to make dosing recommendations” they wrote.

Raltegravir

Raltegravir (RAL) PK was evaluated in a single centre, observational, descriptive study conducted in Paris. Pregnant women treated with twice-daily RAL 400mg containing ART regimens were included. Maternal plasma concentrations 2nd trimester, 3rd trimester and cord blood concentrations 12 hours post dose were performed.

Of 23 women enrolled in the study, 11 received RAL to intensify their existing regimen. All participants received RAL with a boosted PI and 2 NRTIs except for one woman who received RAL plus 2 NRTIs. Boosted PIs were: darunavir/ritonavir (DRV/r) 600 mg twice daily (n=16), DRV/r 800 mg once daily (n=1), lopininavir/ritonavir 400/100 mg twice daily (n=4), and saquinavir/ritonavir 100/100 mg twice daily (n=1).

Median RAL C12h at 2nd, early and late 3rd trimesters was: 85ng/mL (40 to 228, n=19), 74 ng/mL (22 to 238, n=18) and 63 ng/mL (34 to 207, n=22) respectively, p=0.96.

Cord blood/maternal plasma concentration ratio was: 3.56 (2.27 to 4.69, n=4).

The investigators wrote that RAL plasma concentrations are not modified during pregnancy and are similar to historical data in a non-pregnant adult population receiving a twice-daily 400 mg dose. They also noted good placental transfer (cord blood/maternal plasma concentration ratio >1.0) in the small sample of women with available data.

C O M M E N T

Also see report from 5th International HIV& Workshop on HIV and Women below, which showed similar data for ETV in pregnancy.

References

References are to the programme and abstracts of the Conference on Retroviruses and Opportunistic Infections (CROI) 2015, 23-26 February, Seattle, Washington, unless otherwise stated.

1. Mirochnick M et al. Pharmacokinetics of rilpivirine in HIV-infected women during pregnancy and postpartum. Poster abstract 894. http://www.croiconference.org/sessions/pharmacokinetics-rilpivirine-hiv-infected-women-during-pregnancy-and-postpartum
2. Best BM et al. Etravirine pharmacokinetics during pregnancy and postpartum. CROI 2015, Seattle. Poster abstract 892. http://www.croiconference.org/sessions/etravirine-pharmacokinetics-during-pregnancy-and-postpartum
3. Belissa E et al. Raltegravir plasma concentrations on HIV-1 infected pregnant women. CROI 2015, Seattle. Poster abstract 891. http://www.croiconference.org/sessions/raltegravir-plasma-concentrations-hiv-1-infected-pregnant-women
4. Ramgopal M et al. Pharmacokinetics of etravirine in HIV-1–infected pregnant women. CROI 2015, Seattle. CROI 2015, Seattle. Poster abstract 893. http://www.croiconference.org/sessions/raltegravir-plasma-concentrations-hiv-1-infected-pregnant-women

CROI 2015: SIDE EFFECTS & COMPLICATIONS

HIV and cardiovascular disease

Priscilla Hsue MD, for NATAP.org

This year at CROI, there were over 30 abstracts on cardiovascular disease and HIV, which is a noticeable increase from prior years.

This included a plenary session given by Dr. Steven Grinspoon, MGH, as well as three oral presentations, and a special presentation by Dr. Monica Shah, regarding the National Heart, Lung, and Blood Institute High-Impact AIDS Research.

Use of statins and other lipid lowering drugs in HIV positive people

Dr. Grinspoon's plenary session highlighted the work that his group has done evaluating the role of monocyte/macrophage activation in HIV-related vascular inflammation. He discussed the upcoming clinical trial that he is leading in collaboration with ACTG and NHLBI entitled REPRIEVE, which will evaluate the impact of pitavastatin on clinical outcomes among HIV-infected individuals. [1]

Indeed, a major focus this year was on studies investigating the impact of statin intervention in HIV positive people. Dr. Janet Lo reported on results from a randomised double-blind placebo-controlled study of 40 HIV positive people with evidence of increased arterial inflammation using FDG-PET and LDL <130mg/dL. [2]

Individuals were treated with atorvastatin ranging from 20-40mg daily or placebo for one year. Change in FDG-PET uptake of the most diseased segment of the aorta was not different between the two groups, although adequate images could only be compared in 21 patients. In contrast, atorvastatin therapy reduced non-calcified plaque volume as compared to placebo with a median change of -19.4% vs. 20.4% (p=0.009). Overall plaque volume decreased 4.7% with atorvastatin compared to an 18.2% increase with placebo. Direct LDL and lipoprotein-associated phospholipase A2 decreased significantly in the atorvastatin treated individuals. This study has now been published in Lancet. [3]

Similar findings were reported by Dr. Chris Longenecker and Dr. Grace McComsey from the SATURN-HIV study (aka "JUPITER-HIV"). [4]

This was a 96 week double-blind randomised clinical trial of 10 mg rosuvastatin daily vs placebo among HIV positive individuals with LDL-C less than or equal to 130mg/dL and evidence of heightened T-cell activation or increased inflammation. While CCA (common carotid artery) intima media thickness in the placebo group progressed significantly, it was unchanged in the statin group, with a mean difference between groups of 0.014 mm/year, and a between group p-value of 0.074 (p<0.05). There was no difference between the development of new plaque among those without plaque at baseline between the two groups, while there was a trend toward more detectable CAC in the statin treated group among those without CAC at baseline, (15% statin vs. 6% placebo, p=0.19).

The impact of switching ART compared to statin therapy was evaluated in by Dr. Baker and colleagues. [5]

This was a 12 week study of 43 individuals on a ritonavir boosted regimen who had either a detectable HIV RNA level or total cholesterol less than or equal to 272 mg/dL. Within the switch group, most individuals were changed to raltegravir, rilpivirine or unboosted atazanavir. The rosuvastatin treated individuals had greater declines in total cholesterol, LDL

cholesterol, and total/HDL ratio as compared to the ritonavir boosted individuals who switched regimens, and there were non-significant decreases in both the Framingham score and DAD score in the HIV positive individuals on rosuvastatin. In contrast, the people who switched ART had greater decreases in VLDL and triglycerides as compared to the rosuvastatin treated patients. Individuals who switched regimens had more drug-related adverse events. (See Table 1).

Table 1: Percent changes in primary and secondary endpoints at week 12: rPI switch vs rosuvastatin

Endpoint	Baseline mean (SD) All subjects (n=43)	Change at week 12 mean (SD)		Difference (95%CI)	p value
		rPI switch (n=20)	rosuvastatin (n=20)		
Fasting lipids					
TC	6.2 mmol/L (1.2)	–8.7% (10.8)	–21.4% (19.2)	12.7% (2.9 to 22.5)	0.003
LDL	4.0 mmol/L (0.9)	–1.0% (20.0)	–29.9% (27.3)	28.9% (14.0 to 43.8)	<0.001
VLDL	1.1 mmol/L (1.1)	–37.0% (25.3	–15.0% (26.6)	22.1% (6.0 to 18.1)	0.006
HDL	1.2 mmol/L (0.3)	+0.3% (15.0)	+2.4% (12.1)	2.2% (–10.5 to 6.2)	0.574
Total:HDL ratio	5.3 (1.4)	–7.6% (14.1)	–22/7% (18.3)	15.1% (5.0 to 25.3)	0.002
TG	2.2 mmol/L (1.3)	–34.1% (28.0)	–9.8% (31.7)	24.3% (5.7 to 42.8)	0.005
Framingham score (10 yr risk)	13.7% (5.1)	–2.1% (2.7)	–3.5% (5.9)	–1.4% (–1.4 to 4.3)	0.080
D:A:D score (5 yr risk)	8.4% (4.6)	–0.5% (3.1)	–1.6% (3.2)	1.1% (0.9 to 3.1)	0.098
Study drug-related side effects		11 (55%)	1 (4%)	10 (51%)	0.001

CI: confidence interval; TC total cholesterol. LDL low density lipoprotein, VLDL very low density lipoprotein, HDL high density lipoprotein.

The impact of the new ACC/AHA Cholesterol guidelines which were released in autumn 2013 was evaluated in two studies in the setting of HIV. Dr. Clement and colleagues used the Veterans Affairs (VA Clinical Case Registry, CCR), to evaluate the impact of the new guidelines among HIV positive veterans. [6]

She found that overall, 11.6% of HIV-positive adults (n=13,293 males) not previously eligible for statin therapy using the prior guidelines (ATP-III) would now be recommended for statin treatment using the new ACC/AHA guidelines (representing an increase from 53.3% previously eligible to 64.9% eligible).

Most of the increase was from individuals meeting criteria for primary prevention with 9.1% newly recommended based on the revised ASCVD risk score, 1.7% recommended base on diabetes, and 0.8% recommended due to CVD.

A similar study was performed by Dr. Susan Regan and colleagues in the Partners HealthCare System HIV longitudinal cohort of 2239 HIV positive adults. [7] In this Boston cohort, 41.8% were recommended for statin therapy using the new ACC/AHA guidelines as compared to 25.7% using the 2008 ATPIII guidelines and similar to the prior abstract, the most common indication for statin use was CVD risk of 7.5% using the new risk prediction algorithm.

Among individuals with a CVD event, statin therapy was recommended for 44% of individuals using ATPIII and 62% using ACC/AHA. Interestingly, despite more individuals being recommended for statin therapy, around 40% of patients with CVD events would not qualify for statin treatment using the ACC/AHA guidelines. This study underlies the issue that even among individuals with HIV, traditional risk factors only account for approximately 20% of cad and unknown factors which may be more prominent in HIV infection are likely not captured using traditional risk calculators.

So, should we as doctors prescribe statins for all HIV patients? Will statin target the inflammatory pathways of interest in HIV?

The data on clinical outcomes and statin intervention are largely mixed and will be the focus of the REPRIEVE study. Data from the SATURN study [4] along with Janet Lo's atorvastatin study [2] suggest that inflammatory markers and immune activation are largely not reduced by statin therapy. New drugs for lipid lowering and inflammatory interventions are being evaluated by other ongoing clinical trials.

Payal Kohli and colleagues presented a post on PCSK9, a promising new target of pharmacologic inhibition that has had impressive results for lowering low-density lipoprotein-cholesterol (LDL-C) in the general population – and may prove to be a valuable therapy in HIV positive people. Patients with HIV are at high risk for CVD and tend to be difficult to treat due to drug-drug interactions with antiretroviral therapies and limited efficacy of stains. This group aimed to collect preliminary data on PCSK9 levels and its homeostasis in this small cohort study. They found that PCSK9 is elevated in HIV infection, with high levels of PCSK9 that was not been previously observed in studies with >20,000 patients. PCSK9 elevation was not related to HIV-specific parameters, such as viral load or CD4 count. They also showed, in a pilot study of six patients inadvertently enrolled into clinical trials of PCSK9 inhibitors, that PCSK9 inhibition with a monoclonal antibody was highly effective and appeared to be safe, with reductions in LDL-C of around 60%.

Predicting CVD risk in HIV positive people

To further investigate the issue of CVD risk prediction in HIV, investigators in Boston calculated the Framingham risk scores and ACC/AHA risk scores in the Partner's Cohort (n=2270 patients) in a 3 year interval ending in 2009. [9] Risk scores were discordant in 17% of individuals with the ACC/AHA risk calculator predicting risk in 10% of patients and FRS predicting high risk in 7% of individuals. Both the ACC/AHA risk score and the FRS underestimated CVD risk in HIV patients, comparing 5-year observed to predicted event rates.

Four different risk calculators were compared in the HIV Outpatient Study which represents 2,392 individuals receiving care at 10 US clinic sites as of September 2013 and had a year of follow up, one assessment of cholesterol and two measurements of blood pressure. [10]

The Framingham point score, pooled cohort equation, systematic coronary risk evaluation and DAD equations were compared as shown in Table 2.

Table 2. Comparison of four risk calculators in HIV positive people

HOPS participants (n=2,392)	10 years CVD risk estimation			
	Framingham point score (FPS)	Pooled cohort equations (PCE)	Systemeic coronary risk evaluation (SCORE)	D:A:D equation
Harrell's C-statistic *	0.71	0.71	0.57	0.72
Expected events (E)	126	147	19	193
Observed events (O)	149	178	19	256
Ration E/O	0.85	0.83	0.83	0.75
p-value	0.002		0.02	

* Harrell's C-statistic assessed the ability of each prediction model to discriminate patients who did or did not experience incident CVD events.

Overall all four risk prediction equations underestimated the 10 year risk of CVD in this HOPS cohort of HIV positive adults in the U.S. The FPS, PCE, and D:A:D equations had moderate discrimination with a c-statistic ranging from 0.68 to 0.72 and SCORE had poor discrimination (c-statistic = 0.57).

The Veterans Aging Cohort Study Virtual Cohort (VACS VC) was used to evaluate the role of copy years of viraemia, CD4 years, and VACS index years (age, HIV-1 RNA, CD4, LFTs, Hg, platelet, creatinine, and known HCV infection). [11]

Among 12,131 individuals included in the analysis, three cumulative measures provided added information about risk of acute myocardial infarction: HIV viral load copy years (VCY), CD4 count years (CD4Y), and the VACS index years (VISI).

While all three cumulative measures predicted the studied outcome, VCY ≥63,000 copy years/mL (HR=4.17; 95%CI=3.59-4.85) and CD4Y3 (HR=5.61; 95%CI=4.56-6.90); patients with higher VACS Index score-years had the highest risk of AMI (VISY ≥250; HR=40.56; 95%CI=33.25-49.47).

The authors concluded that participants with the highest cumulative viraemia (in the upper quartile of viraemia copy-years) ran a 2.6-fold increased risk of MIs. Cumulative CD4 counts were not statistically significantly associated with an increase of MI incidence.

Participants in the highest quartile of VACS index score years ran a 4 times higher risk of MI incidence during the study.

These results showing that risk predictor algorithms developed in non-HIV populations do not apply to HIV infected individuals is not surprising. They do not take into account HIV-related features that likely contribute including ART, chronic inflammation, and immune activation. Interestingly, even the D:A:D calculator which was developed in HIV performed similarly to the other calculators demonstrating that even in HIV, one size does not fit all – suggesting perhaps differences in the HOPS patient populations as compared to the DAD individuals. Validation of HIV-specific risk calculators in different HIV cohorts will be needed in the future.

Further support for abacavir link to MI

Two studies from NA-ACCORD were also featured. Frank Palella and colleagues looked at recent abacavir use and incident MIs using MESA criteria in the North American Cohort (NA-ACCORD). [12]

There were a total of 301 incident MIs in 16,733 adults and 64,607 person-years of follow up. Recent abacavir use (defined as prescription within 6 months) was associated with an increased risk of MI (aHR 1.71; 95%CI 1.11 to 2.64) in an adjusted models that were analogous to ones used in DAD, and the results linking current abacavir use to MI risk is similar to the original DAD result reported in 2009. In the full study population in the adjusted analysis, the significance was lost. However, in the restricted population, the finding remained significant even after adjustment. Of note, this is the

first study to show risk of ABC present among ART naive individuals initiating ART, which is a new contribution to the field. The controversy over abacavir seems to ebb and tide but has not gone away.

Daniel Drozd and colleagues from NA-ACCORD determined the incidence of adjudicated primary MIs distinct from secondary MIs and examined baseline risk factors for primary MIs. The Universal Definition of MI, includes primary (type 1) MIs due to atherothrombotic plaque, and secondary (type 2) MIs due to a mismatch in supply/demand - for example, troponin leak in the setting of sepsis. Seven NA-ACCORD cohorts were included in the study between 1996-2010, resulting in 24,919 individuals with 262 type 1 MIs and 205 type 2 MIs. Traditional risk factors, along with lower CD4 counts were associated with type 1 MIs. In contrast, sepsis, cocaine, respiratory failure, and hypertensive emergency were responsible for 50% of type 2 MIs.

This study is an important contribution as it is the first to acknowledge the differences in MI definitions which impact treatment and conclusions drawn from studies. For example, type 2 MIs are not usually treated with aspirin, beta blockers, statins etc but typically by addressing the primary issue - ie drug use, sepsis which is in contrast to type 1 MIs. The distinction between type 1 and type 2 MIs in HIV cohorts thus is a critical one and may underlie some of the contrasting data that has been previously reported in different cohort studies.

Impact of intestinal microbiota on CVD risks

Suman Srinivasa and colleagues described the association between a microbiota-derived precursor of TMAO, namely TMA, and coronary plaque. [14]

The study included 155 HIV positive individuals along with 67 HIV negative controls. Serum choline trimethylamine (TMA) and trimethylamine-N-oxide (TMAO) were assessed using mass-spectometry and cardiac CT angiography was used to assess coronary plaque. Among HIV positive patients, TMA was associated with number of plaques, calcified plaques, calcium score, plaque volume and mass and LPS. After adjustment for Framingham risk score, TMA remained significantly associated with total, calcified, calcium score, plaque volume and mass. After additional adjustment for LPS, TMA remained associated with total plaque segments, calcium score, and plaque mass. There was no association of TMAO to plaque in contrast.

Trimethylamine-N-oxide (TMAO) is metabolised by intestinal microbiota from dietary lipids. In HIV negative people, TMAO levels are associated with cardiovascular events.

Arjun Sinha and colleagues evaluated TMAO levels and carotid IMT in a small study from UCSF. [15]

The median TMAO levels were similar among HIV patients and controls; however, TMAO levels between HIV patients were similar to HIV negative patients with CAD. Traditional risk factors along with current ARV were associated with higher TMAO levels and TMAO was weakly associated with carotid IMT.

Conclusion

In summary, HIV and cardiovascular diseases were an expanding arena of investigation at CROI 2015.

The emphasis this year was on statin interventions, evaluation of the new ACC/AHA cholesterol guidelines in HIV, abacavir and risk of MI, comparison of risk calculators in HIV, and new markers of CV risk such as TMAO.

New event driven studies such as REPRIEVE and other smaller proof of concept studies designed to target inflammation in HIV are ongoing and NHLBI along with NIAID is committed to supporting studies in HIV with dedicated funding for HIV-related investigations.

Source

Hsue P. HIV and Cardiovascular Disease: Report from 2015 CROI. natap.org. The full report includes additional slides and tables. This article in HTB was lightly edited for a print format.
http://www.natap.org/2015/CROI/croi_256.htm

References

Unless stated otherwise, all references are to the Programme and Abstracts of the 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle.
http://www.croiconference.org/abstracts/search-abstracts

1. Grinspoon S. Cardiovascular disease in HIV patients: an emerging paradigm and call to action.
   http://www.croiwebcasts.org/console/player/25786 (webcast)
   http://www.croiconference.org/sessions/cardiovascular-disease-hiv-patients-emerging-paradigm-and-call-action
2. Lo J et al. Statin therapy reduces coronary noncalcified plaque volume in HIV patients: a randomized controlled trial. Oral sbstract 136.
   http://www.croiwebcasts.org/console/player/25790 (webcast)
   http://www.croiconference.org/sessions/statin-therapy-reduces-coronary-noncalcified-plaque-volume-hiv-patients-randomized
3. Lo J et al. et al. Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. Lancet HIV. 2015; (published online Jan 9)
   http://dx.doi.org/10.1016/S2352-3018(14)00032-0
4. Longenecker C et al. Rosuvastatin arrests progression of carotid intima-media thickness in treated HIV. Oral abstract 137.
   http://www.croiwebcasts.org/console/player/25791 (webcast)
   http://www.croiconference.org/sessions/rosuvastatin-arrests-progression-carotid-intima-media-thickness-treated-hiv

5. Baker D et al. Rosuvastatin vs. protease inhibitor switch for hypercholesterolaemia: a randomised trial - the statin or switch (SoS) study. Poster abstract 733.
http://www.croiconference.org/sessions/rosuvastatin-vs-protease-inhibitor-switch-hypercholesterolemia-randomised-trial
http://www.croiconference.org/sites/default/files/posters-2015/733.pdf (PDF)
6. Clement M et al. HIV-infected veterans and the new ACC/AHA cholesterol guidelines: got statins? Poster abstract 750.
http://www.croiconference.org/sessions/hiv-infected-veterans-and-new-accaha-cholesterol-guidelines-got-statins
http://www.croiconference.org/sites/default/files/posters-2015/750.pdf (PDF)
7. Regan S et al. Application of new ACC/AHA cholesterol guidelines to an HIV clinical care cohort. Poster abstract 734.
http://www.croiconference.org/sessions/application-new-accaha-cholesterol-guidelines-hiv-clinical-care-cohort
http://www.croiconference.org/sites/default/files/posters-2015/734.pdf (PDF)
8. Kohli P et al. PCSK9 Is elevated in HIV+ patients and may mediate HIV-associated dyslipidemia. Poster abstract 731.
http://www.croiconference.org/sessions/pcsk9-elevated-hiv-patients-and-may-mediate-hiv-associated-dyslipidemia
http://www.croiconference.org/sites/default/files/posters-2015/731.pdf (PDF)
9. Regen S et al. Evaluation of the ACC/AHA CVD risk prediction algorithm among HIV-infected patients. Poster abstract 751.
http://www.croiconference.org/sessions/evaluation-accaha-cvd-risk-prediction-algorithm-among-hiv-infected-patients
http://www.croiconference.org/sites/default/files/posters-2015/751.pdf (PDF)
10. Thompson-Paul A et a. Cardiovascular disease risk prediction in the HIV Outpatient Study (HOPS). Poster abstract 747.
http://www.croiconference.org/sessions/cardiovascular-disease-risk-prediction-hiv-outpatient-study-hops
http://www.croiconference.org/sites/default/files/posters-2015/747.pdf (PDF)
11. Salinas J et al. Cumulative HIV care measures highly associated with acute myocardial infarction. Poster abstract 746.
http://www.croiconference.org/sessions/cumulative-hiv-care-measures-highly-associated-acute-myocardial-infarction
http://www.croiconference.org/sites/default/files/posters-2015/746.pdf (PDF)
12. Palella F et al. Abacavir use and risk for myocardial infarction in the NA-ACCORD. Late breaker poster abstract 749LB.
http://www.croiconference.org/sessions/abacavir-use-and-risk-myocardial-infarction-na-accord
http://www.croiconference.org/sites/default/files/posters-2015/749LB.pdf (PDF)
13. Drozd D et al. Incidence and risk of myocardial infarction (MI) by type in the NA-ACCORD. Poster abstract 748.
http://www.croiconference.org/sessions/incidence-and-risk-myocardial-infarction-mi-type-na-accord
http://www.croiconference.org/sites/default/files/posters-2015/748.pdf (PDF)
14. Suman Srinivasa S et al. Calcified plaque burden Is associated with serum gut microbiota-generated TMA in HIV. Oral abstract 138.
http://www.croiconference.org/sessions/calcified-plaque-burden-associated-serum-gut-microbiota-generated-tma-hiv
15. Sinha A et al, TMAO and HIV-associated atherosclerosis. Poster abstract 755.
http://www.croiconference.org/sessions/tmao-and-hiv-associated-atherosclerosis
http://www.croiconference.org/sites/default/files/posters-2015/755.pdf (PDF)

CONFERENCE REPORTS

5th International Workshop on HIV & Women

21-22 February 2015, Seattle, Washington

Introduction

The 5th international Workshop on HIV and Women was held this year just before CROI.

The programme from the meeting together with the abstract book and some presentations are available on the conference website.

http://www.virology-education.com/5th-hiv-women_online-program

Reports in this issue of HTB are:

- Pharmacokinetics in pregnancy: darunavir/r and etravirine
- Low prolactin and high 20alpha-HSD might contribute to ART-associated progesterone deficits in pregnancy
- Pregnancy rates among women using ART and hormonal contraceptives in Kenya
- Adolescents at increased risk of vertical transmission and poor pregnancy outcome in South Africa
- Gender difference in virological response to ART

Pharmacokinetics in pregnancy: darunavir/r and etravirine

Polly Clayden, HIV i-Base

Physiologic changes during pregnancy can affect pharmacokinetics (PK). Two small studies presented at the 5th International Workshop on HIV & Women evaluated the PK of darunavir/ritonavir (DRV/r) and etravirine (ETV) respectively in pregnancy. [1,2] In both studies drug exposure was altered – lower for DRV and higher for ETV.

The DRV/r evaluation compared PK in pregnancy that with post partum. The study was open label, multicentre, phase 3b. Women were enrolled in the 2nd trimester of pregnancy and received DRV/r (600/100 mg twice daily or 800/100 mg once daily), ETV (see below) or rilpivirine plus optimised background regimen.

PK evaluations were performed in the 2nd and 3rd trimesters and 6 to 12 weeks post partum. Total and unbound DRV plasma concentrations and total ritonavir plasma concentrations were evaluated predose and 1, 2, 3, 4, 6, 9, 12 and 24 hours postdose. Data for participants receiving DRV/r 800/100 mg were reported.

Seventeen women were enrolled: 5 black, 2 Latina, 7 white and 3 other. Sixteen had evaluable PK data.

The PK evaluation revealed reductions in total DRV AUC24h, Cmin and Cmax of: 34% (LS mean ratio, 90% CI: 0.66, 0.60 to 0.74), 32% (0.68, 0.56 to 0.83) and 34% (0.66, 0.59 to 0.75) in the 2nd trimester, compared with post partum. The respective values were: 35% (0.65, 0.57 to 0.74), 50% (0.50, 0.35 to 0.73) and 31% (0.69, 0.63 to 0.77) in the 3rd trimester.

Unbound DRV concentrations were also lower during pregnancy but to a lesser extent. Compared with postpartum, DRV AUC24h, Cmin and Cmax were decreased by: 24% (0.76, 0.67 to 0.85), 13% (0.87, 0.69 to 1.10) and 25% (0.75, 0.65 to 0.87) in the 2nd trimester; and 20% (0.80, 0.71 to 0.89), 38% (0.62, 0.43 to 0.90) and 16% (0.84, 0.74 to 0.96) in the 3rd trimester.

Ritonavir parameters decreased by approximately 45-50% overall in pregnancy compared with post partum.

Viral suppression <50 copies/mL increased and was maintained over time: 59%, 87%, 100% and 93% at baseline, 2nd trimester, 3rd trimester and postpartum respectively.

There were no deaths and 6 serious adverse events. All the events were considered to be pregnancy-related; only 1 (gestational diabetes) was considered possibly related to DRV/r. There were 3/16 infants born before week 37. All infants were HIV negative.

The PK (total concentrations) of ETV 200 mg twice daily was evaluated in a study of the same design. For this assessment 11/15 women had evaluable data.

ETV AUC24h, Cmin and Cmax were higher by: 46% (LS mean ratio, 90% CI: 1.46, 1.12 to 1.90), 131% (2.31, 1.26 to 4.22) and 39% (1.39, 1.15 to 1.67) during the 2nd trimester compared with postpartum. For the third trimester the increases were: 28% (1.28, 0.98 to 1.69), 93% (1.93, 1.03 to 3.61) and 31% (1.31, 1.08 to 1.59).

Higher exposures of ETV did not result in increased occurrence of adverse events. Four participants had serious adverse events, none of which were considered related to ETV. One participant had grade 1 treatment emergent atopic dermatitis that was considered possibly related to ETV. All infants were HIV negative.

The investigators noted that caution might be warranted with concomitant medicine or situations that could further increase ETV exposure.

References

1. Crauwels HM et al. Total and unbound pharmacokinetics of once-daily darunavir/ritonavir in HIV-1– infected pregnant women. 5th International Workshop on HIV & Women, 21–22 February 2015, Seattle, WA. Oral abstract O1.
   http://regist2.virology-education.com/2015/5thHIVwomen/03_Crauwels.pdf (PDF)
2. Ramgopal M et al. Pharmacokinetics (PK) of etravirine (ETR) in HIV-1– infected pregnant women. 5th International Workshop on HIV &Women, 21–22 February 2015, Seattle, WA. Oral abstract 02.
   http://regist2.virology-education.com/2015/5thHIVwomen/04_Ramgopal.pdf (PDF)

Low prolactin and high 20alpha-HSD might contribute to ART-associated progesterone deficits in pregnancy

Polly Clayden, HIV i-Base

A Canadian study presented at the 5th International Workshop on HIV & Women suggested that low progesterone (P4) levels observed in ART-exposed HIV positive pregnant women could be due to higher levels of 20alpha-hydroxysteroid dehydrogenase (20alpha-HSD) induced by low hPL levels.

ART has been linked to low birth weight, preterm delivery and other pregnancy complications. The study investigators had previously demonstrated that ART was associated with decreased levels of P4 mid-pregnancy in HIV positive women that correlated with birth weight.

For this study they investigated molecular mechanisms leading to ART-associated P4 level alterations in 33 HIV positive women receiving ART with 15 HIV negative women as controls.

The study assessed the expression levels of key enzymes of P4 synthesis and metabolism by PCR on placenta tissue. Plasma P4 and human prolactin (hPL) levels were quantified at week 33 to 37 of pregnancy by EIA. Human choriocarcinoma (BeWo) cells were treated with increasing doses of hPL for 24hours, 20alpha-HSD expression and P4 levels were measured by PCR and EIA respectively. P4 levels in ART-exposed BeWo cells were assessed with or without 20□HSD inhibition.

The investigators found P4 levels to be significantly lower in the HIV positive compared to the HIV negative group: median 131.0 (IQR 93.3-158.9) vs 171.1 (139.6-198.8) ng/mL respectively, p=0.014.

They noted that placental expression of most P4 metabolism enzymes was similar between groups. Only the P4-eliminating enzyme 20alpha-HSD was significantly higher in the HIV positive women: median 2.81 (IQR 0.89 to 26.05) vs 1.09 (0.623-1.56) arbitrary units in the HIV positive and HIV negative groups respectively, p=0.0084.

They found hPL, the main regulatory hormone for 20□HSD, to be significantly lower in the HIV positive group compared to controls: median 0.50 (IQR 0.38 to 0.72) vs 0.77 (0.48-0.89) ng/mL, respectively, p=0.043.

20□HSD expression significantly correlated with hPL levels in women's plasma at week 33 to 37 of gestation, p<0.0001. In BeWo cells hPL down-regulated 20□HSD expression and P4 production – this was dose-dependent, p <0.0001. ART-exposed BeWo cells produced significantly less P4 compared to controls: median 2.8 (IQR 2.5 to 3.1) vs 3.6 (3.5 to 3.7) ng/mL, p=0.028. Inhibiting 20□HSD activity (3.6 [3.4-4.0] ng/mL) restored P4 levels.

The investigators concluded that low P4 levels observed in ART-exposed HIV positive pregnant women could be the result of higher levels of 20alpha-HSD induced by low hPL levels. And they suggested that this observation might help to identify potential new therapeutic targets that could improve birth outcomes for HIV positive pregnant women receiving ART.

Reference

Papp E et al. Low prolactin and high 20alpha- HSD may contribute to cART-induced progesterone deficits in pregnancy. 5th International Workshop on HIV & Women, 21–22 February 2015, Seattle. Oral abstract O3.

Pregnancy rates among women using ART and hormonal contraceptives in Kenya

Polly Clayden, HIV i-Base

Incident pregnancy rates in HIV positive women using the subdermal hormonal implant with efavirenz (EFV)-based ART were 2.6 times higher than in women using nevirapine (NVP)-based ART – according to a study conducted in western Kenya, presented at the 5th International Workshop on HIV & Women. [1]

Concerns have been raised by recent analyses showing EFV reduces the efficacy of subdermal contraceptive implants.

The aim of the Kenyan study was to determine whether pregnancy rates differed in women using implants or injectable depomedroxyprogesterone acetate (DMPA) and EFV- or NVP-based ART. It was a retrospective analysis of a longitudinal cohort of women aged 18 to 45 years enrolled in HIV treatment facilities and followed from January 2011 to December 2013.A total of 24,562 women contributed 94,716 observations to the analysis, with 3,331 incident pregnancies.

Adjusted incident pregnancy rates among women using implants were 5.4 (95% CI: 1.9 to 8.8) and 2.1 (95% CI: 1.1 to 3.1) per 100 women years, for women receiving EFV- and NVP-based ART respectively. For DMPA users these rates were 13 (95% CI: 9.5 to 17) and 9.3 (95% CI: 8.0 to 11.0), respectively.

In the multivariate Cox proportional hazards models, the hazard of incident pregnancy among women using implants and receiving EFV- vs NVP-based ART was 2.6 (95% CI: 1.5 to 4.5), p=0.001. For DMPA the hazard of was 1.1 (95% CI: 0.87 to 1.4), p=0.41. But DMPA users had 3 times higher incidence pregnancy than implant users.

The investigators noted that this was the largest cohort to date to suggest that the concomitant used of hormonal contraception with EFV-based ART might reduce the effectiveness of contraception.

C O M M E N T

These findings reinforce those reported previously, including at CROI earlier this year. [2]

Increased eligibility for treatment – particularly following the START results – will significantly increase the number of women of child bearing age indicated for ART. For this and other reasons, EFV-based regimens might not be the ideal first line treatment.

References

1. Patel R et al. Pregnancy rates among HIV-positive women using various forms of antiretroviral therapy and contraceptives in Kenya. 5th International Workshop on HIV & Women, 21–22 February 2015, Seattle. Oral abstract O4.
2. Scarsi K et al. Levonorgestrel implant + EFV-based ART: unintended pregnancies and associated PK data. CROI 2015. Seattle, Washington. 23-26 February 2015. Oral abstract 85LB.
   http://www.croiconference.org/sessions/levonorgestrel-implant-efv-based-art-unintended-pregnancies-and-associated-pk-data

Adolescents at increased risk of vertical transmission and poor pregnancy outcome in South Africa

Polly Clayden, HIV i-Base

Adolescent pregnant women had an increased risk of vertical transmission of HIV and poorer maternal and infant outcomes, compared to non-adolescent women, in a high HIV prevalence district in South Africa.

The study, presented at the 5th International Workshop on HIV and Women, followed a cohort of HIV positive pregnant women and their infants at three urban sentinel surveillance facilities between January 2009 and March 2012. Enhanced routine individual clinical data were captured electronically. Adolescents were defined as 19 years or younger at their first antenatal visit. Multivariate models were used to compare outcomes between adolescents and women above 19 years of age.

The evaluation included 956 mother-infant pairs, of whom 65 (6.8%) were adolescents. At baseline the adolescents were a median age of 18 years (range 13 to 19) and the older women were 28 years (20 to 44). Their baseline CD4 count was 350 cells/mm^3 (IQR 233 to 489) and this was similar between age groups, p=0.16. The median gestational age at booking was 22 weeks (IQR 17 to 27) and was similar between groups, p=0.64.

Treatment or PMTCT prophylaxis was according to WHO guidelines. ART eligible at <200 CD4 cells/mm^3 before 2010 and <350 cells/mm^3 from April 2010. Ineligible women received AZT from 28 weeks and single dose NVP in labour, and AZT from 14 weeks, single dose NVP and TDF/FTC to cover NVP tail during the respective time periods. Infants received NVP.

Adolescents were more likely to be unaware of their HIV status when booking: 75.4% vs 48.3%, adjusted risk ratio (aRR) 1.56 (95% CI: 1.34 to 1.82). They also were more likely not to be on ART at booking: 100% vs 82.8%. Median time of starting ART after first antenatal visit was 64 days (IQR 28 to 92) vs 36 days (IQR 20 to 62) for adolescents vs older women.

Adolescents were at increased risk of not receiving ART by delivery, aRR 1.32 (95% CI: 1.23 to 1.38), of being unbooked before labour, aRR 3.24 (95% CI: 0.96 to 10.9) and increased maternal mortality, aRR 35.1 (95% CI: 2.89 to 426).

Stillbirth among adolescent and older women was 9.4% and 4.5%, respectively, aRR 3.40 (95% CI: 1.61 to7.20). Vertical transmission at 6 weeks was 8.3% and 3.1% amongst infants of adolescent and older women, respectively, aRR 2.94 (95% CI: 1.01 to 8.60).

The study investigators emphasised that interventions targeting adolescents are increasingly needed if South Africa is to attain its Millennium Development Goals.

Reference

Fatti G et al. Adolescents at increased risk of mother to child transmission of HIV in South Africa. 5th International Workshop on HIV & Women, 21–22 February 2015, Seattle. Oral abstract 05.

http://regist2.virology-education.com/2015/5thHIVwomen/11_Shaikh.pdf (PDF)

Gender difference in virological response to ART

Polly Clayden, HIV i-Base

A study conducted in the UK found that although rates of virological failure are low in people starting first line ART, women and men who have sex with women (MSW) remain more likely to experience this than men who have sex with men (MSM). [1] There was no evidence that the gap is narrowing for those starting ART in more recent years.

A related US study suggested gender and ethnicity differences in ART disruption might explain some of the differences seen in treatment outcomes among HIV positive women and especially African American women. [2]. Both studies were presented at the 5th International Workshop on HIV & Women.

The first study was in ART-naive participants with a sexual risk for HIV transmission attending the Royal Free Hospital. Those included started ART between January 2001 and July 2013 and had documented viral load measurements at 12 to 18 months and 24 to 30 months from initiation.

The investigators assessed the proportion of participants with viral load non-response (>200 copies/mL) by gender/sexual orientation group and by year of ART initiation. Logistic regression adjusted for ethnicity, age and ART regimen was used to evaluate whether the association between gender/sexual orientation and virological failure changed over time.

A total of 1606 participants were included: 864 were MSM, 283 MSW and 458 were women. For MSM, MSW and women respectively: 1%, 52% and 66% were of black African ethnicity; 83%, 27% and 15% were white; and 16%, 22% and 22% were other. Median baseline age was 38, 41 and 36 years, CD4 was 268, 160 and 205 cells/mm3 and viral load was 5.0, 5.0 and 4.8 log copies/mL. First line ART regimens were similar with slightly more women starting with PI-based regimens (49%) compared to the other two subgroups (44%).

For MSM, MSW and women respectively: 7%, 14% and 21% had viral load >200 copies/mL at 12 months and 9%, 14% and 20% at 24 months, all comparisons p<0.0001.

Across all three subgroups, proportions of participants with virological failure after 12 and 24 months of ART were improved in later years, all comparisons p<0.001.

For MSM, MSW and women respectively, change in 12-month viral load non-response per calendar year by gender/sexual orientation (adjusted OR): 0.77 (95% CI: 0.07 to 0.84), 0.85 (0.75 to 0.96) and 0.86 (0.79 to 0.93), p=0.15. Change in 24-month viral load non-response per calendar year by gender/sexual orientation (adjusted OR): 0.73 (95% CI: 0.66 to 0.81), 0.82 (0.71 to 0.94) and 0.86 (0.78 to 0.95), p=0.072.

The investigators noted that women had more ART disruptions (switched or interrupted treatment) so non-adherence might contribute to the observed differences. They also suggested that poorer viral load outcomes in women and MSW might be related to: socio-economic status, time in the UK, family circumstances, psychological factors and comorbidities.

Their findings show that even in a high income setting with universal free access to healthcare, women are at higher risk of virological failure. Emphasis should be placed on improved/tailored support for HIV positive women.

The University of Alabama at Birmingham conducted the second study. This was designed to evaluate differences in ART discontinuation by gender and ethnicity. It was a retrospective medical chart review including ART naive, HIV positive patients, aged 18 and above, attending an urban outpatient clinic in Birmingham, AL between January 2004 and February 2009.

The evaluation included: socio-demographic and clinical factors, ART regimens with start and stop dates, and reasons for change.

Regimens were considered discontinued or changed if any antiretroviral within the regimen was discontinued or if any additional one was added.

The investigators used Cox proportional hazards regression to model time to individual regimen discontinuation and Poisson regression to model the numbers of days of treatment interruption (≥14 days).

There were 422 HIV positive participants included in the analysis: 90 (21%) were women and 226 (54%) were African American (64 African American women, 162 African American men, 22 white women, 151 white men and 23 with ethnicity other/unknown).

Overall 243 (58%) participants discontinued or changed at least one antiretroviral during a median follow up of 2.8 years. With white men – who had the lowest discontinuation rate – as reference the hazard ratios for discontinuation for African American women, African American men and white women were respectively: 1.6 (95% CI: 1.2 to 2.2), p=0.004; 1.4 (1.1 to 1.8), p=0.011; and white women 1.2 (0.70 to 2.0), p=0.538.

The most frequent reasons for discontinuing ART for African American women were: poor adherence (57.5%), other medical conditions (15.1%%), and GI toxicity (9.6%).

The overall treatment interruption rate was 13.9 days per year, with African Americans interrupting treatment for more days per year than white participants: 17.5 vs 9.4 days/year, p=0.05.

The investigators suggested that the differences in rates of discontinuation might account for some of the less favourable ART outcomes observed in African American women.

References
1. Burch LS et al. Is the gender difference in virological response to ART declining over time? 5th International Workshop on HIV & Women, 21 – 22 February 2015, Seattle. Oral abstract 14.
http://regist2.virology-education.com/2015/5thHIVwomen/24_Burch.pdf (PDF)
2. Kempf MC et al. Gender and race differences in persistence of HIV treatment regimens. 5th International Workshop on HIV & Women, 21 – 22 February 2015, Seattle. Oral abstract 15.
http://regist2.virology-education.com/2015/5thHIVwomen/24_Burch.pdf (PDF)

TREATMENT ACCESS

Generic dolutegravir submitted to FDA for tentative approval

Simon Collins, HIV i-Base

On 26 May 2015, the most recently approved, and possible most advanced, HIV medicine was submitted to the US FDA for tentative approval as a generic formulation. [1]

This is significant move towards greater equity of access to modern treatment between high and low income countries.

Dolutegravir is a once-daily low millgram (50 mg) dose integrase inhibitor that does not require PK boosting and that can be taken with or without food, and that has a high genetic barrier to drug resistance. These are all properties that argue for the global need for dolutegravir in all countries.

After FDA approval in 2012 [2] dolutegravir was rapidly included as preferred as a first-line option in US treatment guidelines. [3] This was based on superiority or non-inferiority data to other commonly used first and second line drugs.

FDA filing for the generic version has come less than two years after US approval, and well within the existing patent life. This was achieved by a collaboration between ViiV Healthcare, Aurobindo Pharma and the Clinton Health Access Initiative (CHAI).

Tentative approval will enable generic dolutegravir to be prescribed in generic-accessible low- and middle-income countries (LMIC), including under PEPFAR funded projects.

Dolutegravir was approved by the EMA in January 2014 (and by the NHS in the UK in January 2015).

C O M M E N T

During the regulatory and approval process for dolutegravir, based on the PK profile, the need for better first and second line drugs in LMIC and the complex pricing for new drugs, we suggested in HTB that rapid access to dolutegravir in LMIC had the potential to drive better standards compared to high-income countries, if access was prioritised as an advocacy issue for global health.

This is an example for how global health care can work for the benefit of all citizens and is only possible because of the previous work since 2000 to establish access to HIV treatment as a global right.

This remarkable progress with dolutegravir access is also largely due to CHAI deciding to prioritise access to medicines with the highest global need. Previously CHAI responded to community demands tor effective and affordable second-line therapy by achieved the lowest cost access to second-line therapy by negotiating bulk discounts for atazanavir/ritonavir.

References
1. ViiV press statement. ViiV Healthcare and CHAI collaboration delivers second milestone with first filing with the FDA of generic dolutegravir by Aurobindo Pharma for the treatment of HIV. (26 May 2015).
https://www.viivhealthcare.com/media/
2. FDA press statement. FDA approves new drug to treat HIV infection. (12 August 2013).
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm364744.htm
3. US DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.
http://aidsinfo.nih.gov/guidelines
4. ViiV Healthcare press statement. ViiV Healthcare's new HIV medicine Tivicay (dolutegravir) is approved in Europe. (21 January 2014).
http://www.viivhealthcare.com/media.aspx
5. NHS England. Clinical Commissioning Policy: Dolutegravir for treatment of HIV- 1 in adults and adolescents. Reference: NHS England B06/P/a. January 2015.
http://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b06

Lopinavir/ritonavir pellets tentatively approved by the FDA

Polly Clayden, HIV i-Base

On 21 May 2015, the US FDA tentatively approved lopinavir/ritonavir (LPV/r) 40/10mg pellets manufactured by Cipla for infants and young children less than three years old.

C O M M E N T

This is the first solid form of LPV/r for this age group. The World Health Organization (WHO) recommends LPV/r-based regimens as preferred for infants and young children. Compliance with the recommendation has been difficult as this boosted protease inhibitor was previously only available as syrups, which are too complicated to use for many programmes in low- and middle-income countries.

The Drugs for Neglected Diseases initiative (DNDi) is waiting for the production of the clinical batch of the pellets to begin the LIVING study (implementation study using the new formulation) in Kenya. All the necessary regulatory approvals are in place in Kenya to start.

DNDi is working on an improved taste masked granule formulation of LPV/r (a component of a fixed dose combination 4-in-1 regimen), which will be tested in HIV negative adults very soon.

We hope that this approval will lead to early access for young children to a solid LPV/r-based formulation.

References

US Food and Drug Administration. Tentative approval letter. (21 May 2015).

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/205425Orig1s000TAltr.pdf (PDF)

http://www.fda.gov/InternationalPrograms/PEPFAR/ucm119231.htm

ANTIRETROVIRALS

EMA approves coformulated atazanavir/cobicistat

EMA press release

On 21 May 2015, the Committee for Medicinal Products for Human Use (CHMP) recommended approval in the EU for the combined formulation of atazanavir/cobicistat (300 mg/150 mg) film coated tablets.

The indication is for use with other antiretrovirals to treat HIV-1 in people without mutations associated with drug resistance to atazanavir.

This combines the protease inhibitor atazanavir with the PK booster cobicistat in a single pill. The brand name is Evotaz and it is manufacted by Bristol-Myers Squibb.

For full details see the summary of product characteristics (SmPC).

Source: ommittee for Medicinal Products for Human Use (CHMP). Evotaz Summary of opinion (initial authorisation). EMA/CHMP/277547/2015. (21 May 2015).

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003904/smops/Positive/human_smop_000830.jsp&mid=WC0b01ac058001d127

Dual F/TAF formulation under evaluation by EMA

Gilead press release

On 28 May 2015, Gilead issues a press statement noting that regulatory submission for the dual formulation of FTC (emtricitabine) plus tenofovir alafenamide (TAF) has been accepted by the European Medicines Agency (EMA).

This includes two different doses for F/TAF: 200/10 mg and 200/25 mg.

Source: Gilead press statement. European Medicines Agency Validates Gilead's Marketing Application for Fixed-Dose Combination of Emtricitabine and Tenofovir Alafenamide for HIV Treatment. (28 May 2015).

http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-newsArticle&ID=2054021#sthash.qmj4GCeW.dpuf

TREATMENT GUIDELINES

US guidelines shift to integrase-based combinations for first-line treatment: Atripla relegated due to side effects

Simon Collins, HIV i-Base

The latest update of the leading US treatment guidelines, produced by a panel from the Department of Health and Human Sciences (DHHS) was published online on 9 April 2015. [1]

These comprehensive, evidence-based guidelines now run to almost 300 pages including over 30 tables previous. This is the first update since May 2014.

Starting treatment: choice of ART

One of the main changes is that choice of first-line combinations (see Tables 6 and 7) are predominantly integrase inhibitor based combinations or the protease inhibitor darunavir/ritonavir. All are graded A1 and all-but-one include tenofovir/FTC as background NRTIs.

- Dolutegravir/abacavir/3TC single tablet (Triumeq) - if HLA-B*5701 negative.
- Dolutegravir plus tenofovir/FTC.
- Elvitegravir/cobicistat/tenofovir/FTC single tablet (Stribild) - if CrCl is >70 mL/min.
- Raltegravir plus tenofovir/FTC.
- Darunavir/ritonavir plus tenofovir/FTC.

Four alternative combinations are included, all with a lower grade B1.

- Efavirenz/tenofovir/FTC single tablet (Atripla) - due to CNS-related side effects.
- Rilpivirine/tenofovir/FTC single tablet (Eviplera/Complera) - but only if viral load is <100,000 copies/mL and CD4 counts >200 cells/mm^3.
- Atazanavir/ritonavir plus tenofovir/FTC.
- Atazanavir/cobicistat plus tenofovir/FTC - but only if estimated CrCl >70 mL/min.

Two alternative combinations are included with an even lower grade (BII or BIII).

- Darunavir/ritonavir or darunavir/cobicistat plus abacavir/3TC (only if HLA-B*5701 negative)
- Darunavir/cobicistat plus tenofovir/FTC - but only if estimated CrCl >70 mL/min.

Seven other combinations are included as “Other options” with a CI or CII rating, mostly with appropriate clinical restrictions.

Virologic failure

The following key updates have been made to the management of virologic failure. This includes new text for options depending on current and previous drug class and history. (Section H 5-7)

Discordant CD4 responses on treatment

A new expanded section has been included for people on treatment who have poor CD4 responses and/or persistent inflammation.

This section notes that there are currently no proven strategies for people in this category and that monitoring of immune activation or inflammation markers is not recommended. This is because no interventions to reduce these markers have shown clinical benefits. (see section H12-14).

Acute/early HIV Infection

This section has been updated to include the 2014 recommendation in the US for diagnosis of HIV infection, including in individuals with acute/early HIV infection.

Viral failure with new onset neurological symptoms

A new short section has been added to highlight a rare form of virologic failure related to viraemia in CSF despite viral suppression in peripheral blood. (Section H-7)

Additional updates have been included for hepatitis C coinfection, drug interaction mechanisms and tables, management of HIV-2, stopping ART, therapeutic drug monitoring, drug characteristics and drug pricing.

C O M M E N T

The guidelines produced for use in the US heath care system are an essential reference document for an evaluation of evidence in that setting.

Importantly, the emphasis on individualised treatment notes that the most appropriate combinations for some people might be different to those prioritised in the guidelines.

The rational for dropping Atripla is due to "concerns about the tolerability of efavirenz (EFV) in clinical trials and practice, especially the high rate of central nervous system (CNS) related toxicities" and also references the higher rate of suicide or suicidal ideation in an analysis of four randomised studies.

EFV-associated side effects have been a long-standing community concern since approval in 1998, when it quickly became clear that tolerability was significantly different in practice than that reported in registrational studies.

UK (BHIVA) guidelines are currently in the process of being updated and a draft for comments is expected within the next two months.

Reference

US DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, April 2015.
http://aidsinfo.nih.gov/guidelines
Direct PDF link:
http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf (PDF)

EACS guidelines: translations in 11 languages now available online

EACS news release

The combined HIV clinical guidelines from the European AIDS Clinical Society are now available in 11 languages in PDF format.

Languages for the translations are: Albanian, Croatian, English, French, Greek, Portuguese, Romanian, Russian, Serbian, Slovak, Spanish and Turkish. A Japanese version is also being produced.

http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

The EACS guidelines are developed as a practical resource based on summary table and notes. They are organised in five main sections;

- Assessment and monitoring.
- Antiretroviral treatment.
- Complications and comorbidities.
- Hepatitis B and C.
- Opportunistic infections.

Translations are from the November 2014 edition. The English version is available online and as a mobile App (for Apple and Android). The next revision of the guidelines is due to be published at the EACS conference in October 2015.

BASIC SCIENCE & CURE RESEARCH

Timing of very early ART to limit early HIV-related mucosal dysfunction

Simon Collins, HIV i-Base

A paper published recently by Alexandra Schuetz and colleagues as an open access article in PLoS Pathogens is important for providing important data on the timing of early antiretroviral treatment (ART). The results highlight that in the context of the very early window after infection, each day might be time-critical to limit mucosal damage to the gastrointestinal (GI) tract. [1]

This is an ongoing, prospective, open-label Thai study that enrolled 42 people between May 2009 and March 2012 who were diagnosed either prior to or shortly after HIV seroconversion (Fiebig stages I-V) as part of the RV304/SEARCH 013 study. The study included optional sigmoid biopsy of gut-associated lymphoid tissue (GALT) at baseline and month six and the option to start early treatment.

The participants were gay men (n=35), bisexual men (n=4) and heterosexual women (n=3) with 75% of participants infected with HIV recombinant subtype CRF01_AE. Median age was 29 (range 19 to 48). Median time since infection was an estimated 16 days (+/-SD 6.6) with 13, 4, 21, 1 and 3 participants diagnosed in Fiebig stages I, II, III, IV and V respectively. Due to low numbers, participants with stages I/II and IV/V were combined for the analyses. In people using ART, treatment was started an average of 3 days post-enrolment (range 0 to 5 days). At baseline, median CD4 and viral load were 465 cells/mm^3 (range 132 to 1127) and 5.5 log copies/mL (range 2.8 to 7.7), respectively.

In addition, 10 HIV negative people (matched for age, gender and risk group) and 5 treatment naive HIV positive people in chronic infection (CHI) - mean 298 days (SD +/– 154) duration of infection; Fiebig VI, p31 positive), were enrolled as controls.

The Fiebig classification for stages of seroconversion includes median (95%CI) cumulative days since infection of 5.0 (3.1, 8.1), 10.3 (7.1, 13.5), 13.5 (10.0, 17.0), 19.1 (15.3, 22.9) and 88.6 (47.4, 129.8), for stages I, II, III, IV and V respectively. Diagnostic results include being PCR positive from stage I, p-24 positive from stage II, third generation ELISA positive from stage III, Western blot (WB) indeterminate at stage IV and WB determined (2 out of 3: p24, p41, p120; but p31 negative) at stage V.

Within weeks of HIV infection, an early CD4 depletion in GALT occurs and subsequent increased levels of microbial translocation ("leaky gut") are generally hypothesised as playing a key roll in persistent immune activation during chronic HIV infection.

Gut mucosal function was determined by number and function of Th17 cells which play an essential role in maintaining the gut epithelium by responding to extracellular bacterial and fungi and in producing IL-22 which enhances epithelial regeneration.

Reduced immune and gut function

In a complicated data set looking at absolute and percentage CD4 and CD8 counts and related cellar sub-sets in both plasma and gut tissue and Th17/Th22 cells, results tended to show significant differences by Fiebig stage III.

For example, at baseline the percentage of CD4 cells in gut tissue and plasma were already established depending on time from infection: 49% FI/II, 35% FIII and 17% FIV/V compared to 18% in CHI and 56% in HIV negative controls in sigmoid colon and 35% FI/II, 26% F III, 21% F IV/V compared to 18% in CHI and 53% in HIV negative in blood.

The timing for the decrease in proportion of Th17 cells (in the subset of patients with viable mononuclear cells from sigmoid tissue) was 12.8% in FI/II to 7.9% in FIII, and 2.3% in F IV/V. This compared to 0.9% in the CHI and 13.5% in the HIV negative control groups. Similar results were reported for Th22 cells: 2.9% FI/II, 1.3% in FIII and 0.4% in F IV/V, compared to 3.6% in HIV negative controls.

In gut tissue, the frequencies of IL-17 and IL-17/IL-22 producing CD4 cells also correlated positively with CD4 cells ($p < 0.001$) and inversely with colonic viral load ($p<0.03$).

Th17 cell function was assessed by co-expression of IFN-alpha, IL-2 and/or IL-22 and showed a dramatic loss from 6.5% in FI/II to 0.3% in FIII ($p=0.02$) with these polyfunctional cells entirely depleted in the chronically infected control group.

A reduced proportion of Th17 cells was inversely correlated with plasma markers of immune activation: C-reactive protein ($r = –0.42$, $p=0.03$), hyaluronic acid ($r = –0.53$, $p=0.003$), TNF-alpha ($r = –0.49$, $p=0.03$) and IP-10 ($r = –0.71$, $p<0.001$). However, no correlations were seen with biomarkers for intestinal damage (I-FABP), microbial translocation (LPS and sCD14) or coagulation (D-dimer).

Impact of early ART

After six months on ART, 29 participants had a second sigmoid biopsy: 14 from stage FI/II and 15 stage FIII. All patients experienced CD4 increases and had undetectable viral load in plasma (with 28/29 undetectable in sigmoid tissue).

Participants treated at FI/II maintained polyfunctional TH17 cells, with no loss of either total TH17 cells or the proportion of triple cytokine producing Th17 cells post-ART. Participants treated during FIII showed a restoration of TH17 cells (7.9% pre- to 10.2% post-ART, p=0.05) but not a restoration of functional triple-cytokine producing cells, which remained comparable to untreated controls in chronic infection.

However, treatment at FIII significantly decreased plasma levels of CRP (from 1343 to 483 pg/mL, p=0.02) and D-dimer (from 359 to 146 pg/mL, p<0.001). Markers of activated (HLA-DRCD38+) CD8 T cells that were significantly higher in both FI/II and FIII participants in plasma and colon tissue prior to ART, only normalised in people treated during FI/II. Although participants treated at FIII had reductions in CD8 activation, this failed to normalise after 6 months treatment (sigmoid colon: 5.0% post-ART vs 8.9% pre-ART, p<0.001; vs 0.1% for HIV negative controls, p<0.001; peripheral blood: 9.0% post-ART vs 15% pre-ART, p=0.003; vs 3.0% HIV negative, p<0.001).

While the researchers noted that limitations of the study included relatively low numbers for some sample analyses, and for the control group, and that a control group of patients treated during chronic infection would also be important, they emphasised that their cohort is currently unique in regard to early diagnosis, sampling and responses to early ART.

C O M M E N T

Similar to other research, this study reported that the depletion of CD4 and CD4+CCR5+, including in the lamina propria (main effector GI site) and correlating viral HIV viral load, often occurs within days of HIV infection, and prior to Fiebig stages I/II.

Treatment during FI/II normalised immune activation and some other important markers of mucosal immunity and function were protected when ART was started during FI/II, but not when treatment was delayed to FIII. However, while such early diagnosis may still be rare, aligning these cases to a research setting with this focus could have important clinical as well as research outcomes.

A significant and increasing percentage of people in the UK are diagnosed during acute HIV infection. Of these, a recent patient survey presented at BHIVA 2015 indicated a positive interest in starting earlier treatment that was not matched by being offered early treatment. [2] Conversely, a similar survey of health providers attitudes by the same researchers, showed than some doctors are reluctant to offer treatment in early infection, and do not always follow BHIVA guidelines to discuss the roll of TasP in this patient group. [3]

The RIVER study is currently enrolling UK patients diagnosed in early infection and will follow patients irrespective of whether ART is used. This cohort will be an important opportunity to contribute data to the field of HIV cure research. [4]

In people diagnosed at later stages of acute infection, the study also reports that early ART might have plausible benefits, including reduced CD8 activation compared to chronic infection (if not normalised compared to HIV negative).

As BHIVA guidelines include the recommendation to discuss the benefit of ART in reducing HIV infectiousness to all HIV positive people, including at the initial diagnosis, greater awareness of this early clinical window is an area of patient care that could perhaps be improved. [5]

References

1. Schuetz A et al. Initiation of ART during early acute HIV infection preserves mucosal Th17 function and reverse HIV-related immune activation. PLoS Pathogens, December 2014: 10(12)e1004543.
   http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004543
2. Fox J et al. UK clinicians' approach to ART in primary HIV infection; comparison with the BHIVA guidelines. 21st Annual BHIVA Conference, 21-24 April 2015, Brighton. Oral abstract O13.
3. Fox J et al. UK survey of HIV-positive people's attitudes towards research. 21st Annual BHIVA Conference, 21-24 April 2015, Brighton. Poster abstract P39
4. RIVER study. Research In Viral Eradication of HIV Reservoirs. EudraCT number 2014-001425-32.
   http://www.isrctn.com/ISRCTN83717528
5. BHIVA guidelines, British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012, (updated November 2013). HIV Medicine (2014), 15 (Suppl. 1), 1–85. DOI: 10.1111/hiv.12119.
   http://www.bhiva.org/documents/guidelines

Broad CD8 T cell responses are required to overcome dominance of CTL escape in the latent HIV reservoir

Gareth Hardy, HIV i-Base

Results published on 15 January 2015 in Nature reveal that in chronic HIV infection the latent reservoir is almost entirely composed of viral sequences that have evolved escape mutations against cytotoxic T lymphocytes (CTL). [1]

The results published by Kai Deng et al from Johns Hopkins University School of Medicine, have implications for candidate cure protocols that seek to modulate host immune responses against reactivated latent virus. They also suggest that the latent reservoir may be subject to more turn-over than previously thought.

Reservoir elimination strategies might be made more effective by modulating immune responses to prevent viral spread to uninfected cells. CTLs exert strong selective pressure on HIV during acute infection, against which escape mutations rapidly evolve. It is not clear to what degree CTL escape variants constitute the latent reservoir, as infection progresses. If viruses induced from the latent reservoir are resistant to CTL responses, any protocol that relies on boosting CTLs against immunodominant epitopes is unlikely to be effective.

The researchers investigated whether individuals who start ART in chronic infection (at least 3 months after infection), when most of their HIV will have evolved CTL escape mutations, have CTLs that can recognise their own latent virus. They conducted deep-sequencing of gag proviral DNA in resting CD4 T cells to investigate the presence of CTL escape mutations, in 25 HIV-infected individuals, of whom 10 initiated ART during the acute phase (AP) of infection, defined as within 3 months of infection, and 15 initiated ART during the chronic phase (CP).

Deng et al found that proviral sequences from CP-patients were completely dominated by previously documented CTL escape mutations. In several CTL epitopes (SL9, RK9 and TW10) close to 100% of sequences contained CTL escape mutations. In contrast, very few CTL escape mutations were found in the proviral sequences of AP-patients. This striking difference between AP and CP-treated patients suggests that unless ART is started very early, the viral reservoir becomes dominated by variants resistant to common CTL responses.

ELISpot assays were conducted to assess the reactivity of patients' CTLs to the mutant epitopes versus their wild types, in 7 CP-subjects. Their CTL responses to peptides containing escape sequences were very low, if detectable at all. In contrast, strong CTL responses were observed against wild type peptides. As most proviruses are not replication competent, it was important to determine whether the CTL escape mutations found in patients' proviruses were capable of replicating and therefore able to contribute to viral rebound. Virus was grown from 9 CP-patients' CD4 cells following T cell activation and found to include all the CTL escape mutations observed in proviruses. This suggests that the CTL escape variants that dominate the reservoir will be released and replicate if viral latency is reversed.

Deng at al next assessed whether CTLs from CP-patients retained the ability to kill cells infected with escape variants. Autologous CD4 T cells from 13 CP-subjects were infected with autologous, replication-competent virus derived from their own reservoirs and co-cultured with pre-stimulated CTLs. CTLs pre-stimulated with a gag peptide mix eliminated a median of 61% of infected cells from culture, compared with a median of 23% for CTLs that had not been pre-stimulated. Therefore, while patients' CTLs could still eliminate infected cells despite the presence of CTL escape mutations, they required pre-stimulation with antigen in order to do so.

To characterise which CTL population contributed to killing activity, Deng et al compared the CTL population that targets wild type epitopes in which the reservoir has been found to contain escape mutations, versus the population that targets epitopes which are not mutated in the reservoir. For example in one CP-patient, the viral sequence in the CTL epitope SL9 was found to have escape mutations in close to 100% of that patient's proviruses, whereas the CTL epitope WF9 had no escape variants observed in the proviruses. CTLs from two CP-patients were pre-stimulated with IL-2 or different synthetic peptides representing the wild-type forms of the relevant epitopes (eg SL9 or WF9) and subsequently co-cultured with autologous CD4 T cells that had been infected with autologous reservoir-derived viruses. The proportion of target CD4 T cells infected with HIV was significantly reduced by CTLs stimulated with single peptide epitopes to which no escape had occurred, in comparison to IL-2 treated cells ($p < 0.01$). In contrast, CTLs stimulated with single peptide epitopes to which escape had occurred had no effect on the proportion of HIV infected target CD4 T cells. The greatest killing effect was observed with CTLs that had been stimulated with a mixture of gag peptides ($p < 0.001$).

In order to assess whether CTLs that recognise unmutated viral epitopes are capable of inhibiting HIV replication and clearing infected cells, Deng et al generated a humanised mouse model using bone marrow from two CP-patients. Autologous virus was grown in the lab from the two patients viral reservoirs, which were used to infect the mice. Two weeks later, the mice were infused with autologous CD8 T cells from the donor patients that had been stimulated with viral peptides.

In control mice (where infused patient CD8 T cells had not been pre-stimulated with viral peptides) or mice that had received CD8 T cells that had been pre-stimulated with the wild type variant of the SL9 peptide (against which CTL escape had evolved), both plasma viral load and proviral DNA increased from day 14 to day 29 after infection. In contrast,

mice infused with CD8 T cells that had been pre-stimulated with the wild type variant of the WF9 peptide (against which no CTL escape had evolved) experienced significantly lower levels of viral replication than controls or SL9-CD8 T cell-treated mice ($p < 0.05$). Mice infused with CD8 T cells that had been pre-stimulated with a peptide mix experienced 100-1000 fold less viral replication than control or SL9-CD8 T cell-treated mice ($p < 0.05$). Dramatically, two of three of the mice infused with CD8 T cell stimulated with the peptide-mix achieved undetectable levels of both plasma viral load and peripheral blood proviral DNA.

These data demonstrate that only CTL clones that target subdominant unmuated epitopes are effective against the CTL escape variants that dominate the viral reservoirs of patients who initiate ART during chronic infection. However, CTLs that target immunodominant epitopes, to which HIV will have evolved escape, are unlikely to have an effect on viral replication. These results have implications for immune-based viral eradication strategies, and suggest that reversal of viral latency should be supported by induction of subdominant CTL responses.

Another important implication of this data is that the viral reservoir may be less stable than thought. To be reconstituted with immune escape variants between acute and chronic HIV infection the reservoir must undergo replenishment. This observation alone should be grounds for reconsidering the assumed stability of the HIV reservoir.

Reference

Kai Deng et al. Broad CTL response is required to clear latent HIV-1 due to dominance of escape mutations. Nature. 15 January 2015. Vol 517. 381-387.

http://www.nature.com/nature/journal/v517/n7534/full/nature14053.html

Broadly neutralising antibody suppresses HIV in clinical trial

Richard Jefferys, TAG

The past decade has seen a boom in the identification of antibodies capable of potently neutralising a broad array of different HIV isolates (broadly neutralising antibodies or bNAbs).

New technologies that allow antibodies to be fished from huge numbers of individual B cells and tested for activity have spurred this rapid acceleration of discovery. There is now intense interest in learning whether the blossoming array of bNAbs can be put to therapeutic and preventive use. A paper published yesterday in Nature describes encouraging results from a phase I trial involving the bNAb 3BNC117. [1] Reflecting the level of interest in the topic, the paper has attracted extensive press coverage.

Led by Marina Caskey from Rockefeller University, the study enrolled 12 HIV negative and 17 HIV positive individuals (including two on ART) who received a single infusion of 3BNC117 at various doses (1, 3, 10 or 30 mg kg−1). The infusions were well tolerated; there were no grade 3 or greater adverse events and no laboratory abnormalities. HIV positive participants receiving the two highest doses showed significant declines in viral load, with the exception of one individual whose virus turned out to be resistant to 3BNC117 at baseline. The eight recipients of the 30 mg kg−1 dose experienced reductions in viral load ranging from 0.8 to 2.5 logs, with four remaining below baseline at the last reported follow-up (day 56 post-infusion). Evidence of HIV evolving resistance to 3BNC117 was documented, particularly in the lowest dose grouThe study confirms that bNAbs are active against HIV in humans, consistent with experiments in humanised mice [2] and macaques [3, 4]. A number of pathways toward the therapeutic and preventive use of bNAbs can now be explored, but could still prove challenging to navigate. As the authors of the paper note, bNAbs will likely need to be used in combination to maximise activity and prevent resistance; they may also benefit from additional modifications to enhance their potency and persistence in the body.

On the therapeutic side, there is the potential to combine bNAbs with latency-reversing agents with the aim of promoting clearance of the viral reservoir via antibody-mediated cellular cytotoxicity (ADCC) [5]. Another approach is to test whether combination bNAbs could provide a long-acting alternative or supplement to daily ART. A trial involving the combination of the bNAb VRC01 plus ART is due to start later this year in individuals with acute HIV infection in Thailand (see Jintanat Ananworanich's presentation at last year's Forum for Collaborative HIV Research cure research meeting for background). [6] Dan Barouch has plans to study the bNAb PGT121 in several different populations, as outlined in his talk at CROI 2015. [7]

On the preventive side, there is interest in evaluating the efficacy of passive immunisation (either intravenous or subcutaneous) with bNAbs in both high-risk adults and infants exposed to HIV via breastfeeding (see the webcast of Barney Graham's presentation at the 2014 R4P conference for additional information). [8]

While this research is likely to move forward, there are many lingering uncertainties regarding passive immunisation: the need for repeated injections raises the concern of practicality (particularly in the prevention context), and another issue that has to be considered is the complexity and cost of bNAb manufacture (for an informative excursion into the industry of bNAb production, see Michael Dumiak's 2014 IAVI Report article [9]. As has been covered previously, there is at least one alternative, potentially simpler method of bNAb delivery: gene transfer with adeno-associated virus (AAV), which is being tested in an ongoing phase I trial in the UK. But it is not yet known if AAV can deliver bNAb levels high enough to be efficacious.

Source
TAG Basic Science blog (09 April 2015)
http://tagbasicscienceproject.typepad.com

References
1. Caskey M et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralising antibody 3BNC117. Nature (2015) doi:10.1038/nature14411. http://www.nature.com/nature/journal/vaop/ncurrent/pdf/nature14411.pdf (PDF)
2. Klein F et al. HIV therapy by a combination of broadly neutralising antibodies in humanised mice. Nature. 2012 Dec 6; 492(7427): 10.1038/nature11604. doi: 10.1038/nature11604. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3809838
3. Barouch DH et al. Therapeutic efficacy of potent neutralising HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys. Nature (2013) doi:10.1038/nature12744. http://www.nature.com/nature/journal/v503/n7475/abs/nature12744.html
4. Shingai M et al. Antibody-mediated immunotherapy of macaques chronically infected with SHIV suppresses viraemia. Nature (2013) doi:10.1038/nature12746. http://www.nature.com/nature/journal/vaop/ncurrent/abs/nature12746.html
5. http://en.wikipedia.org/wiki/Antibody-dependent_cell-mediated_cytotoxicity
6. Ananworanich J. RV397: Therapeutic efficacy of broadly neutralising HIV-1 specific monoclonal antibodies in Thai patients who initiated antiretroviral therapy during early acute HIV infection. Forum for Collaborative HIV Research cure research meeting, 2014. http://www.hivforum.org/storage/documents/2014/HIVCure/case_study_rv397_ja.pdf (PDF)
7. Barouch D. Harnessing antibodies for prevention and therapeutics. 22nd CROI, 23-26 February 2015, Seattle. http://www.croiwebcasts.org/console/player/25642
8. Graham B. Differential use of antibodies in prevention. R4P conference, 28-31 October 2014, Cape Town. http://webcasts.hivr4p.org/console/player/25262
9. Dumiak M. Making it to manufacturing. IAVI Report 18(2):2014. http://www.iavireport.org/Back-Issues/Pages/Making-it-to-Manufacturing.aspx
10. A Phase 1, randomised, blinded, dose-escalation study of rAAV1-PG9DP recombinant AAV vector coding for PG9 antibody in healthy male adults. https://clinicaltrials.gov/ct2/show/NCT01937455

TB COINFECTION

New clinical trial for extensively drug resistant TB (XDR-TB)

Simon Collins, HIV i-Base

On 14 May 2015, the TB Alliance announced the launch of a new clinical trial to test a new all-oral regimen for extensively drug-resistant TB in South Africa. [1]

The Nix-TB study is important for the development of a universal treatment for all types of TB. The study also has the potential to shorten, simplify, and improve treatment for XDR-TB.

XDR-TB is defined as being resistant to four commonly used anti-TB drugs. XDR-TB has been reported in 100 countries. Treatment is complicated, taking two years or longer, is associated with high rates of side effects and low rates of success. There are currently no regulatory-approved drugs to treat XDR-TB. In a recent review, only 16% of people with XDR-TB were cured after two years of treatment in South Africa. [2]

The three drugs being tested in Nix-TB are:

- Bedaquiline (B), which received conditional regulatory approval in several high-TB disease burden countries.
- Pretomanid (Pa), a new antibacterial drug compound, currently in clinical trials.
- Linezolid, an oxazolidinone, which has been used off-label to treat TB.

The TB Alliance is sponsoring the trial, collaborating with and Janssen, the manufacturer of bedaqualine. In 2009 Janssen granted a royalty-free license to the TB Alliance for the development and marketing of bedaquiline in the field of drug-susceptible TB.

The cost for the initial phase of Nix-TB is covered by a group of long standing TB Alliance donors. TB Alliance is starting to bring together additional funding to expand the study and the number of sites.

References
1. TB Alliance press release. TB Alliance launches “Nix-TB” clinical trial to test new XDR-TB treatment. (14 May 2015). http://www.tballiance.org/newscenter/view-brief.php?id=1125
2. Pietersen E et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. The Lancet, Volume 383, No. 9924, p1230–1239, 5 April 2014. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)62675-6/abstract

MSF report and call to action: Promising new TB drugs are not reaching patients

Simon Collins, HIV i-Base

A new report from Médecins Sans Frontières (MSF) highlights disappointment in how little has changed in terms of global access to new TB treatments over the last two years. This is despite the development of two new drugs to treat drug-resistant TB - the first for over 50 years. [1]

The MSF press release for the report states: "The reality has not yet matched our hopes. In the intervening two years, companies and researchers have received awards, accolades and reams of media coverage for introducing two new drugs to tackle TB, but meanwhile patients are largely stuck facing the same dismal outcomes they have for decades. To date, fewer than 1,000 people worldwide have been able to access the two new TB drugs – bedaquiline (made by Janssen/Johnson & Johnson) and delamanid (made by Otsuka) – just a fraction of those who desperately need them."

The report includes an analysis of why progress has been so slow.

MSF and more than 80 other organisations have signed a call to action for a new a consortium to speed up change that the World Health Organization (WHO) will convene.

Three key goals are:

1. To quick start access to new drugs. To ensure 500 patients are started on regimens that include bedaquiline by July 2015, and 500 patients are started on regimens that include delamanid by January 2016.
2. To optimise DR-TB treatment. Provide technical assistance for implementation plans for the top 25 endemic countries by 2016. Ensure the two new TB drugs are part of routine treatment in 20 countries by the end of 2016 and 52 countries by the end of 2019. And ensure that key re-purposed drugs are in use by the national TB programmes.
3. Prioritise regulatory approvals. Ensure that both new drugs have been filed for registration in 25 countries by the beginning of 2016 and in 52 countries by 2017. To ensure that the drugs are registered for use, or import waivers are in place, by 2016.

Reference

1. MSF press statement. Ready, set, slow down: new and promising DR-TB drugs are grabbing headlines but not reaching patients. (14 May 2015). https://www.msfaccess.org/content/ready-set-slow-down-new-and-promising-dr-tb-drugs-are-grabbing-headlines-not-reaching
2. MSF call to action. Accelerate access to DR-TB drugs. https://www.msfaccess.org/content/call-action-accelerate-access-dr-tb-drugs

HEPATITIS COINFECTION

Sofosbuvir access: new patent challenges to sofosbuvir

Simon Collins, HIV i-Base

The ongoing struggle to enable access to sofosbuvir globally at affordable prices continues with several new developments.

On May 20th, additional patent challenges against Gilead's sofosbuvir in Argentina, Brazil, China, Russia and Ukraine were filed by community organisations. [1]

The challenges were filed by Initiative of Medicines, Access and Knowledge (I-MAK), Grupo de Trabalho sobre Propriedade Intelectual (Brazil), All-Ukrainian Network of People Living with HIV/AIDS, Treatment Preparedness Coalition (Russia) and Fundación Grupo Efecto Positivo (Argentina).

On the same day, demonstrations and protests were announced in Thailand and Tunisia by AIDS Access Foundation (Thailand), The Tunisian Association of Fight Against STDs and AIDS and International Treatment Preparedness Coalition (Middle East North Africa).

In January, the Indian Patent Controller rejected one of Gilead's key patent applications for sofosbuvir. [2]

Other activists in Asia are tracking the approval status and price of eleven current generic versions of sofosbuvir being manufactured in India under license form Gilead. This is updated when new information becomes available. [3]

A month later, the Paris-based Médecins du Monde (MDM) group challenged the patent in the EU, alleging that the active ingredient in Sovaldi (sofosbuvir) "is the result of work by many public and private researchers [and] is not sufficiently innovative to warrant a patent." [4]

In England, delays and restrictions to access - especially for anyone who does not have cirrhosis - were highlights by the Hepatitis C Trust. [5]

"Sofosbuvir will be available from 1 August 2015 – with peginterferon and ribavirin for genotype 1 and for those with cirrhosis who have genotypes 3, 4, 5 or 6 (or who have previously tried treatment for those with genotype 3) and in very limited cases without interferon. NICE's assessments of sofosbuvir in combination with ledipasvir (Harvoni), daclatasvir in combination with one or more other drugs and ombitasvir with paritaprevir and dasabuvir have all been paused while NICE considers a request from NHS England to limit availability because of the cost."

The Hepatitis C Trust is urging patients to write to their MPs and include a template letter online. [6]

References
1. Pollack A. High cost of Sovaldi hepatitis C drug prompts a call to void its patents. The New York Times (19 May 2015) http://www.nytimes.com/2015/05/20/business/high-cost-of-hepatitis-c-drug-prompts-a-call-to-void-its-patents.html?_r=0
2. MSF. Gilead denied patent for hepatitis C drug sofosbuvir in India. (14 January 2015). http://www.msfaccess.org/about-us/media-room/press-releases/gilead-denied-patent-hepatitis-c-drug-sofosbuvir-india
3. Summary of generic sofosbuvir availability in India and pricing. (18 May 2015). http://hepcasia.com https://testandtreathepatitisc.files.wordpress.com/2015/05/summary-of-generic-sofosbuvir-availability-in-india-and-pricing.pdf (PDF)
4. Doctors of the World. Médecins du monde opposes sofosbuvir patent in Europe. (10 February 2015). http://www.medecinsdumonde.org/gb/Press/Hepatitis-C-Doctors-of-the-World-Medecins-du-Monde-opposes-sofosbuvir-patent-in-Europe
5. Hepatitis C Trust newsletter.
6. http://www.hepctrust.org.uk/write-your-mp

TRANSMISSION & PREVENTION

Methmephangee – ChemSex vs recreational drug use: a proposed definition for health workers

David Stuart, 56 Dean Street and Simon Collins, HIV i-Base.

The following definition was produced to help health workers and researchers understand differences between ChemSex and using recreational drugs for sex.

This information is also available as a PDF leaflet.

http://i-base.info/simoncollins/wp-content/uploads/2014/12/ChemSex-definition-19dec14-FINAL.pdf (PDF)

ChemSex is NOT the same as recreational drug use.

It is a specific form of recreational drug use.

This is important for health workers and researchers who are working in this field but who perhaps have limited personal experience of meth, meph and G. These are the three key drugs that characterise a much more complex situation.

For lots of people, including gay men, alcohol and drugs are an important part of life. ChemSex is different to this.

ChemSex: meth, meph and G

- ChemSex is a common term used by gay men on sexual networking sites and smartphone Apps.
- ChemSex is NOT the same as recreational drug use.
- It is a specific form of recreational drug use.

ChemSex is defined by the use of three specific drugs ("chems") in a sexual context.

These three drugs are meth, meph and G.

- Methamphetamine (crystal/crystal meth/Tina/meth).
- Mephedrone (meph/drone).
- GHB/GBL* (G, Gina).

ChemSex involves using one or more of these three drugs, in any combination, to facilitate or enhance sex, with or without other drugs.

ChemSex commonly refers to sex that can sometimes last several days. There is little need for sleep or food. The heightened sexual focus enables more extreme sex, for longer, often with more partners and with less fear of STIs including HIV and HCV. Sharing injections is common.

Reasons for ChemSex are similar to using other drugs.

- To feel more sexually free and to overcome intimacy issues.
- To overcome fear of rejection, sexual shame.
- To cope with stigma over HIV/hepatitis C (HCV).
- To overcome problems in the past, including sexual abuse.
- To overcome internalised homophobia.
- Wanting 'better' sex, that lasts longer.
- Loneliness.
- Wanting intimacy, to connect to others, to feel part of a community.
- Wanting sexual affirmation.
- Because "everyone's doing it".
- Because it is an online hook-up 'norm'.
- Peer pressure.

However, side effects from ChemSex both when high and afterwards are more severe than other commonly used recreational drugs.

ChemSex is associated with more extreme behaviour and risk:

- Extended sex for many hours. A session can last several days. It is common to not sleep.
- Sometimes just two people for an extended period. Sometimes multiple partners, multiple times. New people might join and leave a party over several days.
- Extreme sexual disinhibition. People use ChemSex to do things that they don't usually do. Safe sex is less important or not important.
- Extreme sexual focus.
- Side effects include overdose (fatal), paranoia, psychosis and black-outs.
- Not being able to consent to sex when unconscious or highly intoxicated; increases risk of assault.
- Drug interactions can be serious and difficult to predict (i.e. between alcohol and GBL/GHB).
- Meth and meph are often injected. Injecting is called "slamming". This risks injection-related infections and blood-borne infections like HIV and HCV.
- STIs are common and frequent. This includes HIV, HCV and, currently, a shigella outbreak.
- Multiple and repeat use of PEP.
- Multiple HCV re-infections.
- Low adherence to ART by HIV positive people on treatment.
- Serious short and long term impact includes chronic depression, anxiety, weight-loss, paranoia, psychosis.
- Loss of lifestyle stability in terms of employment, debt, housing, partnerships and friendships.
- Increased use of GUM, STI, HIV and counselling clinics and services.

These links have been well documented at GUM/HIV clinics in London over the last decade.

London has the most concentrated ChemSex culture in Europe and perhaps globally. Similar trends have been observed in larger cities in Europe, the USA and Australia.

Other recreational drugs are also used in sexual contexts. They can also play a role in ChemSex, but this is less important than use of meth, meph and G.

* Chemical names for GHB/GBL are Gammahydroxybutyrate/Gammabutyrolactone

56 Dean Street is the first UK GUM/HIV clinic to provide ChemSex support to MSM around drug use, sexual health, and sexual wellbeing. It receives over 100 ChemSex referrals each month.

This definition was produced by ReShape's ChemSex lab as contribution to the ongoing dialogue on MSM and sexual health. ReShape (www.ReShapenow.org) is an activist think-tank that supports the need for new community responses to ChemSex. ReShape hosts ChemSex Labs to develop strategic community response to ChemSex in the UK and Europe.

OTHER NEWS

WHO statement for public disclosure of clinical trial results

Simon Collins, HIV i-Base

On 14 April 2015, the World Health Organization (WHO) updated its 2005 statement on the public disclosure of results from all interventional clinical trial. [1, 2]

A paper outlining the rationale for the new position was also published online in the free-access journal PLoS Medicine. [3]

The new statement now defines time lines for reporting, including calls older but still unpublished trials, and outlines ways to improve the links between clinical trial registries and the published results. This includes reporting studies that produced negative or inconclusive results.

Similar demands are stated in the latest version of the Declaration of Helsinki. [4, 5, 6]

A paper published last year on large studies (>500 participants) registered on clinicaltrials.gov and completed by 2009, reported that 23% still had not published results after a median of 60 months since the studies ended. [7]

Although shorter timeframes are strongly encouraged, maximum reporting time frames include that:

1. The main findings of clinical trials are to be submitted for publication in a peer reviewed journal within 12 months of study completion. They are to be published through an open access mechanism unless there is a specific reason why open access cannot be used, or otherwise made available publicly at most within 24 months of study completion.
2. Key outcomes are to be made publicly available within 12 months of study completion by posting to the results section of the primary clinical trial registry.
3. Unreported clinical trials conducted in the past are to be disclosed in a publicly available, free to access, searchable clinical trial registry. In addition, it is desirable that unreported clinical trials are published in a peer-reviewed journal.
4. Publications should always include the trial ID number.

References

1. World Health Organization (WHO). WHO statement on public disclosure of clinical trial results (14 April 2015). http://www.who.int/ictrp/results/en
2. Link to the statement. http://www.who.int/ictrp/results/reporting/en
3. Moorthy VS et al. Rationale for WHO's new position calling for prompt reporting and public disclosure of interventional clinical trial results. PLoS Med 12(4): e1001819. doi:10.1371/journal.pmed.1001819.
4. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013; 310(20):2191–2194. doi: 10.1001/jama. 2013.281053. http://jama.jamanetwork.com/article.aspx?articleid=1760318
5. Hudson KL, Collins FS. Sharing and reporting the results of clinical trials. JAMA. 2015 Jan 27; 313 (4):355–6. doi: 10.1001/jama.2014.10716. http://jama.jamanetwork.com/article.aspx?articleid=1939045
6. Chalmers I. Underreporting research is scientific misconduct. JAMA. 1990 Mar 9; 263(10):1405–8. http://www.ncbi.nlm.nih.gov/pubmed/2304220
7. Manzoli L, Flacco ME, D'Addario M, Capasso L, De Vito C, Marzuillo C, et al. Non-publication and delayed publication of randomized trials on vaccines: survey. BMJ. 2014 May 16; 348:g3058. doi: 10. 1136/bmj.g3058. http://www.ncbi.nlm.nih.gov/pubmed/24838102

FUTURE MEETINGS

Conference listing 2015/16

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.

7th International Workshop on HIV Paediatrics

17 – 18 July 2015, Vancouver

http://www.virology-education.com

Towards an HIV Cure Symposium

18 – 19 July 2015, Vancouver, British Columbia, Canada

http://hivcure.ias2015.org

8th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015)

19 – 22 July 2015, Vancouver, British Columbia, Canada

http://www.ias2015.org

6th International Workshop on HIV & Ageing

5 – 6 October 2015, Washington DC

17th International Workshop on Co-morbidities and Adverse Drug Reactions

Date and venue TBC, but linked to EACS in Barcelona

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

15th European AIDS Conference (EACS)

21 – 24 October 2015, Barcelona

http://www.eacs-conference2015.com

BHIVA Autumn Conference including CHIVA Parallel Sessions

12–13 November 2015, London

http://www.bhiva.org

European HIV Hepatitis Coinfection (EHHC) Conference

10–11 December 2015, London

http://www.bhiva.org

7th International Workshop on HIV Persistence During Therapy

8 – 11 December 2015, Miami

http://www.hiv-persistence.com

23rd Conference on Retroviruses and Opportunistic Infections (CROI 2015)

22 – 25 February 2016, Boston

http://www.croiconference.org

22nd Annual Conference of the British HIV Association (BHIVA)

19–22 April 2016

http://www.bhiva.org

i-BASE PUBLICATIONS & SERVICES

i-Base website

All i-Base publications are available online, including editions of the treatment guides.

http://www.i-Base.info

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

i-Base treatment guides

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

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

- Introduction to combination therapy (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).

Other publications

- HIV Treatment Bulletin (HTB)
- HTB South
- HTB Turkey
- HTB West Balkans

Translations

i-Base resources have been adapte in over 35 languages. PDF version of many of these are online.

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.

HIV i-Base, 57 Great Suffolk Street, London SE1 0BB

T: +44 (0) 20 7407 8488 F: +44 (0) 20 7407 8489

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.

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

STANDING ORDER DONATION **THANK YOU FOR YOUR SUPPORT**

Title: _____ First Name _____ Surname _____

Address _____

_____

_____ Postcode _____

Email _____ @ _____

Telephone (s) _____ _____ _____

Please pay HIV I-Base £ _____ each month until further notice

Please debit my account number _____

Name of account (holder) _____ Bank sort code _____/_____/_____

Starting on _____/_____/_____ (DD/MM/YY)

Signature _____ Date _____/_____/_____ (DD/MM/YY)

To: Manager: (Bank name, branch and address)

_____

_____

Please complete the above and return to: HIV i-Base, 57 Great Suffolk Street, London SE1 0BB

(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA.
Sort Code: 60-12-14. Account Number: 28007042)

ONE-OFF DONATION

I do not wish to make a regular donation at this time but enclose a one-off cheque in the sum of £ _____ .

I wish to make a one of donation (minimum £12.50 inc p&p) for the Treatment Literacy Photogrpahy Book £ _____.

GIVE AS YOU EARN

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

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

REFUNDS FROM THE TAX MAN

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

However you chose to donate to i-Base,
we would like to thank you very much for your support.

REG IN ENGLAND WALES WITH LIMITED LIABILITY REG NO 3962064 CHARITY REG 1081905

i-base
4th Floor, 57 Great Suffolk Street, London SE1 0BB
T: +44 (0) 20 7407 8488 F: +44 (0) 20 7407 8489

i-base 0808 800 6013

Fax-back orders and subscriptions

Please use this form to amend subscription details for HIV Treatment Bulletin and to order single or bulk copies of publications. All publications are free, but donations are always appreciated - please see the form on the previous page.

Name _____ **Position** _____

Organisation _____

Address _____

_____

Telephone _____ **Fax** _____

e-mail _____

☐ I would like to make a donation to i-Base - *Please see inside back page*

- **HIV Treatment Bulletin (HTB) every two months** ☐ **by e-mail (PDF file)** ☐ **by post**
- **HIV Treatment 'Passports' - Booklets for patients to record their own medical history**
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Guide To HIV Testing and Risks of Sexual Transmission** *(February 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Guide To HIV, Pregnancy and Women's Health** *(March 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Introduction to Combination Therapy** *(April 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Guide to Changing Treatment and Drug Resistance** *(February 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **HIV and your Quality of Life: Side Effects and other Complications** *(July 2012)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Guide To HIV and hepatitis C coinfection** *(November 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Clinical Trials: a community guide to HIV research** *(March 2009)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____

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

- **Phoneline support material** *(please specify quantity of each)*

  A3 posters _____ ***A5 leaflets*** _____ ***A6 postcards*** _____ ***Small cards*** _____

Please fax this form back, post to the above address, or email a request to HIV i-Base:

020 7407 8489 (fax) subscriptions@i-Base.org.uk