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EDITORIAL

Spring in London began with a visit from the European Association for the Study of Liver (EASL) that held its 49th annual meeting here in April.

Although – as the name suggests – the meeting mostly focused on the liver, HIV/hepatitis C (HCV) coinfection was highlighted in several sessions and the exciting results from studies of the new oral HCV drugs seem to apply equally to HIV positive people.

Less of a reason to celebrate has been the news that a key new HCV drug sofosbuvir was launched at such an eye watering price that treating those in need would wipe out vast proportions of annual national health budgets – or, in the case of Egypt with 12 million HCV positive adults, would reach four times the country's annual health costs, even at a discounted price. The NEJM described the price of new HCV meds as being as "as breathtaking as their effectiveness" and criticisms abound, not least from activists attending the conference who held a protest as the meeting kicked off.

Just prior to EASL 2014 the World Health Organisation (WHO) launched the first guidelines for the care and management of people with HCV. Our HCV reports cover the pricing controversy, summarise - with co-author Tracy Swan - the interferon free studies with the new, and review the new WHO guidelines.

BHIVA also held its annual meeting in April in collaboration with BASHH. Our reports include a look at recent UK data showing that three quarters of HIV positive people start treatment within two years of infection, an expanded analysis from the PIVOT PI-monotherapy study, HCV issues for the UK and HIV positive attitudes to organ transplants from positive donors.

We also include our final reports from CROI 2014 – although there is always far more data than we can cover at this conference. These reports include pharmacokinetics of antiretrovirals in pregnancy, superior virological outcomes with efavirenz compared to lopinavir/r in Ugandan pregnant women, and some of the issues associated with starting ART in infants soon after they are born.

And Richard Jefferys provides an excellent catch up with pathogenisis and cure research presented at CROI 2014, including a caution that ART may have benefits for long term slow progressors.

Other news is a large study reports no increase in death rate in HIV positive people with renal dysfunction receiving tenofovir in Zambia,

The US adult treatment guidelines have been updated and new PrEP guidelines have been significantly expanded. PrEP is an increasingly important option in the US and tracking the approach and range of responses there is very relevant for our approaches in the UK.

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CONFERENCE REPORTS

49th Annual Meeting of the European Association for the Study of the Liver (EASL 2014)

9-13 April 2014, London

Introduction

This year the European International Liver Conference was held from 9-13 April at the ExCell Centre in east London.

This was a five day meeting and the programme included 170 oral abstract presentations and over 1320 poster presentations.

Although this is primarily a liver conference, HIV/HCV coinfection featured in several sessions including an overview lecture by Dr Sanjay Bhagani from the Royal Free Hospital.

Most of the news focused on new oral drugs for hepatitis C (called Directly Active Agents or DAAs) - and there are a lot of new drugs. Some companies have several compounds that are only being studied together as in-house combinations (including Gilead, Abbott and Merck).

Dramatic results were seen in efficacy and safety of these drugs - with cure rates approaching 100% for treatment naive patients. Many presenters commented that 2014 for hepatitis C is perhaps comparable to the first years of combination therapy for HIV in 1996. The meeting also included promising results in advanced and difficult to treat patients including people with cirrhosis and who did not respond to previous HCV treatment.

Although most of the DAA studies focus on HCV mono infection, some HIV/HCV coinfection studies are included. Importantly though, DAAs appear to have similar success rates irrespective of HIV status, so the monoinfection studies are highly relevant for HIV positive people. Regulatory decisions on approving new DAAs are likely to recommend broad use, irrespective of HIV status.

Highlights of the DAAs with new data at EASL 2014 included:

- ABT-450/r/ABT-267, ABT-333 (AbbVie combination)
- sofosbuvir - already approved in Europe and the US - but with new data from different genotypes and populations
- sofosbuvir plus ledipasvir (Gilead combination)
- sofosbuvir plus GS-5816 (another Gilead combination)
- MK-5172 and MK-8742 (Merck combination) - including date from HIV positive people with genotype 1.
- daclatasvir (from BMS) - including its use with sofosbuvir (in research not supported by Gilead)
- simeprevir (Janssen) - already licensed in the US and available on early access in the EU.

The details are as important as the headline news. Some studies, especially in sub-groups, have small study numbers. A surprising number of abstracts promised "SVR results will be presented" which is a convention that HIV conferences restricted years ago. If the data is not in the abstract when submitted, it doesn't get in.

This excitement is also tempered by issues of cost and access. this is an issue both for developed countries (based on the launch price of sofosbuvir) and in middle and low income countries where most HCV positive people live (where dramatically reduced pricing will be needed).

The programme, abstract books (published as a supplement to Journal of Hepatology) and related Apps are already available as open access online from the conference website.

http://www.ilc-congress.eu

The meeting doesn't seem to webcast sessions, but a series of 26 press conferences and interviews are available on YouTube:

https://www.youtube.com/channel/UCj3g-4YJ3MhDOjkJ3x8_r_Q

Reports in this issue of HTB are:

- Activists protest the price of sofosbuvir: "So-Valdi, So-Expensive" - UK access already rationed
- EASL 2014: summary of interferon-free HCV studies with new DAAs
- WHO launch treatment guidelines for hepatitis C

Activists protest the price of sofosbuvir: "So-Valdi, So-Expensive" - UK access already rationed

Simon Collins, HIV i-Base

A community-led protest that took place at the European Liver Conference was notable (and newsworthy) for apparently being the first time that a demonstration had been held at a medical liver conference. [1]

The action was to protest against setting the US price of the newly approved hepatitis C (HCV) drug sofosbuvir at $1000 a day. [2]

This price is also likely to limit access to sofosbuvir in the UK and other European public health systems to people with the most advanced liver damage, and perhaps to those who have already not responded to less effective and less tolerable older treatments.

Tens of thousands of people in the UK, who could easily be cured of HCV with a short course of easy-to-tolerate oral meds, will now be told they are not sick enough yet for the best treatment. People who want to treat their HCV may be only be offered what are now clearly older sub-standard treatments.

Sovaldi, so expensive: an unethical model for pricing

The standard model for pricing a new drug is to cover research and development costs, to allow for future research to keep the company active and to compensate commercial investors. Although research budgets are never publically disclosed, and the price also has to fit the market, this is a model that supports both continued investment and future research.

In a new approach, the price for sofosbuvir has been justified by adding up the expected LIFETIME health costs that could potentially be saved. This includes years (potentially decades) of appointments, doctors visits, monitoring tests and scans - through to cost of less effective treatment; and finally hospitalisation, liver transplant and subsequent aftercare.

Gilead want to charge all these costs, up front, irrespective of how many people need treatment and whether this is affordable to the health system. This model makes no mention of people who drop out of care, who can't access care, or who die before they access treatment.

This model is unethical and the company should be challenged for suggesting it is fit for purpose.

UK access: cost effective but not affordable

The NHS list price for sofosbuvir in the UK is close to £35,000 for a 12-week course (£11,661 for 28 tablets), making each single film-coated pill cost more than £400. [3]

On 16 April 2014, NHS England announced that £18.7 million would be made available for sofosbuvir treatment for 500 people. [4] This was based on a decision that individual treatment is cost effective, even at this price. But in the UK, 216,000 people are estimated to have chronic HCV, and treating only half these patients would cost £ 3.8 billion (the total drug budget of is £10 billion [5]). The price needs to affordable to healthcare systems in order for people to access treatment (see Table 1).

Sofosbuvir is not an expensive or particularly complex drug to manufacture. A well-publicised study by Andrew Hill and colleagues into the manufacturing costs for sofosbuvir and other new hepatitis C drugs, estimated that a 12-week course of treatment should cost no more than US $150 (less than £1 per pill). [6]

Gilead has not yet challenged the figures from this analysis.

This makes for a very expensive "film-coating".

Egyptian 99% discount

A similar model matching need to available budget is needed in other countries, especially for middle-income countries which have the greatest HCV burden.

On 22 March 2014, Reuters reported that Gilead had agreed to sell sofosbuvir for use in Egyptian government clinics at $900 for a 12-week course. [7] This may sound reasonable – or even generous: it is a 99% reduction on the US list price.

Approximately 12 million people in Egypt have chronic hepatitis C. It has the highest global prevalence at 14% of the general population. Even at the discounted cost of $900, treating half of the people with HCV would cost US$ 5.4 billion. This is more than twice the entire 2011 Egyptian health budget. [8]

In the US, 3.2 million people are estimated to have chronic HCV, even treating half of them would cost US$134 billion. This is approximately one-eighth of the US health federal health budget for 2014. [9]

Similar profits for greater access

Although Gilead purchased the biotech company Pharmasset in November 2011 for $11 billion dollars, principally to acquire rights to sofosbuvir, much of that investment has already be recouped from the increase in the company's stock price which has more than doubled.

In the first three months of 2014, Gilead announced product sales of US$ 4.8 billion with US$ 2.2 billion coming from sobosbuvir. [10]

But the same profits could be made by setting a much lower price to enable more people to benefit from this drug. If profit is the important bottom-line for both the company and investors, this could still be achieved. Instead, Gilead is even holding people in rich countries to ransom. The price restricts health payers from being able to offer treatment to only a tiny margin of people who need treatment. See Table 1.

Globally, 150 million people have acute HCV. The five countries with the highest numbers of people living with HCV are China (29.7 million), India (18.2 million), Egypt (11.8 million), Indonesia (9.43 million) and Pakistan (9.42 million). This is where the majority of the 500,000 HCV-related deaths each year occur. This drives the community demand for setting a target price of US$ 500 goal in low and middle-income countries - for a package that covers testing, treatment and cure HCV. [11]

The scientific and medical advances now offer the potential to eradicate HCV, but the current price and plans for access makes this impossible.

Table 1: Current sofosbuvir costs for universal treatment and country budgets

	No. of HCV+ adults	Current cost for universal treatment *	Proportion of annual health costs
UK	216,000	£ 7.5 billion	7.5% of total NHS budget (75% of current drug budget)
Egypt	12 million	$ 11 billion	4 x total annual health costs
US	3.2 million	$ 270 billion	25% of annual US federal health budget

* Costs are based on current prices, including 99% reduced price in Egypt and using 12 weeks treatment.

NEJM: price "as breathtaking as their effectiveness"

An editorial in the New England Journal of Medicine, written on the predicted costs of the new oral hepatitis C drugs (as they will need to be used in combination) stated that the predicted prices were "as breathtaking as their effectiveness".

In a commentary to support the publication of several important Phase 3 studies of new hepatitis C drugs, including sofosbuvir, it highlighted that as the medical barriers to treatment disappear, they are blocked by economic ones - even for wealthy countries like the US, concluding that "Costs alone cast a pall over the stunning success in achieving the long-hoped-for goal of a safe and effective therapy for hepatitis C". [12]

C O M M E N T

The highly lucrative short-term financial benefits for Gilead threaten to become a public relations disaster.

Shareholders should be ashamed. They could make similar profits from treating a greater percentage of the population who need treatment.

Activists at the demonstration in EASL seemed to have no difficulty handing out leaflets, even though liver meetings are generally conservative events. More importantly, the response from most of the doctors, from a wide range of countries, was both supportive and encouraging. A common theme was "these drugs are too expensive, I will never be able to prescribe them".

The UK should not be satisfied with treating a few hundred people when the potential to eradicate hepatitis C is being withheld.

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EASL 2014: summary of interferon-free HCV studies with new DAAs

Simon Collins, HIV i-Base and Tracy Swan, TAG

Numerous studies at the 2014 European Association for the Study of the Liver (EASL) meeting presented an impressive volume of new data, all moving steadily towards broadly curing HCV with effective and tolerable short course oral treatment.

The WHO and EASL both launched new treatment guidelines. EASL now recommend all the latest approved direct-acting antiviral (DAA)-based treatment, with the same indications and choice of treatments irrespective of HIV status. These first WHO guidelines to cover HCV treatment have been produced for low- and middle-income countries, where most people with hepatitis C in the world live.

Many companies have in-house combinations, some of which are already coformulated into fixed-dose combinations. Studies of the most advanced drugs in development reported dramatically high SVR12 (sustained virologic response rates twelve weeks after stopping treatment, equivalent to cure) in more than 95% of patients.This is from using 12 weeks treatment – and shorter treatment duration may also be possible.

Unlike HIV, baseline HCV drug resistance (hepatologists refer to RAPs and RAVs: resistance-associated polymorphisms and variants), is often easily overcome by treatment or not clearly related to treatment outcome. This is likely due to the higher viral potency of the drugs, the lack of an archived viral reservoir and the greater number of drugs to combine. However, there is currently little data to help understand the impact on subsequent treatment of emergent mutations or due to cross-resistance amoung drugs in the class.

Rapid viral clearance is now reported in patients both with compensated and decompensated liver disease, including people with prior treatment an DAA experience; after HCV recurrence after post-transplant; and in people with HIV/HCV coinfection.

Most of these drugs are extremely tolerable with very few serious side effects and few drug-related discontinuations.

Most combinations are mainly active against genotype 1. Sofosbuvir and GS-5816 from Gilead and daclatasvir by BMS have activity against the

broadest range of genotypes. High SVR12 rates from combinations by other manufacturers may make treating G1 and 4 a more competitive market given the importance of drug pricing in access to treatment.

DAAs appear to have similar efficacy irrespective of HIV status. This was supported by HIV coinfection studies using combinations from Gilead and from Merck. It is also important that key studies using Gilead and AbbVie combinations were simultaneously published online in the New England Journal of Medicine (NEJM).

As a caution, some of the studies were presenting interim results and some data is tentative due to small patient numbers.

As with HIV, especially given the global burden of HCV, the success of treatment, needs to be matched by an approach to healthcare that will enable broad and affordable access. This was also highlighted at the meeting by a peaceful demonstration by activists who distributed pill capsules filled with gold glitter, together with leaflets and stickers based on the USD $1000 a day launch price of Gilead's sofosbuvir: "Sovadi, So Expensive".

Summary of results with key compounds by manufacturer

Sofosbuvir, ledipasvir and GS-5816 (Gilead)

Sofosbuvir is already approved in Europe and the US. New results were presented for sofosbuivir in different populations, including patients with advanced liver disease (including decompensated cirrhosis and post-transplant recurrence), in people who previously used sofosbuvir and other DAAs, and in HIV coinfection. Sofosbuvir is active against all genotypes (but slightly less so against G3).

Ledipasvir (previously GS-5885) is mainly active against G1. Gilead has already produced a coformulation of sofosbuvir and ledipasvir (400 mg/90 mg) in one pill. Studies using the fixed dose combination (FDC) at EASL 2014 included first results in people with HIV/HCV coinfection.

GS-5816 is an NS5A inhibitor from Gilead that is active against genotypes 1 to 6 and produced SVR12 results >95% in a Phase 2 study with sofosbuvir (though few people had G 4, 5, and 6).

ABT-450/r/ABT-267, ABT-333 (AbbVie)

The AbbVie "2D" combination includes ABT-450/ritonavir and ABT-267 (ombitasvir) coformulated in a once-daily pill (150 mg/100 mg/25 mg); AbbVie's "3D" combination includes ABT-333 (dasabuvir) in a 250 mg twice-daily dose. High SVR12 rates (>95%), equally active in genotype 1a and 1b, including people previously treated with pegylated interferon and ribavirin. The SAPPHIRE I and II phase 3 studies, in G1 treatment-naïve and -experienced patients respectively, were published in the NEJM to coincide with EASL.

For genotype 4, ribavirin is used instead of ABT-333 (since it is only effective against genotype 1). The phase II PEARL study reported 100% SVR12 with ribavirin and 91% without, after 12 weeks treatment.

The TURQUOISE-II study using 3D + ribavirin in people with compensated cirrhosis reported impressive SVR12 rates of 92% and 96%, after 12 and 24 weeks of treatment, respectively.

MK-5172 and MK-8742 (Merck)

MK-5172 (NS3/4A protease inhibitor) and MK-8742 (NS5A inhibitor) are active against genotype 1, (with ongoing studies looking at other genotypes). New data was presented on use with and without ribavirin in people with compensated cirrhosis, prior treatment experience, and in HIV coinfection. A fixed dose single pill formulation (dose 100 mg/50 mg) has already been produced that will be used in phase 3 studies, and these studies will include people with Child-Pugh B cirrhosis.

A small HIV/HCV coinfection study (n=40) in HIV positive people on stable ART with high CD4 counts produced SVR4 results of 97% with ribavirin and 90% without. Future phase 3 studies will include HIV positive people, including in an opiate substitution study.

Daclatasvir, asunaprevir and BMS-791325 (BMS)

Daclatasvir produced best results in combination with sofosbuvir (in research not supported by Gilead) but another study also looked at an all-BMS combinations of daclatasvir with asunaprevir (NS3 protease inhibitor) and BMS-791325 (non-nucleoside NS5B inhibitor).

The HALLMARK DUAL study in a mixed population (with and without cirrhosis) of genotype 1b treatment naïve, IFN-ineligible or intolerant and null-responders reported slightly less impressive results with greater than 80% SVR12 rates.

Asunaprevir is active against G1 and G4.

Phase 3 studies are underway in the US with daclatasvir and sofosbuvir for genotype 1, 2, 3 and 4 (the ALLY studies).

Simeprevir (Janssen)

Simepravir is already licensed in the US and the EU. This is another compound studied with sofosbuvir (again, this research was not supported by Gilead).

At EASL 2014, final results and sub analyses from the COSMOS study were reported. Studies were also presented using simeprevir with pegylated interferon and ribavirin (of less interest and not reported in this article).

Faldaprevir and deleobuvir (Boehringer Ingelheim)

Although several presentations included study results using faldaprevir, the associated side effects make it difficult to know whether this drug will have advantages over other DAAs.

Deleobuvir has already had development stopped due to high rates of side effect-related discontinuations. Active against genotype 1a. Studied with and without ribavirin. The only other DAA that faldaprevir has been tested with is PPI-668, an NS5A inhibitor (manufactured by Presidio).

Boehringer Ingelheim will not actively market faldaprevir which is expected to obtain approval in the EU this summer. Deleobuvir will not be further developed.

A summary of these studies is included in Table 1.

Table 1: Summary SVR rates in all-oral DAA-based studies at EASL 2014

This table does not include information on other important factors - all of which affect results of ITT analyses. For example, side effects or the role of ribavirin (side effects are usually higher in study arms where ribavirin is included); for discontinuation due to these; or loss to follow-up for other reasons. Some studies only report interim data.

Drugs and duration	Population studied, genotype, duration	Summary results	Abstract & reference
Gilead: Genotype 1-6 for sofosbuvir and GS-5816, ledipasvir mainly active against G1			
sofosbuvir/ledipasvir FDC (400/90 mg). ELECTRON-II study. 12 weeks.	G1 with decompensated cirrhosis (n=20); G1 with sofosbuvir experienced (n=19); G3 (n=51).	SVR12: 65% (13/20) in decompensated cirrhosis; 100% (19/19) in experienced; 100% (26/26) in G3 with ribavirin	O6. Gane E et al. [1]
sofosbuvir + ribavirin +/- PEG-IFN. Open label. 12 weeks with 3 drugs or 24 weeks with 2 drugs. Investigator choice to use PEG-IFN.	G2 (n=16), G3 (n=97) sofosbuvir experienced. 12 weeks SOF + IFN + RBV (n=34) and 24 weeks with SOF + RBV only (n=73).	Interim data for people who have SVR12 data: 92% (24/26) using sofosbuvir with pegylated interferon + ribavirin vs 63% (25/40) using sofosbuvir + ribavirin. Better responses with PEG-IFN and ribavirin for 12 weeks for both G2 and G3 and for people with and without cirrhosis.	O8 Esteban R et al. [2]
sofosbuvir/ledipasvir SYNERGY study. 12 weeks.	G1 (n=14) Treatment experienced.	Small NIH study reporting high SVR12 rates in people who previously used sofosbuvir. SVR12: 100% (14/14)	O11. Osinusi A et al. [3]
sofosbuvir/ledipasvir FDC – HIV coinfection. ERADICATE study. 12 weeks.	G1 (n=50; 13 with F3). HCV treatment naïve. HIV/HCV coinfected (n=37 on ART, n=13 no ART).	Interim results only. SVR4: 100% irrespective of ART use (12/12 not on ART and 22/22 on ART). SVR12: 100% (10/10) not on ART	O14. Osinusi A et al. [4]
sofosbuvir + PEG-IFN + ribavirin. Open label. 12 weeks.	G1a and 1b (n=80) Treatment experienced (including with resistance from prior use of DAAs)	Interim data for 67 patients with SVR12 data, 13 are still on treatment. SVR12: 74% (37/50). Response by prior treatment: NS3 only: 50% (6/12); NS3 + NS5a: 75% (18/24); NS3 + NS5a + NS5b: 93% (13/14). Number of mutations was not related to response.	O55. Pol S et al. [5]
sofosbuvir/ledipasvir FDC +/- ribavirin Randomised to +/-RBV for 8 weeks or no-RBV for 12 weeks. ION-3 study.	G1 n=647 treatment-naïve. non cirrhotic.	SVR12: 94% (95%CI: 90 to 97) with 8 weeks without ribavirin. 93% (95%CI: 89 to 96) with 8 weeks with ribavirin, 95% (95%CI: 92 to 98) with 12 weeks without ribavirin. Results showed 8 week without ribavirin to be non-inferior.	O56. Kowdley KV et al. [6]
sofosbuvir + ribavirin +/- peg-IFN. Open label. Compassionate access. Investigator choice of PEG-IFN. Up to 48 weeks.	G 1, 2, 3, 4 and mixed (n=87 post-transplant). High risk patients (life expectancy < 1 year): n=48 early recurrence post-transplant and 56 compensated and non-compensated cirrhosis including cholestatic fibrosis.	SVR12: overall 62% (53/85) >50% with SOF+RBV and 44% with SOF+RBV+PEG-IFN. Death and transplant excluded. 62% also had improved symptoms. 13 deaths, 8 on treatment. "Spectacular results in patients with acute recurrence – better than chronic cirrhosis". 22/100 used PEG-IFN, with results not yet analysed.	O62. Forns X et al. [7]
sofosbuvir + ribavirin vs observation only as control for 24 weeks until roll-over to active arm. Randomised. 48 weeks treatment.	G 1, 2, 3, 4 (most G1, n= 2 for each of G2, G3 and G4). n=50 (25 each arm). Included cirrhosis with portal hypertension (CBT 5-6 compensated and CPT 7-9, decompensated).	Interim week 24 analysis – ie active 24 weeks and end of observational period. Only virologic and safety responses available. No SVR data as still on treatment. CPT 5-6: 50% undetectable at week 2, 100% from week 4. CPT 7-9: 75% by week 4 and 94% later. MELD score dropped in both active and placebo but improvement in liver function was greater in the active arm.	O68. Afdhal N et al. [8]

sofosbuvir/ledipasvir FDC +/- ribavirin. Randomised to use of ribavirin and duration: 12 or 24 weeks. ION-2 study.	G1a and 1b (n=440) Treatment experienced. 20% with cirrhosis	Stratified by subtype, cirrhosis and prior response. SVR12: 96% and 99% with ribavirin (12 and 24 week). SVR12: 94% and 99% without ribavirin (12 and 24 week). In patients with cirrhosis, SVR12 with and without ribavirin was 82% and 86% with 12 weeks treatment and 100% irrespective of ribavirin use with 24 weeks treatment.	O109. Afdhal N et al. [9]
sofosbuvir + GS-5816 (NS5A inhibitor) Randomised to open label GS-5816 dose. 12 weeks.	G1-6 (mainly G1a, 2 and 3; n=154) G1=55, G2=21, G3=54, G4=14, G5=1, G5 and G6=9. Treatment naïve. No cirrhosis.	Phase 2 dose ranging (25 mg and 100 mg for GS-5816). SVR12: 95% (73/77) with 25 mg and 96% (74/77) with 100 mg. SVR12 results by genotype were: G1 (96% and 100%), G2 (91% and 100%), G3 (93% and 93%), G4 (100% vs 87%), G5 (100%) and G6 (100% vs 100%) in the 25 mg and 100 mg arms respectively.	O111. Everson GT et al. [10]
sofosbuvir/ledipasvir FDC +/- ribavirin. Randomised to ribavirin and duration: 12 or 24 weeks. ION-1 study.	G1a and 1b N=865 Treatment-naïve 16% cirrhotic (Child A)	SVR12: 97%-99% across four arms. No differences by ribavirin use or duration. Similar responses in cirrhotic and non-cirrhotic – 94%-100%.	O164. Mangia A et al. [11]
AbbVie: 3D (ABT-450/r/ABT-267 + ABT-333): G1 and G4, plus ribavirin			
Abbott 3D (ABT-450/r/ ABT-267 + ABT-333) + ribavirin vs matching placebo for 12 weeks (then open label active). 48 weeks follow-up. SAPHIRE II	G1a and 1b (n=394; 297 active and 97 placebo) PEG+RBV-experienced No cirrhosis.	SVR12: 96.3% (95% CI: 94.2% - 98.4%). Similar for both G1a and 1b and for all PEG-IFN response groups. (~95% for relapsers and prior null response and 100% for partial response).	O1. Zeuzem S et al. [12]
AbbVie 2D +/-ribavirin. 12 weeks. PEARL I	G4 - treatment naïve: (n=96; n=44 with RBV and n=42 without RBV). PEG-IFN + RBV experienced: (n=49). No cirrhosis.	Phase II study. Treatment naïve: SVR12: 100% 2D + ribavirin vs 91% 2D only PEG-IFN experienced: SVR4: 100%	O58. Hezode C et al. [13]
AbbVie 3D + ribavirin for 12 weeks vs matching placebos for 12 weeks (then roll-over to open label). 48 weeks f/u in all. 12 weeks. SAPPHIRE I	G1 (n=631; active arm 473 and 178 placebo). 45% women. F2 and F3 (68%)	SVR12: >95% SVR12 (initial randomisation): 96% (455/473) No difference by G1a vs 1b (both >95%)	O60. Feld JJ et al. [14]
AbbVie 3D + ribavirin. Open label. 24 weeks.	G1 (n=34) Non-cirrhotic transplant recipients with recurrent HCV. >12 months post-transplant, naïve since transplant.	Interim analysis. To date, all patients achieved RVR (34/34) and EOTR (13/13). Current SVR4 is 97% (32/23). Current SVR12: 96% (25/26).	O144. Kwo P et al. [15]
AbbVie 3D + ribavirin open label, randomised to duration. 12 or 24 weeks. TURQUOISE II	G1a and 1b (n=380; 12 week n=208 and 24 week n=172) Naïve (42%) and experienced (58%). cirrhotic (Child Pugh A)	SVR12: 92% with 12 weeks (191/208) and 24 weeks (165/172). G1a: 88% and 94% by 12 and 24 week. G1b: 98% and 100% by 12 and 24 week. Naïve (92% and 93%; prior relapse (93% and 100%), prior partial response (100% and 100%) and prior null response (80% and 92%).	LB O163. Poordad F et al. [16]
AbbVie 3D + ribavirin +/- randomised to ribavirin or placebo. PEARL-III	G1b (n=419) treatment-naive	>99.5% SVR with or without ribavirin. No relapsers or failure in the non-ribavirin group.	LB P1299. Ferenci P et al. [17]
Merck/MSD: MK-5172, MK-8742 - G1, naïve and experienced, with ribavirin. Also HIV/HCV coinfection.			
MK-5172 (100mg)/MK-8742 (dose finding) +/- ribavirin. 8 and 12 weeks. C-WORTHy. study.	G1 a and 1b (n=94) Part A: (n=65) 12 week dose-finding study for MK-8742; Part B (n=91) using 50 mg dose included an 8 week arm (n=30). Treatment naïve, non-cirrhotic.	Note: SVR12: 96%-100% rates were reported for Part A at AASLD 2103. SVR12: 94%-100% in Part A, with or without ribavirin, after 12 weeks treatment. No differences were seen for G1a compared to 1b or by use of ribavirin. SVR4-8: 83% (25/30) after 8 weeks treatment.	O10. Herzode C et al. [18]
MK-5172 (100 mg) + MK-8742 (50 mg) +/- ribavirin. 12 or 18 weeks. C-WORTHy. study	G1 (n=253). Include naïve with compensated cirrhosis (n=123) and experienced +/- cirrhosis (n=130)	Abstract report 94-100% virological response. Interim results. SVR4-8: 90-97% cirrhotic. SVR4-8: 91-100% in non-responders. No difference with or without ribavirin. No difference in G1a vs G1b. SVR4-8: Naïve cirrhotic: 90-97% at 12 week and 97% in 18 week. SVR4-8: experienced: 91-94% - 12 week treatment and 100% with 18 weeks. Duration will be a variable in phase 3 studies.	O61. Lawitz E et al. [19]

MK-5172 (100 mg) + MK-8742 (50 mg) + ribavirin. 12 weeks. C-WORTHy. study.	G1 (n=59; n=29 with RBV and 30 without) HIV/HCV coinfection. On raltegravir-based ART (high CD4 > 600). HCV-naïve. Non cirrhotic.	SVR4: 90-97% With ribavirin: 97% (28/29) Without ribavirin: 90% (26/29)	O63. Sulkowski M et al. [20]
MK-5172 + ribavirin Randomised to duration. 12 or 24 weeks. C-SPIRIT study.	G1 (with IL28B CC genotype). n=26. Non-cirrhotic.	People unsuppressed at week 12 roll over to extended 24 weeks treatment. In people using 24 weeks treatment: SVR4 in 13/17 (76%) SVR12 10/16 (63%)	P1233. Gane E et al. [21]
BMS: dalcatasvir, asunaprevir and BMS-791325			
daclatasvir + sofosbuvir +/- ribavirin Some patients used 7-day lead-in with sofosbuvir monotherapy. 12 or 24 weeks.	G1,2,3 Mixed naïve and experienced. n=211 (n=126 G1 naïve; n= 44 G2 or 3 naïve; n=41 G1 non responders to PEG+RBV with either boceprevir or telaprevir. non-cirrhotic	Note: SVR12 results of 98-100% from this study were previously published in NEJM on 16 January 2013 (doi: 10.1056/NEJMoa1306218). This new analysis was based on resistance results. No apparent impact of NS5a RAPs at baseline and not pattern between mutation and failure. G1a: 24/97 had RAPs at baseline all achieved SVR12. G1b: 13/25 had RAPs at baseline all achieved SVR12. G2 – 23/23 had RAPs at baseline all had SVR12. G3 – 11/18 had RAPs at baseline - one relapsed. Three G1 relapsers were in the sofosbuvir. lead-in group – one SVR after PEG-IFN and ribavirin salvage.	O64. McFee F et al. [22]
daclatasvir + asunaprevir vs placebo 24 weeks. HALLMARK DUAL study.	G1b Randomised DCV 60 mg QD plus ASV 100 mg BID in naïve (n=203) vs placebo (n = 102). Open label for prior null responder (n=205) and intolerant (n=235).	SVR12: 91% in naïve 82% no responders 83% intolerant/ineligible. No difference in response by cirrhosis (84%; n = 206 with cirrhosis vs 85% in 437 without cirrhosis). No difference by treatment experience or IL28 genotype.	O166. Manns M et al. [23] LB P1300. Kao J-H et al. [24]
daclatasvir, asunaprevir and BMS-791325 (75 and 150 mg)	G4 (n=21) 12 weeks	Randomisation for BMS-79135 doses. SVR in 11/12 and 9/10 in 75 mg and 150 mg arms respectively. 92% SVR12.	P 1 1 3 3 . Hassenein et al. [25]
daclatasvir (60 mg) + VX-135 (100 mg or 200 mg).	N=23	Small dose-finding study of NS5B inhibitor VX-135 (100 mg and 200 mg) SVR12 in 83% and 91%, respectively. Note: further investigation into the 200 mg dose of VX-135 is currently halted by the FDA in the US. Although promising, it's future is therefore uncertain.	LB P1303. Gane E et al. [26]
Janssen: simeprevir - G1, used with PEG-INF, ribavirin and Gilead's sofosbuvir			
simeprevir + sofosbuvir +/- ribavirin. Randomised to +/- ribavirin open label and 12 or 24 weeks. COSMOS study (Cohort I)	G1a and 1b (n=80). Prior null responders. Metavir stage 0-2.	Subset analysis of Phase 2 COSMOS study. 12 weeks treatment: SVR12: 96% (26/27) with ribavirin and 93% (13/14) without ribavirin. 24 weeks treatment: SVR12: 79% (19/24) with ribavirin and 93% (14/15) without ribavirin. The Q80K polymorphism at baseline and having the IL28 TT genotype appeared to predict risk of non-response.	O7. Sulkowski M et al. [27]
simeprevir + sofosbuvir +/- ribavirin. Randomised to +/- ribavirin open label and 12 or 24 weeks. COSMOS study (Cohort II)	G1a and 1b (n=87). Naïve and prior null-responders. Metavir stage 3/4.	Subset analysis of Phase 2 COSMOS study. 93% in 12 week arm (25/27 with ribavirin and 13/14 without ribavirin). 93% and 100% in 24 week arm (28/30 with ribavirin and 16/16 without ribavirin. No difference by cirrhosis stage, treatment history or G1 subtype (1a vs 1b).	LB O165. Lawitz E et al. [28]
Boehringer ingelhiem: faldaprevir, deleobuvir (since terminated): G1a +/- ribavirin			
faldaprevir (BI) and deleobuvir (BI, since terminated), PPI-668 (Presidio) +/- ribavirin. 12 weeks.	G1a (n=36). Treatment naïve. Non-cirrhotic. Three arms - cohort 1 and 2: 400 mg or 600 mg faldaprevir. cohort 3 used PPI-668 instead of ribavirin.	Cohort 1 and 2: SVR12: 92% (22/24) Cohort 3: SVR12: 75% (9/12, 2 replacements). Good virological responses irrespective or ribavirin use but difficult side effects – 75% nausea, GI etc and 18% photosensitivity despite use of sunscreen. Side effects were lower grade without ribavirin, but these patients were also more likely to stop.	O65. Lalezari J et al. [29]

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WHO launch treatment guidelines for hepatitis C

Simon Collins, HIV i-Base

Just prior to EASL 2014, the World Health Organization launched the first guidelines for the care and management of people living with hepatitis C (HCV).

WHO currently estimates that 130-150 million people globally are chronically infected with HCV, 3-4 million people are newly infected each year and that HCV is responsible for up to 500,000 deaths annually.

The guidelines make nine recommendations, divided into four key areas:

- Increasing screening.
- Reducing HCV progression and liver damage in people with chronic HCV.
- Guidelines for HCV treatment.
- Reducing future new infections.

The guidelines include appropriate sections on people who inject drugs (PWID), coinfection with HIV (and sexual transmission of HCV in HIV positive gay men), with recommendations for using the most recently licensed antivirals sofosbuvir and simeprevir.

They reference the issue of cost by recognising that these drugs will remain unaffordable for most people who need treatment.

The guidelines are due to be revised in 2016 with an interim update in 2015 to refer to newly approved treatment.

At the WHO press launch for the guidelines, held at 7.30 am on Thursday morning, comments were broadly very supportive and encouraging.

> "These guidelines are a powerful tool for activists who are working for access to affordable treatment"
>
> "A great first step – now we need the resources to implement them without bankrupting health budgets. Drug prices must come down."
>
> "I hope the message is clear: although the first generation protease inhibitors increase cure rates in genotype 1, they are too toxic and difficult to manage – wherever the setting. These drugs really should not be used anymore."

The guidelines were funded by the US Centers for Disease Control and Prevention and the Ministry of Health, Labour and Welfare of Japan.

The guidelines are online at:

http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/

Direct PDF link (1.7 Mb)

http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1

CONFERENCE REPORTS

3rd Joint Conference of BHIVA/BASHH

1 – 4 April 2014, Liverpool

Introduction

The Third Joint BHIVA/BASHH conference was held from 1-4 April 2014 in Liverpool.

This was a lively meeting attended by over 1000 delegates and with the overlapping interests of each society benefitting the overall programme. Although the four-day meeting only included 45 oral abstract presentations, there were close to an additional 450 posters.

The abstract book from the meeting is available online as a PDF file and BHIVA continues to webcast some of the oral sessions online with PowerPoint slides from all other oral presentations.

http://www.bhiva.org/AnnualConference2014Presentations.aspx

Reports in this issue are:

- 75% of UK seroconverters start ART within two years of infection: treating during primary infection should be a patient choice
- PIVOT study: further analysis from five-year PI/r monotherapy strategy study
- Sexually transmitted HCV in HIV positive and negative gay men
- Annual HCV testing and use of core antigen to reduce costs and increase diagnosis during acute HCV
- HIV positive attitudes to involvement as donors and recipients in organ transplant programmes

75% of UK seroconverters start ART within two years of infection: treating during primary infection should be a patient choice

Simon Collins, HIV i-Base

Latest data from the UK seroconverters register highlighted the importance for people diagnosed during primary HIV infection (PHI) to have the option for early treatment.

Currently, the 6-month window period during which HIV-specific immune response are often retained, is often lost due to the misplaced belief that treatment may not be needed for many years.

The UK HIV Seroconverters Register enrols adults diagnosed within 12 months of likely infection date, with this confirmed by either RITA/STARHS or a prior recent negative HIV test.

As such, it provides an important dataset for tracking natural history of infection prior to treatment, responses to treatment and for questions related to seroconversion itself. The BHIVA conference included a review from this cohort on changes in CD4 counts and trends in the time to starting ART since the cohort was first established. [1]

This analysis was based on 1734 people enrolled in the rsgister since 1998 (all diagnosed within 12 months of infection), with increasing numbers of patients over time. Approximately 17% of the total cohort was diagnosed within a month of infection (during seroconversion).

The analysis also uses the term 'seroconversion interval' for estimating the time between the last negative and the first positive HIV test, with median seroconversion interval of 151 days (IQR 39, 294). The cohort involves largely male participants (94%), with median age at seroconversion of 33 years (IQR 27 – 40).

Thie analysis reported that the median CD4 count at ART initiation increased from 284 cells/mm^3 (IQR 190, 378) prior to 2000 to 375 cells/mm^3 (IQR 296, 511) in 2010-11. However, the ranges for nearly all years varied from <50 to >600 cells/mm^3. The range indicates wide use of treatment both within and outside BHIVA guideline recommendations. The slightly higher CD4 count over time (approximately 6 cells/mm^3 higher per year in univariate analysis, $p < 0.001$) might be expected, given that the guidelines have increased the CD4 threshold for starting treatment over the same period. This data needs also to be verified in multivariate models.

In a sub-analysis of 967 people who were diagnosed within 6 months of infection, the percentage of people starting treatment during primary HIV infection also varied over time, reflecting both changing research data and guidelines: steadily dropping from 50% in 2000-1 to 13% in 2008-9 but increasing to 20% for 2010-11.

More significantly, the median time from seroconversion to starting ART steadily reduced from 3.7 years (95%CI: 3.2, 4.9) before 2000 to 1.4 years (95%CI: 1.3, 1.7) in 2010-11 (see Table 1). This is a much shorter period than most people expect: 25% of participants started within 1.3 years and 75% started within 1.7 years.

This shows that the majority of people diagnosed in early infection in the UK start treatment within two years. For the most recent data from 2010-11, the CD4 count when starting treatment was >500 for 25% of people but less than 350 for 50%. These results largely predate the wider use of earlier treatment to reduce infectiousness.

Also, in line with changes in guidelines, far fewer people who started treatment in the first 6 months of infection later stopped treatment (dropping from as high as 80% prior to 2008 down to only 11% since 2008). Prior to 2008, ART was mainly used as a short intervention with median time on ART of approximately 6 months (based on sub-analysis of n=967).

Table 1: Time to starting ART in UK seroconverters register (n=1734)

Year	Pre 2000	2000-1	2002-3	2004-5	2006-7	2008-9	2010-11
n	194	244	246	254	224	225	347
Years to ART (95%CI)	3.7 (3.2, 4.9)	2.8 (2.2, 3.5)	2.9 (2.3, 4.0)	2.6 (2.2, 3.0)	2.3 (1.8, 2.7)	2.2 (1.8, 2.7)	1.4 (1.3, 1.7)
CD4 at ART (IQR)	284 (190, 378)	280 (221, 410)	297 (227, 380)	314 (241, 450)	330 (272, 412)	337 (282, 437)	375 (296, 511)

Table 2: Trends in proportion starting ART in primary HIV infection * (n=937)

Year	Pre 2000	2000-1	2002-3	2004-5	2006-7	2008-9	2010-11
n	61	98	114	175	148	139	232
% starting ART during primary infection *	27.9	50.0	35.1	29.1	20.3	13.0	19.8
% stopping <12 mo	47.1	59.2	70.0	80.4	83.3	11.1	10.9

* Primary infection defined as within 6 months of infection.

C O M M E N T

The temporal changes in use of ART appear modest and are against a background of guideline changes over this time.

But, the recent data for time to starting treatment should alert doctors to the importance of offering early ART to people who are diagnosed in primary infection (within 6 months of infection).

This study shows that deferring treatment based on an expectation of having five or more years without treatment, is no longer supported by UK data.

Conversely, potential benefits of treating acute infection include:

- **Reduce viral evolution and diversity**
- **Limit the reservoir of latently infected resting CD4 cells**
- **Potential benefit from future advances in cure research**
- **Retaining HIV-specific immune profile similar to long term slow progressors**
- **Replicate circumstance reported in the VISCONTI cohort**
- **Reduce infectiousness for sexual partners ('normalise' HIV impact on this area of life)**

The immunologic benefits of treating during the six-month window are very different to earlier treatment at some later point during chronic infection. Also, given the increased focus on cure research, this is an option for which people should be able to decide for themselves.

The VISCONTI cohort reported that a small number of patients have been able to discontinue ART and maintain viral suppression, in some cases for over a decade. These individuals used ART for several years, started during acute infection. [2]

The Seroconverters Registry data shows that an expectation of five years without needing treatment is not appropriate for people diagnosed in early infection. Indeed, for more than 75% of people this is well under two years.

In line with BHIVA guidelines, the option to use earlier treatment during primary infection should be actively offered to all patients, including people with recent infection, and including those with CD4 counts >500 cells/mm^3.

However, while BHIVA guidelines are clear, the i-Base phoneline service has been contacted over several recent cases of people diagnosed during acute infection where the option of early treatment was neither offered nor discussed.

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PIVOT study: further analysis from five-year PI/r monotherapy strategy study

Simon Collins, HIV i-Base

BHIVA 2014 included an expanded analysis from the MRC-sponsored PIVOT study whose primary endpoint was the preservation or loss of treatment options after three years. [1]

PIVOT randomised 587 patients on stable ART to either maintain standard triple therapy or switch to ritonavir-boosted PI monotherapy.

In the last issue of HTB we reported top-line results from the PIVOT study, presented as a poster at CROI 2014, which noted a significantly higher rate of virological rebound (three viral load results >50 copies/mL) in the monotherapy group (35% vs 3%: difference 31.8%, 95% CI 24.6 to 39.0%; p <0.001). This difference was partially driven by a low rate of viral rebound in the standard therapy group (certainly compared to most published studies). [2]

Median duration of follow-up was 44 months, with only 2.7% of patients lost to follow-up or discontinuing over five years. Although the choice of PI/r was an investigator decision, data emerging from other studies supported greater safety from using darunavir/r or lopinavir/r. In PIVOT, darunavir/r was used by 79% (n=231) of the monotherapy group, 14% used lopinavir/r, 6% used atazanavir/r and one person used saquinavir/r.

Viral rebound was defined as three consecutive results $\geq$ 50 copies/mL, including an option to retest the initial sample, and with a confirmatory test 4-8 weeks later. All patients with viral rebound resuppressed, following the addition of dual-NRTIs, switching back to the previous combination, or spontaneously.

New drug resistance to one or more class (the definition used for the primary endpoint of "loss of treatment options") occurred numerically more frequently during PI/r monotherapy. However, resistance was uncommon in both arms [2.1% vs 0.7%, difference 1.4% (-0.4 to 3.4%), at three years] and the between-arm difference was not significant (p=0.15).

These results supported a conclusion of non-inferiority for the PI/r monotherapy strategy. The one person who developed PI resistance in the monotherapy arm was using atazanavir/r (now known to be insufficiently potent for use as monotherapy) who developed I50L/I. There were no significant differences in other secondary clinical endpoints, or in results at five years.

Grade 3/4 events were more common in the triple therapy arm (46% vs 55%, p=0.043) with this driven by laboratory (p=0.002) rather than clinical (p=0.12) events. There were more deaths in the monotherapy arm (6 vs 1) but these were not related to treatment or strategy (suicide, pulmonary embolism, breast cancer, lung cancer, glioblastoma and anal cancer with PI monotherapy and metastatic adenocarcinoma in the control group).

No differences were seen between the two strategies in changes in neurocognitive function from baseline (NPZ-5 score from verbal learning tests, colour trails and grooved pegboard). Given the concern about CNS penetration for patients using PI/r monotherapy, it is important and reassuring that there appear to be no marked functional CNS consequences.

C O M M E N T

This is the largest HIV study to be run in the UK for 20 years (since DELTA). It is also notable that only 3% of patients on the triple therapy arm had viral rebound over five years.

Although the primary endpoint shows non-inferior results well within the predefined upper margin of error, the significantly higher rate of viral rebound may complicate patient management and limit enthusiasm for doctors in the UK to use this strategy.

Cost effectiveness analyses are planned and will need to model this additional care required for people with viral rebound, especially as dual nucleoside components may soon become available as generics.

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Sexually transmitted HCV in HIV positive and negative gay men

Simon Collins, HIV i-Base

Several studies at BHIVA 2014 focused at HCV sexual transmission, together with the social complications this brings.

Of note, two studies reported sexual transmission of HCV to HIV negative gay men.

Sexual HCV transmission to HIV negative gay men

In an oral presentation, Dr Juan Tiraboschi, Guy's & St Thomas', reported on acute HCV infections that were detected during the PROUD study. [1]

This is an ongoing PrEP study that will randomise approximately 500 HIV negative gay men at risk of HIV to either immediate or deferred use of daily oral tenofovir/FTC. HCV testing was not routinely incorporated into the study design because the risk of sexual HCV testing has generally only been reported in HIV positive gay men. Neither positive HCV antibody status nor raised LFT levels were exclusion criteria for entering PROUD.

However, 160/393 (41%) patients enrolled in PROUD by December 2013, had been tested for HCV at least once during follow-up and 5/160 were found to have recent HCV infection. All men had a negative HCV test three months earlier. This correlates to an incidence of 3.1% of the tested cohort or 1.3% of the cohort as a whole.

The five cases (3 in the immediate PrEP arm and 2 in the deferred arm) ranged in age from 24 to 64 years old. HCV was diagnosed during the screening period in one person and from 7 to 64 days since enrollment for the others. Mean HCV RNA was 6.2 log copies/mL (range 9000 to 25,000,000). Only one patient was symptomatic (jaundice) with HCV testing prompted by recent risk behaviour including having an HCV positive partner for the others. All men reported anal sex (without condoms). One man was diagnosed with rectal chlamydia and gonorrhea and another man reported injecting drug use.

The high and unexpected rates of HCV in high risk gay men, lead the researchers to conclude that HCV testing should be considered in PrEP studies.

The second study was a retrospective review of acute HCV in HIV negative men diagnosed over four years at the sexual health clinic of the Chelsea and Westminster Hospital from January 2010 and December 2013. Of 36 acute HCV diagnosed by positive HCV antibody, ten were RNA negative at baseline and categorised as spontaneously cleared. Acute HCV was diagnosed by previous recent negative antibody status for 9 people, by positive HCV RNA in 4 people and by risk history in another 13. [2]

Risk factors included having an HCV positive partner (27%), multiple sexual partners in the previous three months (median 2, range 1- 60), group sex (35%), fisting (35%), recreational drug use (58% including cocaine, GHB, mephedrone, crystal methamphetamine and ketamine), intravenous use (27%). Most people reported having anal sex without condoms (85%) and 30% had an additional STI.

Genotype was only documented in 13 individuals (12 genotype 1 and 1 genotype 4). Three men (11%) with positive RNA at baseline spontaneously cleared HCV. Nine men were treated with pegylated interferon +/- ribavirin, of whom, seven achieved SVR clearance. Of the remaining 14 men, 6 had persistent infection, and 8 were lost to follow up.

Implications of detectable HCV RNA in semen

Although blood-to-blood transmission of HCV appears more plausible as the route for sexual HCV transmission, an oral presentation looked at HCV levels in semen, looking for differences by HIV status and in acute compared to chronic HCV infection. [3]

Of 66 HCV positive men, 40/66 were HIV positive, Of the HIV positive men, 18 with acute HCV (median duration 3.5 months (IQR 2.0, 6.3) and 22 had chronic HCV. Of these, 35/40 were on ART with undetectable HIV viral load. All 26 HIV negative men had chronic HCV infection.

At baseline, HCV RNA was detected in semen sample from 29 (43.9%) at median 2.1 log IU/mL (IQR 1.8-2.6) with no relationship reported for either HIV status or acute compared to chronic HCV. This was approximately 4 logs lower than median plasma HCV RNA (5.5 logs IU/mL; IQR 5.5, 6,5) again without differences between groups. For people in acute HCV infection, plasma RNA levels were higher (approximately 6.1 vs 4.2 log IU/mL) in those with detectable levels in semen, though this was not observed for with groups with chronic HCV.

HCV shedding in semen was intermittent in 40% of men. Of 35 men with a follow-up sample (at median 4.5, IQR 3.8-6.5 months), HCV was detected in semen in at least one sample for 26/35 men (74%), and in both samples in 12 men (34%).

Social complications of coinfection

Two posters looked at the social issues associated with a new HCV diagnosis.

Saxon and colleagues reported on the difficulty of disclosure of HCV status to new sexual partners experienced by HIV positive gay men in Manchester. [4]

Only 16/52 men with coinfection agreed to participate in a semi-structured, face-to-fact interview, about HCV disclosure to sexual partners. At the time of the interview, most (12/16) were no longer HCV positive. Four men reported abstinence while HCV positive, highlighting the impact of HCV in this group. HCV disclosure was reported always, mostly, sometimes and never, by 3, 2, 4 and 3 men respectively.

Perceived stigma of HCV and fear of rejection or reaction to disclosure, but also safer sex and behaviour and lack of HCV awareness were associated with non-disclosure. Themes for disclosure included increasing HCV awareness, fear of legal prosecution, responsibility, trust and feelings for partner.

These results suggest that a larger study may be worthwhile, perhaps using an anonymised survey, especially given the low numbers of men agreeing to participate.

Also concerned with anecdotal reports of stigma associated with hepatitis C, Archibold and colleagues at the Bloomsbury Clinic in London ran two peer-led workshops for HIV positive people who were newly diagnosed with HCV. [5]

Evaluations completed by 16 people generally reported generally high satisfaction scores associated with acceptance of their HCV diagnosis and a better understanding of treatment. Greater confidence about disclosure scored 3.13 (out of a maximum 4.00)

The workshop reported that isolation felt by HIV positive men with coinfection led to wider psychological issues causing lack of confidence and depression, and that this was helped by this format for support.

C O M M E N T

Studies on the incidence of HCV sexual transmission in HIV negative men have not reported a consistent pattern. In Brighton, 9 cases of acute HCV were in HIV negative men and 5 in men who HIV status was unknown (though some of these men were likely to have become HIV positive at the same time, [5] whereas other surveillance data have not reported this.

These studies add to the complexity of understanding HCV sexual transmission. As the biological route is not yet identified this limits the accuracy of advice for avoiding infection or transmission. Currently, the plausibility is higher for blood-blood exposure during sex explaining these cases than for a new concern about the infectiousness of semen and/or other sexual fluids.

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Annual HCV testing and use of core antigen to reduce costs and increase diagnosis during acute HCV

Simon Collins, HIV i-Base

Routine monitoring for viral hepatitis, at least annually, is recommended for HIV positive people in BHIVA guidelines and this may be improved by use of HCV core antigen testing.

An analysis from the UK-CHIC cohort study reported that 88% of HIV positive people have been tested for HCV, but that annual testing is still not widely incorporated in practice, increasing from 25% in 2004 to 56% in 2011, despite being recommended for all patients. [1]

On the other hand, an encouraging example of integrating HIV testing in a specialist hepatology service was reported. In a retrospective case note review from Newham Hospital (located in an area with high prevalence of HIV, HBV and HCV) approximately 80% of 596 patients had a documented HIV test result (50% through the hepatology clinic). Although no new cases of HIV were identified, it is notable that the refusal rate was only 1.2% (7/596). [2]

Several groups reported on their experience from using HCV core antigen test which has been available for about a year and that has advantages of two-hour turnaround and lower cost (~20% compared to PCR), and the potential to help diagnose acute HCV.

Results from a two-part study at the Royal Free Hospital in North London, were presented by Robert Carney. In the first part, core antigen testing was validated against HCV seroconversion panels (n=45; genotypes 1a, 1b, 2 and 3). In the second part, the test was assessed in samples from 30 HIV positive gay men with recently diagnosed with acute HCV, detecting all acute cases.

Overall, sensitivity was 100% and specificity was 97,5% (one false positive was reported). Both positive and negative predictive values were 100%. HCV RNA levels were reliably detected at 1250 IU/mL but not at 625 IU/mL. [3]

Results from the use of core antigen testing from 2013 at St Georges Hospital in south London were reported from a retrospective case note review of 75 patients tested for HCV. Positive antigen results were detected in 8/75 (10.7%), with one false positive and one equivocal result (both negative on HCV PCR). Four patients had new HCV infection including one acute case, three with known HCV (both antigen and antibody positive) and nine were antigen negative and antibody positive (indicated cleared HCV infection). [4]

At Brighton, 14 cases of acute HCV were identified by HCV PCR from 111 patients with elevated ALT. Core antigen testing also identified 14 people, with one indeterminate result that did not become positive by either test. The positive and negative predictive values in this cohort were 93% and 98% respectively. Notably, 6/11 had a negative HCV antibody result suggesting an advantage in detecting acute infection. [5]

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HIV positive attitudes to involvement as donors and recipients in organ transplant programmes

Simon Collins, HIV i-Base

The views of HIV positive people towards organ transplants from HIV positive donors were presented in results from a simple clinic survey, reported by Huda Tada from Coventry and Warwickshire Partnership Trust.

This is important given the scarcity of donor organs irrespective of HIV status.

Efficacy of ART has extended life-expectancy which both increases the number of people for whom transplant may become a life-saving option and makes benefits post-transplant durable. This issue was also highlighted by the change in US federal law in November 2013 to allow HIV positive-to-positive transplantations, including the provision for living donors.

The current study surveyed 206 HIV positive adults attending a single HIV outpatients centre from January to July 2013. Baseline demographics included 59% women, 70% black African, heterosexual 83%, 90% were stable on ART, with mean duration of 6 years since HIV diagnosis and mean of >5 years on ART. Comorbidities were reported by 41% of participants but only 4% reported drug or alcohol use.

The results showed a high acceptance for both donating organs (62% yes, 16% no and 22% unsure) and receiving an organ from an HIV positive donor (55% yes, 18% no, 7% unsure).

Confidentiality, infection and quality of organ were main reasons against. Approximately half the participants agreed they would be happy to both donate and receive an HIV positive organ, if this was appropriate. Black African ethnicity was associated with greater caution for HIV positive organ transplants.

C O M M E N T

This cross-sectional survey is important for showing a generally high level of both interest and acceptance of involvement of HIV positive people in organ transplant programmes. It is notable that the survey was performed without educational interventions on the benefits and risks and in a population who were not at critical risk for needing a transplant. Both these factors would be likely to increase positive results.

It would be helpful to have results from a larger study, involving some of the HIV centres with both experience and demand for HIV transplant services.

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CONFERENCE REPORTS

21st Conference on Retroviruses and Opportunistic Infections (CROI)

3 – 6 March 2014, Boston

Introduction

We continue our reports from the 21st Conference on Retroviruses and Opportunistic Infections held in Boston from 3-6 March 2014.

Access to abstract and posters for people who were either unable to attend and for reference afterwards is available for most sessions and many posters.

http://www.croi2014.org

http://www.croi2014.org/electronic_materials

Abstract book (a study 61MB PDF file)

http://croi2014.org/sites/default/files/uploads/CROI2014_Final_Abstracts.pdf (PDF)

Reports in this issue of HTB are:

- Pharmacokinetics of antiretrovirals in pregnancy
- Better virologic outcomes with efavirenz vs lopinavir/ritonavir in pregnant women and no difference in risk of preterm birth
- Once daily lopinavir/ritonavir not recommended for routine use in children and adolescents
- Early antiretroviral treatment in infants
- Hospitalisation among elite controllers
- Catching up with pathogenesis and cure research from CROI 2014

CROI 2014: PREGNANCY AND WOMEN'S HEALTH

Pharmacokinetics of antiretrovirals in pregnancy

Polly Clayden, HIV i-Base

Physiological changes during pregnancy can influence the pharmacokinetics (PK) of antiretrovirals and decrease drug exposure. Opinions on whether this is of clinical importance and recommendations for dosing differ.

Four posters at CROI 2014 reported PK data for atazanavir, darunavir and raltegravir suggesting that routine dose adjustment in pregnancy is unnecessary. The PANNA Network of European centres – set up to collect PK data in pregnant women in Europe – conducted three of these studies. [1] David Burger and investigators at the Radboud University Nijmegen Medical Centre, the Netherlands lead this network.

Atazanavir

Ritonavir-boosted atazanavir (ATV/r) is a preferred protease inhibitor for antiretroviral (ARV)-naive pregnant women in European (Including BHIVA) and US perinatal guidelines. The package insert recommends a dose increase in the second and third trimesters of pregnancy with concomitant TDF use. Conflicting data exist about the influence of TDF on ATV concentrations, and whether or not this dose adjustment is necessary.

Results were presented from a French multicentre, cross sectional cohort study investigating steady state ATV plasma concentrations at 24 hours post-dose (C24h) in HIV positive pregnant women. [2]

Women receiving an ATV/r 300/100 mg once-daily containing regimen with available viral load, CD4 and demographic data were enrolled. None of the women in this study received an adjusted dose of ATV.

ATV C24h was determined at delivery, during each trimester and post-partum using UPLC-MA/MS; the target was 0.15 mg/L.

Virological failure was defined as two consecutive viral load results >50 copies/mL within two months prior to delivery.

The investigators also collected weight, gestational age, and APGAR score data from neonates.

A total of 103 pregnant women were evaluated. The women were a median of: 34 years (IQR 31to 37), 7 years (3 to 9) since HIV diagnosis, 5 years (2 to 8) on ART and 1 year (0 to 1) of ATV/r; 13% started treatment in pregnancy. Almost half the women (42%) received a TDF/FTC backbone

A minority: 6%, 4% and 2% were coinfected with HBV, HCV and HBV/HCV, respectively. BMI before pregnancy was a median of 25 (IQR 21 to 28); baseline CD4 197 cells/mm^3 (IQR 101 to 290) and viral load 46,042 copies/mL (IQR 31,066 to 102,800). The majority of women (88%) were from sub-Saharan Africa.

A total of 366 samples were available for analysis. The investigators reported statistically similar ATV C24h values for the different trimesters and delivery compared to post partum: p=0.11 for 1st trimester, p=0.20 for second trimester, p=0.69 for third trimester and p= 0.76 for delivery. The majority of women (85%) were above the 0.15 mg/L threshold across all trimesters. Coadministration of TDF did not affect ATV C24.

Cord plasma ATV concentration was a median of 0.146 mg/L (IQR 0.64 to 0.295) in a subset of 28 maternal/infant pairs. Cord/maternal plasma ATV ratio was 0.19 (0.10 to 0.32) consistent with low transplacental transfer and the protein binding ratio of ATV.

There was no significant change in CD4 count from the start of ATV/r containing treatment to post partum. At delivery, 97% of women were virologically suppressed.

There were no vertical transmissions in this cohort. Of 88 women accessed, 40 delivered vaginally and 48 by caesarean section. Of 82 neonates with available data, 16 were preterm (<37 weeks gestation).

Infant characteristics were median: gestational age 38 weeks (IQR 37 to 39) weeks, weight 2,970 g (IQR 2,755 to 3,358) and APGAR score 10.

Only one woman presented during delivery with grade 3 hyperbilirubinaemia. Of 48 infants, 24 presented with grade 2 and 5 with grade 3 hyperbilirubinaemia.

A related study from the PANNA Network looked at steady-state intensive 24-hour PK in the third trimester and at least two weeks postpartum among pregnant women receiving 300/100 mg ATV/r in regimens with and without TDF. [3]

ATV and RTV plasma concentrations were determined by validated UPLC method.

The investigators calculated geometric mean ratios (GMR) and 90% confidence intervals for PK parameters third trimester/postpartum and compared those with and without TDF.

This analysis included 29 women of whom 11 were treatment naive at conception; 15 of the women were black and 14 white; 19/29 received concomitant TDF. Approaching delivery 76% were virologically suppressed.

Paired PK curves (third trimester and postpartum) were available for 25 women. Exposure to ATV in the third trimester was 34% lower than post partum.

GMR (90% CI) of ATV PK parameters third trimester/postpartum overall were: 0.66 (0.57 to 0.75) for AUC0-24h; 0.70 (0.61-0.80) for Cmax ; 0.59 (0.48 to0.72) for C24h, all comparisons p<00.1.

No statistical difference in AUC24h was found between women receiving TDF vs no TDF: GM (95%CI) third trimester 28.8 mg.h/L (22.2 to 37.4) vs 32.08 mg.h/L (21.1 to 48.7); postpartum 46.1 (36.2 to 58.6) vs 49.2 mg.h/L (34.7 to 69.8).

None of the women had ATV concentrations <0.15 mg/L.

Viral load was detectable in six women around delivery. PK parameters for ATV were similar in these women to those with undetectable viral load around delivery.

The median cord blood/maternal plasma concentration ratio in 12 maternal/infant pairs was 0.20 (range 0.6 to 3.05).

Median gestational age at delivery was 39 weeks.

One infant died (congenital diaphragmatic hernia resulting in respiratory failure and septic shock). The investigators did not consider an association with ATV/r to be likely as it was started in week 21 of pregnancy in this case, and the closure of the pleuroperitoneal canal happens around week 8 of pregnancy.

There were no vertical HIV transmissions.

The investigators noted that therapeutic drug monitoring of ATV should be considered for treatment experienced pregnant women with PI resistance.

Darunavir/ritonavir

European and US perinatal guidelines include ritonavir-boosted darunavir (DRV/r) as an alternative protease inhibitor in ARV-naive pregnant women.

The dosing recommendation for ARV-naive patients is DRV/r 800/100mg once daily but PK data in pregnant women are limited.

A PANNA evaluation of this dose DRV/r during pregnancy performed intensive steady-state 24-hour PK profiles in the third trimester and at least two weeks postpartum, as in the ATV study described above. [4]

Target concentration for DRV is 0.55 mg/L (EC50 for resistant virus).

Of 15 women included in the analysis, 7 were black and 8 white. A third of the women were treatment naïve at conception; 2 conceived on DRV/r; 4, 8 and 1 started DRV/r in the first, second and third trimesters respectively. Seven paired PK curves (3rd trimester and postpartum) were available.

GMR (90% CI) of DRV PK parameters third trimester/ postpartum were: 0.63 (0.51 to 0.77) for AUC0-24h; 0.72 (0.57 to 0.93) for Cmax; 0.36 (0.22 to 0.58) for C24h.

The mean DRV free fraction (95% CI) was 12% (11 to 14%) in the third trimester and 10% (7 to 13%) postpartum. Two of 15 women had DRV concentrations <0.55 mg/L in the third trimester, vs none postpartum.

The median cord blood/maternal ratios in 6 maternal/infant pairs were 0.12 (range 0.08-0.35).

The median gestational age at delivery was 38 weeks. Around delivery 4 women had viral load >50 copies/mL. Two weeks prior to delivery one woman still had a significant viral load (28,711 copies/mL). She was thought to be non-adherent and had directly observed therapy until delivery.

There were no vertical HIV transmissions.

The investigators noted that contrary to previously published data for DRV exposure with DRV/r 600/100 mg twice daily, the decrease in exposure with 800/100 mg once daily does not appear to be compensated by a higher free fraction during pregnancy.

They suggested DRV/r 600/100mg BID to be the preferred dose during pregnancy for treatment-experienced women.

Raltegravir

According to European and US perinatal guidelines, raltegravir (RAL) can be used in HIV positive pregnant women in special circumstances, because safety and PK information is limited.

RAL has been shown to rapidly reduce viral load. BHIVA guidelines recommend RAL for late presenters (>28 weeks) and women with unsuppressed viral load close to delivery.

In the third PANNA evaluation, women receiving RAL 400 mg twice daily during pregnancy also had intensive steady-state12-hour PK profiles in the third trimester and at least 2 weeks postpartum. [5]

The suggested target for RAL is 0.02 mg/L (levels below this threshold were associated with viral failure in QDMRK).

This analysis included 14 women of whom 8 were black and 6 white. Five women were treatment naive at conception, 3 conceived on RAL and 2, 4 and 5 started in the first, second and third trimesters respectively. RAL was combined with a PI-based regimen in 9/14 women; 6/14 women received quadruple ART regimens.

Paired PK curves (third trimester and postpartum) were available for 12 and third trimester only for two women.

Geometric mean ratios (90% CI) of RAL PK parameters third trimester/postpartum were: 0.77 (0.59 to 1.00) for AUC0-12; 0.83 (0.55 to1.25) for C max; 0.54 (0.28-1.05) for C12h; concentrations in the 3rd trimester were respectively: 4.95 (3.01 to 8.13) mg.h/L, 1.40 (0.74 to 2.65) mg/L and 0.05 mg/L (0.03 to 0.09) mg/L.

One woman had a C12h third trimester level below the suggested threshold of 0.020 mg/L. Her viral load was 74 copies/mL in the 3rd trimester and undetectable at delivery.

The median ratio of cord blood/maternal RAL concentrations in 8 mother/infant pairs was 1.24 (range 0.13-4.53).

Median gestational age at delivery was 38 weeks and birth weight was 3115 g. Viral load was detectable in 3 women around delivery; all were <400 copies/mL and none of their levels were below the suggested threshold.

None of the infants were HIV infected and no birth defects were reported.

The investigators reported that the decrease observed in exposure to RAL during 3rd trimester compared to postpartum: 33% for AUC0-12 and nearly 50% for C12h, is not considered to be of clinical importance. There is considerable interpatient variability in PK reported with RAL, which was also demonstrated in this study. RAL showed good transplacental transfer.

C O M M E N T

An important component of ensuring the safe and effective use of antiretrovirals during pregnancy is studying their PK.

To date, most protease inhibitors have shown reduced total plasma concentrations during the third trimester. But pregnancy-related changes in the binding of protease inhibitors also need to be considered. In some cases this partially compensates for the reduction in the total concentration by increasing the protein-free bio-available fraction.

Whether reductions in plasma concentration should lead to dose-adjustment during pregnancy is not always clear-cut. This has certainly been the case for lopinavir/ritonavir in the past and is again with boosted atazanavir and darunavir. The importance of any reduction in total or protein-free drug must also factor in the likelihood of achieving therapeutic efficacy – this can be guided by the absolute concentrations compared to the target concentrations – which in both studies were adequate for atazanavir and then by the clinical outcome, which should include both early and long term viral suppression and of course transmission data.

Such data are emerging for atazanavir and are needed for darunavir. In the latest version – the 2014 interim review – the BHIVA guidelines have taken a cautious but pragmatic view, recognising that twice daily might be preferable to once daily darunavir on the basis of the PK studies but that for many patients established on a fully effective once daily regimen the case for switching to twice daily may not outweigh the advantages of continuing with once daily.

Conversely, where there is less certainty of effect, initiating ART during pregnancy or where HIV is known or suspected to harbour drug resistance mutations, twice daily for the duration of pregnancy should be considered until more clinical and virological data are available.

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Better virologic outcomes with efavirenz vs lopinavir/ritonavir in pregnant women and no difference in risk of preterm birth

Polly Clayden, HIV i-Base

Efavirenz was associated with superior virologic outcomes compared to lopinavir/ritonavir (LPV/r) in a Ugandan study of ART-naive pregnant and breastfeeding women, according to data presented at CROI 2014. The risk of preterm birth was no different between women randomised to LPV/r- or EFV-based ART in this cohort.

Deborah Cohan from the University of California presented findings from secondary analyses of the PROMOTE study in an oral presentation on behalf of researchers from Kampala, Uganda and the United States. [1]

PROMOTE was an open label, randomised study conducted at Tororo District Hospital and HIV clinics in Tororo, rural Eastern Uganda set up to look at risk of placental malaria between women receiving two ART regimens. The study enrolled HIV positive pregnant women who were ART-naïve and between 12-28 weeks gestation. All women received daily trimethoprim-sulfamethoxazole and bednets.

Women received either LPV/r or EFV with AZT/3TC from enrollment until one year of breastfeeding. The LPV/r dose was increased from the standard 400/100 mg twice daily to 600/150 mg at 30 weeks gestation.

A total of 389 women were enrolled in the study: 195 in the EFV and 194 in the LPV/r arms. There were respectively 187 and 190 women at delivery and 173 and 175 completed the study.

There were no significant differences between the two arms at enrollment: mean age was 29 years and gestational age 21 weeks, two thirds of the women had three or more live children. The women's median pre-ART CD4 count was 370 cells/mm3, mean pre-ART viral load was 61,611 copies/mL and 95% were WHO stage 1. About 40% were diagnosed with HIV in this pregnancy.

Dr Cohan noted that there was considerable incidence of malnutrition in this cohort with a median BMI of 21.8 in both arms.

For virologic efficacy the primary analysis was a non-inferiority comparison with 80% power to exclude a significant difference between study arms of 11% at delivery and 24 weeks – in both cases the 95% confidence interval did not indicate inferiority.

But when the investigators looked at the pattern of viral suppression at different time points, compared to LPV/r, women on EFV were significantly more likely to achieve viral suppression (<400 copies/mL) by delivery: 98% vs 86%, p <0.0001. There were no differences in suppression at 8 weeks post ART or 24 and 48 weeks post partum; about 90% of women achieved viral suppression at these time points.

There was significantly more virologic failure in the LPV/r vs EFV arm: odds ratio 0.51(95% CI 0.31 to 0.82), p=0.0062 (n=374).

Women receiving LPV/r had greater CD4 count increase at delivery and 24 weeks post partum vs EFV: respectively +57 vs -7 cells/mm3, p=0.002, and +178 vs +109 cells/mm^3, p<0.01.

There was no difference in grade 3 or 4 adverse events between the arms (one per arm). Unsurprisingly grade 1 or 2 gastrointestinal adverse events were significantly more likely for women on LPV/r vs EFV. There were no reports of increased CNS adverse events with EFV but it was suggested that the questionnaire might not have been specific enough to pick these up.

The HIV transmission rate was 0.5% (2/374) – one in utero and one breastfeeding transmission in LPV/r arm.

HIV-free infant survival was similar between arms LPV/r vs EFV: 92.9% vs. 97.2%, p=0.10.

A poster from the same group, authored by Catherine Koss and colleagues looked at potential risk factors for preterm birth (<37 weeks, very preterm <32 weeks) in this cohort. [2]

Gestational age was calculated by last menstrual period and ultrasound at enrollment. Stillbirths and spontaneous abortions were excluded from the analysis.

The investigators reported, among 356 live-born singleton deliveries, the prevalence of preterm birth was 15.4% and of very preterm birth 1.7%.

Multivariate analysis, controlling for time since HIV diagnosis and ART regimen, revealed maternal gestational weight gain <0.1 kg/week vs ≥ to be significantly associated with preterm birth: aHR 2.21 (95% CI 1.28 to 3.83), p=0.005.

There was a trend toward increased risk of preterm birth with gestational age at ART initiation of 24 to 28 weeks vs 12 to 23 weeks: aHR 1.69(95% CI 0.97 to 2.87), p= 0.065.

Neither placental malaria nor antiretroviral regimen was a risk factor for preterm birth.

C O M M E N T

These results support the WHO guidelines preferred regimen for pregnant women.

The increased LPV dose might not have been necessary and – as noted – the additional gastrointestinal events in the LPV/r arm come as no surprise. CNS events need to be monitored more carefully as this is now a component of the WHO preferred regimen for the vast majority of people receiving first-line ART including pregnant women.

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CROI 2014: PAEDIATRIC CARE

Once daily lopinavir/ritonavir not recommended for routine use in children and adolescents

Polly Clayden, HIV i-Base

A PENTA trial conducted in Europe, Thailand, Argentina and Brazil did not demonstrate non-inferiority of once-daily to twice-daily lopinavir/ritonavir in children and adolescents.

Lopinavir/ritonavir is approved for use in adults once- or twice-daily, but only for twice-daily in children.

KONCERT was a phase 1/2 randomised trial in which children and adolescents 18 years or less, weighing at least 15kg, on lopinavir/ritonavir based ART with suppressed viral load (<50 copies/mL) for 24 weeks or more, either continued twice-daily dosing or switched to once-daily. Dosing was according to FDA approved body weight-based recommendations.

Hermione Lyall from Imperial College London presented data from the trial at CROI 2014 on behalf of the KONCERT investigators.

Participants were followed for minimum of 48 weeks with visits at weeks 0, 4, 8, 12 then every 12 weeks. The primary outcome was the proportion with confirmed viral load >50 copies/mL at 48 weeks. The non-inferiority margin was 12%.

A subset (n=53) of participants in the once daily arm had lopinavir/ritonavir pharmacokinetic (PK) evaluations at baseline (while still on twice daily dosing) and at four weeks (n=26). PK analyses were per-protocol and all others intention-to-treat.

A total of 173 participants were randomised to lopinavir/ritonavir either once-daily (n=86) or twice-daily (n=87). They were a median age of 11 years old (range 3.8 to14.7); 18% were aged 3 to 7, 43% 8 to 12 and 39% 13 to 18 years. There was a broad ethnic mix: 25% white, 27% black, 35% Asian, 6% mixed and 6% other. Median CD4 percent was 33% overall but there were more participants in the twice daily arm with CD4 percent above 30% (67% vs 60%).

At randomisation there was viral rebound in five children in the once-daily arm (none in the twice-daily). Median viral load was 120 copies/mL (range 51 to 91201) vs 134.5 copies/mL (range 57 to 270) in the once- and twice-daily arms respectively.

Over 50% of participants had been exposed to three classes of drugs and only 20% were on their first antiretroviral regimen.

The investigators found the AUC 0-24 and C (last) were less for the subset in the PK study at four weeks (once daily) compared to baseline (twice daily), see Table 1.

Table 1: AUC0-24 and C(last) with once vs twice-daily

	once-daily (95%CI)	twice-daily (95% CI)	once/twice daily GM ratio (90% CI)
AUC0-24 GM h*mg/L	160.9 (138.4 to 187.0)	223.9 (194.8 to 257.4)	0.72 (0.61 to 0.85)
C(last) mg/L	1.03 (0.61 to 1.75)	5.69 (4.58 to 7.07)	0.18 (0.11 to 0.29)

Dr Lyall noted that a C(last) level just above 1 mg/L is considered to be acceptable and 40% in the study were below that level. She added that only two participants who took part in the PK substudy had viral rebound and both had good trough levels: 6.4 mg/L and 2.1 mg/L in the twice- and once-daily arms respectively. This raises the question of whether viral rebound is associated with drug levels or with adherence, she said.

At 48 weeks 12 vs 7 participants in the once- vs twice-daily arms had confirmed viral load >50 copies/mL; the estimated difference was 6% (90% CI -14 to 2), p=0.196. Because the confidence interval crossed the 12% level the study did not demonstrate non-inferiority.

Of the 12 people who had viral rebound at any point in the once-daily arm 7/9 who remained on the same dosing schedule resuppressed.

Changes from baseline to week 48 in CD4 percent, CD4 count, biochemistry, hematology, lipids, resistance and adverse events were similar between arms.

There was a strong preference for once-daily dosing with 84% participants/carers saying they preferred this. There was no significant difference between arms in adherence.

Although the results can be partly explained by chance viral load and CD4 percentage imbalances at baseline, they do not support the routine use of once daily lopinavir/ritonavir in children and adolescents.

C O M M E N T

Although these results do not support the routine use of once daily lopinavir/r in children and adolescents, in settings with close monitoring this might still be an option for a minority.

As with adults, once-daily boosted darunavir and atazanavir are preferred.

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Early antiretroviral treatment in infants

Polly Clayden, HIV i-Base

The recent report of one HIV infected infant with viral control after interrupting antiretroviral treatment (ART) – and maybe a second case – raises the possibility of functional cure for infants started on ART soon after birth.

This spotlight on early ART also raises many issues of diagnosis, treatment and implementation, regardless of whether or not infants are "cured".

A themed discussion at CROI 2014, led by Marc Cotton from Children's Infectious Diseases Clinical Research Unit, Stellenbosch University, Tygerberg, South Africa, focused on response to early ART initiation. [1]

Dr Cotton began the session with a recap of the results from the children with HIV early antiretroviral (CHER) randomised trial, published in The Lancet last year. [2]

In CHER 375 infants with HIV infection, diagnosed before 12 weeks with CD4 percentage $\geq$ 25% were randomised to receive: deferred ART until clinical progression or CD4% drop (standard of care when the trial was conducted); or early ART until 40 weeks, then stop until HIV progression, when ART was restarted; or early ART until 96 weeks, then stop and restart with HIV progression.

The children receiving early ART did so at a median of about 7 weeks of age and those receiving deferred ART at about 20 weeks.

The study showed children receiving early ART had better clinical and immunological outcomes than those receiving deferred ART at 6 years of follow up even with treatment interruption.

Early ART was also associated with less microbial translocation and better neurological development.

Dr Cotton suggested some of the emerging issues with early ART are: virological response, co-factors and coinfection, reservoir kinetics, HIV antibodies and DNA PCR later on, and operational issues. Five posters discussed in this session showed findings from studies looking at aspects of these issues.

Routine use of confirmatory antibody tests not recommended with early ART

Data from CHER suggests that routine antibody tests should not be used to confirm HIV status in children already diagnosed and started on ART at less than six months of age. [2]

Helen Payne and colleagues explained that HIV infected infants starting early ART might become HIV-antibody seronegative after the decay of passively acquired maternal antibody and viral suppression. As immediate treatment for all children under two years is now universally recommended – and WHO guidelines have recently increased this to five years – the frequency of seronegative status following early ART gives rise to questions about clinical management in this age group.

The investigators measured HIV antibody in stored plasma from 75/125 children in the deferred ART arm and 109/126 children in the early ART until 96 week arm at median age of 91.4 weeks (IQR 90.6 - 93.4).

They used three techniques to perform these measurements: 4th generation microparticle enzyme immunoassay HIV antigen/antibody combination; HIV-1/2 qualitative immunochromographic rapid antibody test (assessed by a blinded, independent clinician; and a sensitive in-house ELISA to quantify anti-gp120 IgG and total IgG.

This showed that children in the deferred ART arm had significantly more antibody than those in the early ART until 96 weeks arm according to results from all three tests. Using automated serology, 90% vs 54% of children were seropositive, $p<0.0001$; with rapid test, 88% vs 47%, $p<0.0001$; and quantitative anti-gp120 IgG ELISA, median 6,870 ug/ul (IQR 1,706-53,645) vs 230 (IQR 133-13,129), $p=0.04$.

The investigators noted that levels of total IgG were similar in both groups, suggesting that this effect was specific to HIV responses. All children had detectable anti-gp120 IgG antibody by ELISA.

Eight children (10%) from the deferred ART arm and 49 (46%) from the early ART until 96 weeks arm were seronegative using automated serology. In the deferred arm there was no difference between the automated and rapid test. But in the early ART until 96 weeks arm 9 children with weakly positive automated results had negative rapid tests.

Older age at start of ART was associated with increased anti-gp120 IgG in the deferred arm, $p=0.002$. By automated serology, starting ART between 12 to 24 weeks of age gave 13.7-fold higher odds of being seropositive by 92 weeks old vs starting ART at 0 to 12 weeks (95% CI 3.1 to 60.2), $p=0.001$. All 33 children starting ART at 24 weeks of age or more were seropositive.

Higher anti-gp120 values were associated with higher cumulative viral load to week 84, p<0.0001.

In this study, almost half the children starting ART within 12 weeks of birth and 6% of those starting between 12 to 24 weeks were seronegative by commercial serology or rapid tests at approximately two years of age.

In conclusion the investigators suggested that routine antibody tests should not be used to confirm HIV status among children already diagnosed and started on ART at less than six months of age.

Further investigation is needed to determine whether persistence of anti-gp120 IgG represents slow decay or is a response to low levels of HIV replication, they added.

Varying HIV profiles in early treated children seronegative by ELISA

Data from Cameroon suggested that seroreversion is common in infants receiving early ART. [3] This presentation, by Mathurin Tejiokem and colleagues from Cameroon and France, is from an ongoing project looking at residual HIV in early treated infants using ultra-sensitive virological methods.

ANRS-PEDICAM is a cohort of HIV-infected infants followed from one week of life or diagnosed before seven months of age from 2007 to 2011 in three urban referral hospitals in Yaounde and Douala. Five-year follow up is planned.

Children receive first line ART of two NRTIs plus either lopinavir/r (LPV/r) or nevirapine in accordance with local guidelines.

At the time of analysis 192/210 (91.4%) children had started ART at a median of 4.1 months. Of those, 147/192 (76.6%) children were tested with ELISA at a median age of 19.1 months (IQR 18.2 to 20.1) and 26/147 (17.7%) of them were negative for HIV antibodies. Over a third (38.5%) of the 26 children started ART before three months.

Children with negative antibody tests were younger: 3.2 vs 4.7 months, p<0.001. They were also more likely to be WHO stage 1 or 2 when they started ART: 84.6% vs 59.5%, p=0.01. Weight for age z-score, ART regimen and CD4 percentage at start of ART were not associated with a negative antibody test.

Of 12 children with a median follow up of 47.6 months (range 21.8 to 65.1), nine remained HIV-antibody negative. The investigators then explored residual HIV activity in these children using ultrasensitive virological tests.

This revealed varying HIV-DNA and HIV-RNA profiles in the children. One child had no replicating virus (<24 copies/mL) and no detectable HIV-DNA. Five had no replicating virus and varying HIV-DNA levels (range 2.22 to 2.59 log copies/106 PBMC). Three children had replicating virus (range 36 to 97 copies/mL) and HIV-DNA (1.6 to 2.7 log copies/106 PBMC).

Western blot profiles varied from only one antibody peptide (anti-p24) with no replicating virus to several of the gag and pol peptides with replicating viruses.

The investigators concluded that seroversion is common in early treated infants: 17.7% (95% CI 11.9 to 24.8). They cautioned that misleading interpretation of these results might have public health consequences due to reduced adherence.

Work is ongoing to look at the mechanism of seronegativity, especially in antibody negative HIV-infected infants with quantifiable plasma viral load, and the potential of HIV control in these infants.

Better virologic control in infants started on ART before six months of age

Greater virological control was observed in infants starting ART before 6 months of age – compared to 6 to 24 months – in three cohorts at Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa. [4]

Stephanie Shiau and colleagues from the University of the Witwatersrand, Johannesburg and Columbia University, New York, evaluated viral dynamics by age at start of ART. The three cohorts were:

Cohort 1 (Neverest 2) – children started on LPV/r-based ART <24 months of age and were randomised to stay on this regimen or switch to nevirapine after viral suppression.

Cohort 2 (Neverest 3) – children, suppressed on LPV/r, and aged 3 to 5 years at enrolment were randomised to remain on LPV/r or switch to efavirenz. Only children who started ART <24 months of age were included in the analysis.

Cohort 3 (FinHDER) – children participating in a surveillance study of newly diagnosed HIV infected infants and young children. Those who started ART <24 months of age were included.

The mean age at ART start was between 8 and 10 months across the three cohorts and other characteristics were similiar before starting ART.

The investigators reported two main findings from their evaluation.

1. Age at ART start influenced initial viral suppression:

In cohort 1 (Neverest 2), of 323 children, HIV viral loads were higher before ART in 102 children <6 months vs 221 aged 6 to 24 months: 75.6 vs 58.4% had >750,00 copies/mL; 4.7 vs 10.7 had <100,000 copies/mL, p=0.02.

These children had similar time and likelihood of achieving viral suppression by age at ART start. The investigators noted that this suggested faster decline in the younger age group.

In cohort 3 (FinHDER), 145/236 children with a known date of ART start had viral load data available. Analysis of these children found those who started ART <6 months were more likely to suppress <1000 copies/mL by 6 months (58%) vs those starting ART 6 to 24 months of age (33.3%).

2. Age at ART start influenced virological control after viral suppression:

In cohort 1 (Neverest 2 once suppressed) children <6 months at ART start were less likely to fail >1000 copies/mL by 52 weeks from randomisation, p=0.02. Most failures were in the nevirapine switch arm. Children who stayed on LPV/r <6 months at ART start were less likely to blip >50 copies/mL by 52 weeks after randomisation, p=0.04.

In cohort 2 (Neverest 3), of 293 children, those <6 months of age at ART start were less likely to blip above 50 copies/mL vs 6 to 24 months.

The investigators wrote: "These results are consistent with the notion that early initiation of ART may limit formation of the long-lasting viral reservoir in infants."

Early viral suppression improves neurocognitive outcomes

Virologic suppression during infancy or early childhood is associated with improved neurocognitive outcomes in vertically infected children according to research from IMPAACT 219C and the Paediatric HIV/AIDS Cohort Study (PHACS). [5]

Children and adolescents with perinatally-acquired HIV can have subtle to severe neurocognitive deficits.

Claudia Crowell and colleagues hypothesised that both early ART and use of regimens with better central nervous system (CNS) penetration are associated with improved neurocognitive outcomes in school-aged vertically infected children.

The investigators looked at data from two prospective cohort studies from the United States: PHACS (2007 to 2009) and IMPAACT 219C (2000 to 2006). Children enrolled in the study had completed a cognitive ability assessment (WISC) at >6 years of age, and had at least one viral load measurement before or within 6 months of starting ART.

Viral suppression was defined as two consecutive viral loads <400 copies/mL 1 to 6 months apart, and age of viral suppression was the age at first suppressed viral load.

CNS penetration effectiveness (CPE) scores were determined for first ART regimen. The investigators used multivariate models, adjusted for age, caregiver education level, ethnicity, low birth weight and child's first language. Results were stratified by age and before and after the availability of ART. An average CPE score was calculated for each time period.

A total of 396 children were included in the analysis. At the time of the WISC assessment they were a mean age of 9.6 years and just over half were girls.

The investigators reported that virologic suppression in early childhood was associated with a 2.2 to 4.4 higher WISC score; this association reached statistical significance for ages 4 and 5, respectively p=0.03 and p=0.02. They noted that the effect size was consistent across all age groups and so non-significance in the younger age groups might be due to lower numbers.

There was no association between CPE score and improved neurological outcome in this evaluation.

Future research from this group will explore the relationships between virologic suppression, CPE scores and neurocognitive aspects including language, executive functions, memory, learning and processing speed.

CMV and clinical outcomes with early ART

Finally, another study from the CHER researchers found early cytomegalovirus (CMV) viraemia was strongly associated with breastfeeding exposure and poorer immunological status before starting ART. [6] They also found early ART appears to improve most effects of concurrent CMV infection.

Prior to use of ART, CMV was associated with faster HIV progression. In sub-Saharan Africa, 90% of infants acquire CMV postnatally in their first year of life but its effect on HIV infection in infants on ART is unknown

Nei-yuan Hsiao and colleagues conducted an evaluation to describe the first year clinical outcomes (censored at 40 weeks post enrolment) of young infants with CMV/HIV coinfection who received ART in CHER.

CMV PCR results were available for 363/451 children in the trial (children with CD4 percentage <25% at screening were included). Children were a median age of 7.7 weeks (6.7 to 9.1) at enrolment and 89 (25%) were CMV PCR positive.

Of these children, 342 (94%) started ART during follow-up: 267 100% in the early treatment group and 75 (78%) in the deferred treatment group.

At enrolment CMV viraemia was associated with any history of breastfeeding, p=0.025; lower median CD4 percentage, p<0.0001; viral load >500,000 copies/mL, p=0.0052; and lower median weight for age and height for age z-scores, respectively p=0.004 and p=0.0097.

At one-year time to disease progression and death were similar between infants receiving early ART by CMV status, respectively negative vs positive: HR 0.618 (95% CI 0.292 to 1.2079), p=2079 and HR 0.481 (95% CI 0.193 to 1.20), p=0.1167.

This suggests that early ART attenuates the effect of CMV on HIV in infants.

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All references are to the programme and abstracts of the 21st Conference on Retroviruses and Opportunistic Infections (CROI), 3-6 March 2014, Boston, unless otherwise stated.

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CROI 2014: BASIC SCIENCE, PATHOGENESIS AND CURE RESEARCH

Hospitalisation among elite controllers

Richard Jefferys, TAG

Elite controllers are sometimes cited as a model of a "functional cure" of HIV infection, because they naturally maintain extremely low viral loads in the absence of ART.

However, in recent years it has become apparent that most elite controllers have elevated levels of immune activation and inflammation compared to HIV negative people, and are not entirely free from the risk of disease progression.

Trevor Crowell presented a poster looking at hospitalisation rates among 149 elite controllers compared to 4,704 HIV positive individuals with suppressed viral loads on ART. [1]

Elite control was associated with a significantly higher rate of hospitalisation (approximately two-thirds greater), primarily for cardiovascular and pulmonary disease, compared to the cohort on ART. The data are consistent with research indicating that ART may be beneficial for at least some elite controllers, [2] and also has implications for HIV cure research because it argues that the achievement of virological control in the absence of ART does not necessarily equate to ideal health.

C O M M E N T

The increasing concern about the time off-ART, above that of simply maintaining a robust CD4 count, has led to less confidence in the earlier idea that HIV may not be pathogenic in elite controllers. The prospect of uncontrolled viraemia for decades in other body sites, however low in plasma, may warrant use of ART, even when CD4 counts remain very high.

This point is also highlighted in recent US (DHHS) guidelines. [3]

This research should at least prompt individual patient reviews when an earlier decision has been made to defer treatment and monitor.

Source

TAG Basic Science Blog. Catching Up with Pathogenesis and Cure Research from CROI 2014. (16 May 2014).
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Catching up with pathogenesis and cure research from CROI 2014

Richard Jefferys, TAG

In addition to studies covered in earlier reports (a possible second paediatric cure case, Sangamo's gene therapy and limitations of latency-reversing agents), CROI 2014 featured many other presentations related to pathogenesis and cure research.

Brief summaries of some notable studies are appended below, with links to webcasts and posters included where possible. Abstracts for posters that are unavailable as PDFs can be found in the final program and abstract book. Webcasts of all conference sessions are online, and many posters are now available in PDF format.

HIV rebound in the Boston patients

Timothy Henrich provided details on the two individuals in Boston who experienced a delayed return of HIV replication after a period during which it had been hoped they might be cured - sobering news that was reported earlier this year in HTB. [1]

Henrich's presentation is available via webcast. [2] Although these patients were monitored frequently after interrupting antiretroviral therapy (ART), viral load reached very high levels in both cases, and this was accompanied by symptoms of acute infection. The likely explanation is that their immune systems, having been newly generated by the stem cell transplants they had received to treat cancer, had not previously encountered HIV. Consistent with this possibility, HIV-specific cellular immune responses were undetectable prior to the viral load rebound but appeared afterward. At a community workshop on cure research immediately prior to CROI, Henrich noted that the size of the HIV reservoir had been reduced at least 3 logs in these individuals and was estimated to be very small at the time of the ART interruption; 290-2900 cells in one case, 40-730 cells in the other. [3] The results suggest the bar is set very high for approaches that aim to cure HIV infection by shrinking the latent reservoir.

Treatment of hyperacute HIV infection

A large crowd congregated at a poster presentation by Hiroyu Hatano from UCSF describing extremely early ART treatment in an individual who acquired HIV infection just prior to enrolling in a pre-exposure prophylaxis (PrEP) demonstration project. [4]

The infection occurred during a short 13-day window between a final screening visit and the day Truvada PrEP was first administered. When viral load results from the sample taken at Truvada initiation became available after seven days and showed a reading of 220 copies, the individual was switched to a conventional ART regimen. The viral load seven days later was 120 copies and there was a single measurement of cell-associated HIV RNA at a level of 4.7 copies per million CD4 T cells ~32 days after infection, but all subsequent tests for HIV RNA, DNA and replication-competent virus have been negative. The results raise the possibility that ART given at such an early stage of infection may have led to an adult equivalent of The Mississippi baby case reported at CROI last year. [5] However, the experience of the Boston patients offers a cautionary tale about the interpretation of negative virological assay results. A treatment interruption will be considered after 12 months of ART.

Three cured mice

Qingsheng Li displayed an interesting poster immediately adjacent to Hatano's, but it didn't receive quite as much attention. Li's work attempted to recapitulate the Mississippi baby outcome in the humanised mouse model, by administering ART six hours after the animals were infected with HIV. ART was maintained for two weeks and then interrupted. [6]

HIV RNA and DNA remained undetectable after interruption, even when CD8 T cells were depleted, leading the researchers to conclude that a cure had been achieved. The initial experiment (reported in the conference abstract book) involved three ART-treated mice and three controls, but the poster included data on additional groups that received ART at later timepoints after infection (12 hours and 18 hours). In these animals, HIV rebounded after ART interruption. Unfortunately the poster is not yet available on the CROI website (the link goes to the abstract book).

HIV integration, latency, and CD4 T cell survival

At least two published studies have documented that the homeostatic proliferation of memory CD4 T cells containing integrated HIV provirus can increase the amount of HIV DNA in the body. [7. 8]

These studies tracked copies of grossly defective virus genomes that could only multiply as a result of the proliferation of the host CD4 T cell. Homeostatic proliferation is a normal immunological mechanism that sustains memory T cells, and causes them to expand in the setting of T cell deficiency. The role of this process in maintaining the latent HIV reservoir was first described many years ago, based in part on the finding that lower CD4 T cell counts are associated with an increased rate of CD4 T cell proliferation and higher levels of HIV proviral DNA (although these levels remain extremely low compared to the overall size of the memory CD4 T cell pool). [9]

Several presentations at CROI documented the phenomenon in a different way, by demonstrating the proliferation of HIV proviruses integrated at precisely the same location in the CD4 T cell genome. [10, 11, 12, 13]

Additionally, it was reported by Thor Wagner that HIV proviruses frequently integrate at very similar sites in certain CD4 T cell genes associated with the cell cycle and differentiation, leading to the suggestion that HIV integration into these genes may somehow be promoting the growth and longevity of latently infected CD4 T cells. Wagner highlighted the fact that some of the genes into which HIV appears to preferentially integrate have been identified as having roles in cancers, and this point was echoed in a poster from Stephen Hughes laboratory at the National Cancer Institute.

However, some cited examples such as Bach2 are also involved in CD4 T cell differentiation [14] (this is not mentioned in either CROI presentation), so it would be logical that genes such as this would be active in the CD4 T cells HIV infects, and the virus is already known to preferentially integrate into active genes. [15] Additional research is needed to clarify whether there is anything sinister about these integration sites, or if they just reflect the locations HIV is most likely to have access to in the cells it is infecting. Based on the current evidence, it seems possible

that these genes could simply be those that are active and available to HIV in CD4 T cells that are differentiating into a long-lived phenotype.

In an article about the research by Jon Cohen in the journal Science, [16] Wagner's colleague Lisa Frenkel goes so far as to suggest that there may be a link with cancers that occur in HIV positive people, but to me this is a wildly speculative stretch given that most of these cancers have been shown to be associated with immunodeficiency (in both HIV-positive and HIV negative people) and inflammation.

The article also could be misread as suggesting that long-term HIV treatment causes higher cancer rates, when what the literature reports is that some HIV positive people on ART still have an elevated risk of some non-AIDS defining cancers (NADCs) compared to HIV-negative people (age is the strongest, most consistent risk factor). A review on the subject from 2012 states: "the higher risk of NADCs is primarily among males, with HIV-infected women having no higher rates of NADCs compared with the overall population." [17]

A sex-biased cancer-promoting effect of HIV integration and latency does not appear very plausible, and T cell cancers remain rare in HIV-positive people. In sum, pending further data, I would advocate extreme skepticism about Frenkel's suggestion that there may be a connection between HIV latency and the development of cancer.

Slim success with gut-targeting anti-activation strategies

Among the posters at CROI were results from four different clinical trials of therapies that aimed to ameliorate immune activation by targeting the microbial translocation pathway (the leakage of bacterial products from the gut into the systemic circulation). Sevelamer (a treatment for high blood levels of phosphorus that can bind bacterial lipopolysaccharide) and meselamine (a therapy that reduces mucosal inflammation in inflammatory bowel disease) had no effect on markers of microbial translocation or inflammation. [18, 19]

The antibiotic rifaximin was associated with very small reductions in some markers of immune activation and inflammation. [20]

The probiotic supplement Biola was reported to significantly reduce the levels of the D-dimer by about one third over eight weeks in a small study (12 probiotic recipients, seven placebo recipients and six controls) and there were trends toward reduced CRP and IL-6. Markers of microbial translocation did not change. [21]

These results await confirmation in a larger trial with a longer duration of follow up.

HIV-specific CD4 T cell responses in the VISCONTI cohort

The VISCONTI cohort comprises individuals treated very early after acquiring HIV infection (for an average of around three years) who have maintained undetectable or extremely low HIV viral loads after interrupting ART.

At the last published account, there were 14 members, [22] although anecdotally it has been mentioned that there may now be as many as 20.

The cohort appears to lack the robust HIV-specific CD8 T cell responses observed in most elite controllers, but until CROI no data had been presented on their HIV-specific CD4 T cell responses.

Assia Samri reported in a poster that HIV p24-specific CD4 T cells are detectable at "relatively high frequencies" in the cohort and have a more polyfunctional profile—but are not more abundant—compared to individuals on ART.

However, the data are cross-sectional and cannot answer the question of whether the presence of these responses is a cause or effect of the persistently low viral load in the absence of ART. [23]

Anti-PD-L1 antibody in macaques

Targeting the PD-1 receptor pathway has been proposed as a method for both reversing HIV latency and reinvigorating exhausted HIV-specific T cell responses. The AIDS Clinical Trials Group is on the verge of launching a clinical trial of an antibody against the PD1 ligand, PD-L1. [24]

At CROI, Stephen Mason described results of a preclinical study of the anti-PD-L1 antibody in ART-treated SIV-infected macaques. Administration was found to be safe and associated with a significant but short-term reduction in viral rebound after an ART interruption. [25]

EraMune 02 results

Two of the first clinical trials launched to specifically attempt therapeutic reduction of HIV reservoirs were EraMune 01 and 02, sponsored by the French Objectif Recherche Vaccins SIDA collaboration. Both investigated intensified ART, combined with IL-7 (EraMune 01) or a DNA/Ad5 prime-boost therapeutic HIV vaccine (EraMune 02).

Results from study 01 were presented at a prior CROI, showing no significant HIV reservoir reduction and some evidence of an IL-7-mediated increase in HIV DNA resulting from the proliferation of latently infected cells. Results from study 02 debuted as a poster this year, also showing no significant reduction in levels of HIV DNA.

However, the vaccine did successfully induce significant T cell responses against HIV Gag, Pol and Env antigens in individuals on ART. [26]

Evidence prednisolone can increase CD4 counts and slow progression in the absence of ART

In the early 1990s, there was some excitement about results from an uncontrolled, open-label study of the immune suppressant drug prednisolone in people with HIV infection. [27]

The investigators reported that administration of the drug led to sizable increases in CD4 T cell counts that had not been seen with the antiretroviral drugs that were being given as monotherapy or dual therapies at the time. The advent of three-drug ART consigned this prednisolone study to the haze of history, but at CROI there was a flashback in the form of results from a randomised clinical trial, which suggest that the prior data were not a fluke. [28]

The trial was conducted in Tanzania during a period when ART was only indicated for people with low CD4 T cell counts. Treating individuals for whom ART was not yet indicated with prednisolone was associated with a significant increase in CD4 T cell counts and a reduced risk of clinical progression.

The results underscore the causative role of immune activation in the progression of HIV infection, since prednisolone acts via this pathway without directly inhibiting the virus.

The researchers suggest the drug may be able to inhibit immune activation and improve immune reconstitution in immunological non-responders on ART, and perhaps could have a role as an early therapy for asymptomatic HIV infection in resource-limited settings (the latter suggestion is likely to be controversial given the understandable emphasis on trying to improve global access to ART, the efficacy of which is proven).

Source

TAG Basic Science Blog. Catching Up with Pathogenesis and Cure Research from CROI 2014. (16 May 2014).
http://tagbasicscienceproject.typepad.com

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SIDE EFFECTS

No increase death rate in HIV positive people with renal dysfunction receiving tenofovir in Zambia

Polly Clayden, HIV i-Base

Tenofovir disoproxil fumarate (TDF) did not worsen renal function recovery nor increase death rate in HIV positive adults with renal dysfunction in a large Zambian cohort followed for 12 months.

Zambia introduced TDF as the preferred NRTI for first line therapy in the national programme in 2007 – one of the first countries in sub-Saharan Africa to do so.

An article in the 15 May edition of Clinical Infectious Diseases describes findings from an evaluation of changes in renal function and mortality in adults starting TDF or non-TDF-containing ART in Lusaka between 2007 and 2011. [1]

Lloyd Mulenga and colleagues, for IeDEA Southern Africa performed the analysis. Participants were included if they werer aged 16 years and above, started ART during this time period, and had documented baseline weight and serum creatinine results.

Using the chronic kidney disease-epidemiology (CKD-EPI) formula, the investigators catagorised renal function by estimated glomerular filtration rate (eGFR) as: normal, $\geq$ 90; mild eGFR 60–89, moderate 30–59, or severe $\leq$29 mL/min/1.73m^2.

They looked at the following outcomes: 1. renal function after 6 and 12 months of ART, 2. proportion of patients with moderate or severe eGFR decrease on ART and 3. death.

They used a multivariable mixed-effects model to compare the change in eGFR among participants receiving TDF and non-TDF regimens. Logistic and competing risk regression models were used to assess the odds of developing moderate or severe eGFR decrease and mortality, respectively. All analyses were adjusted for age, sex, calendar year, WHO stage, CD4 and haemaglobin.

The evaluation included 62,230 adults. Of these, 38,716 (62.2%) started a TDF-based regimen.

At baseline, participants receiving TDF started ART with more advanced HIV than those not receiving TDF, respectively 59.4% vs 47.7% were WHO stage 3 or 4. And they were more likely to receive efavirenz-based ART, respectively 60.4% vs16.6%.

Women were more likely to receive a non-TDF regimen than men, respectively 70.4% vs 56.5%, and to have started ART in earlier calendar years.

Overall, participants receiving TDF were more likely to have some renal dysfunction than those receiving non-TDF regimens at baseline, respectively 16.7% vs 12.4%. But double the proportion in the non-TDF than TDF group had moderate or severe renal dysfunction, respectively 4.0% vs 1.9%. All comparisons p<0.001.

After starting ART, 70.4% and 84.9% of participants receiving TDF and non-TDF regimens had at least one repeated creatinine measurement available after either 6 or 12 months on ART.

The investigators observed a slight decline in renal function in participants who started with no renal function at 6 and 12 months in both groups: -15 mL/min and -17 mL/min for those receiving TDF and non-TDF respectively. There was no change in those with mild eGFR decrease at baseline.

Adjusted analyses revealed slightly reduced renal function at 6 and 12 months in participants receiving TDF vs non-TDF based regimens.

There was a higher proportion of participants with no or mild renal dysfunction that had an incident episode of severe eGFR decrease at 6 to12 months in the TDF group but this was not statistically significant at either time point: respectively 0.28% vs 0.6%, p=0.26; and 0.24%vs 0.15%, p=0.2.

The difference was significant for moderate or severe eGFR: respectively 1.90% vs 1.27%, p<0.001; and 1.84% vs 1.37%, p=0.02. Although these comparisons reached statistical significance, the investigators noted that the numbers remained low.

Overall, participants with moderate (n=616) or severe (n=110) renal dysfunction at baseline experienced an improvement in renal function with ART. This included those who received TDF despite severe renal failure (+30mL/min after 12 months).

Adjusted analyses showed an association between marginally lower renal function at 12 months with baseline moderate renal dysfunction. But for participants with available data TDF use appeared to be associated with higher eGFR during follow up for those starting ART with severe renal dysfunction: adjusted difference 21.7 (95% CI 4.33 to 39.10) at 12 months.

Starting a TDF regimen did not increase the odds of progression from moderate to severe renal dysfunction: adjusted odds ratio 1.11 (95% CI 0.46 to 2.70).

Over 111,972 person-years of follow up there were 2,405 (6.2%) and 1,472 (6.3%) deaths documented in the TDF and non-TDF groups respectively. Loss to follow up was respectively 27.4% and 20.7% of participants.

Overall, severity of renal dysfunction starting ART predicted mortality risk: adjusted subhazard ratio (sHR) for severe vs no baseline eGFR decrease 2.00 (1.52 to 2.63), p<0.001.

There was no difference in mortality rates with moderate or severe eGFR decrease between participants receiving TDF vs non-TDF regimens: respectively adjusted sHR 0.79 (95% CI 0.58 to 1.07) and 0.89 (95% CI 0.52 to 1.52).

Other risk factors for mortality were: low CD4 count, anaemia, male sex and advanced clinical stage HIV, all <0.001.

C O M M E N T

This CID article is accompanied by a helpful and carefully considered commentary, which rightly states: "This is the largest study of its kind, and the authors should be commended for its successful completion in a region in which undertaking such studies is challenging". [2]

Worth reading, the commentary emphasises the need for longer follow up and that careful monitoring of kidney function after starting TDF remains important to prevent development or progression of renal disease, particularly in the context of limited resources to provide ART for those who progress to end-stage renal disease.

The authors add, "The conundrum, however, lies in how patients should be monitored for kidney disease" and suggest future studies look at simple tools, such as the combination of serum creatinine-based GFR estimates and a urine dipstick to see if these could cost-effectively identify people at greatest risk of TDF-related toxicity.

They stress that, as with many ARVs, the benefit of TDF to the majority of patients must be weighed against the potential harm to a small minority.

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TREATMENT GUIDELINES

US adult treatment guidelines updated (May 2014)

Simon Collins, HIV i-Base

On 1 May 2014, the latest update to DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents was published online.

As with previous updates, changes in the text are highlighted in the PDF file using a yellow background. It is important to note the strength of the recommendation (A, B or C - with C being optional) and quality of evidence rating for each recommendation (I, II or III - with III being only expert opinion).

Main changes include:

- A new section on ART costs in relation to adherence and use of generic drugs and potential strategies for cost containment.

It is notable that this is the first time the DHHS guidelines have focused on costs in this way. The section highlights the considerable challenges to treatment in the US, with variable health coverage and a complex system of insurance and payment structures, including cost-sharing, co-payments, prior authorisations, and incentives both for and against use of cheaper generics.

The main updates to existing sections include:

- Less frequent CD4 count monitoring is recommended for people with viral suppression on ART for more than two years. The potential for cost savings is also referenced. For people with a CD4 count 300-500 cells/mm3 this is recommended every 12 months (BII). For those with a CD4 count above 500 cells/mm3, CD4 monitoring is now optional (CIII). More frequent CD4 count monitoring is recommended if viral load blips or if clinical symptoms occur (AIII).
- Monitoring of other lymphocyte subsets (e.g., CD8, CD19) is no longer seen as useful given their additional cost. (BIII).
- Viral load monitoring on stable ART is recommended every 3-4 months for the first two years, and extended to every six months thereafter (AIII).
- Although ART is still recommended at CD4 >500 cells/mm3, it has a low rating (CIII).
- Neurological complications are included in a new review (although not accompanied by recommendations for management).
- ART is now recommended for HIV long-term slow progressors if the CD4 count is falling over time (AII).
- The guidelines now refer to "recommended" rather than "preferred" regimens. These are categorised by viral load. If viral load is above 100,000 copies/mL, rilpivirine and abacavir/3TC (except with dolutegravir) should not be used.
- Drugs no longer recommended for first-line therapy include AZT, nevirapine, unboosted atazanavir, ritonavir-boosted fosamprenavir/r or saquinavir/r, and maraviroc.
- A new data review is included for choosing between recommended options within the NRTI, NNRTI, PI and INI classes, updated with recent studies, and including dolutegravir.
- HIV drug resistance with detectable viral load includes the importance of discontinuing integrase inhibitors and preferential use of boosted-PI based treatment.
- The section on adolescents and young adults includes noting that a quarter of the 50,000 infections diagnosed in 2010 were in people aged 13-26, and that in this age group, 75% were MSM and 57% were among black/African Americans. Lower response rates to treatment are highlighted (emphasing the need for greater support) and the positive impact of text messaging to help adherence is included in a new reference.
- The section on adherence has been expanded and updated.
- Suicide is given a greater emphasis as a potential side effect of efavirenz (Table 14).
- Changing treatment to avoid side effects has a new section including a new table on switching options within drug class categorised by symptoms (Table 15).
- Drug interaction tables are updated (including cautions between ritonavir-boosted protease inhibitors and both corticosteroids and antimalarial drugs (also for NNRTIs).

These are important guidelines. All current and archived guidelines are available from the AIDSinfo website.

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US PrEP guidelines: emphasis on broad access may miss optimal use by people at highest risk

Simon Collins, HIV i-Base

On 14 May 2014, the US CDC updated guidelines for using daily oral tenofovir plus FTC (Truvada) as PrEP. [1]

These recommendations for how and when to use PrEP are broadly similar to previous interim advice issued in January 2011, but the resource has been greatly expanded.

The summary of indications stresses that PrEP is an intervention for men who have sex with men (MSM), heterosexual men and women and adult injecting drug users that are "at substantial risk of HIV acquisition".

However, the expanded definition of substantial risk for sexual transmission is:

1. Any penetrative sex (gay or bisexual men, and heterosexual men and women) in the previous six months without a condom; or
2. Any bacterial STI in the previous 6 months; or
3. Having a partner who is HIV positive; or
4. Not being in a mutually monogamous relationship with someone who recently tested HIV negative.

For people who inject drugs, this includes anyone who has "injected illicit drugs in the past 6 months and who has shared injection equipment or been in drug treatment for injecting drug use in the past 6 months".

Another summary of the criteria for significant risk (Table 1 in the guidelines) includes having a high number of sexual partners or a history of inconsistent or no condom use. Sex work is also included as a criteria to use PrEP.

The 67-page guidelines and 43-page clinical providers' supplement are published as PDF files. [2, 3]

The guidelines are designed as a practical guide to support healthcare workers to prescribe PrEP. They include background information on assessing risk, patient materials and an evidence review.

C O M M E N T

These guidelines are a political response to the continued US epidemic, where, similar to the UK, annual numbers of new diagnoses have remained persistently high for the last decade. They are also a response to the low use of PrEP: where less than 1800 at-risk HIV negative people started tenofovir/FTC (Truvada) in the US, eight months after it was approved for this indication. [4, 5]

The guidelines were quickly supported by a statement from 82 US-based community organisations that understandably challenged a high-profile negative campaign against PrEP. [6]

Activists who support PrEP have also responded with other campaigns including the "Truvada-whore" T-shirts in order to positively affirm this can and should be an active choice (in this case, for gay men). [7, 8]

However, even in this context, the guidelines have a few important limitations.

1. **Expanding the indication for PrEP to include virtually anyone who is sexually active, risks diluting the importance of efficacy being dependent on use in people at a significant high-risk.**
2. **Confidence in PrEP is also diminished by avoiding the implications of its high efficacy. While the guidelines emphasise daily PrEP reduces the relative risk of infection by 99%, they go on to recommend PrEP should be used IN ADDITION to condoms.**

   Rather than simplifying HIV prevention, the guidelines therefore create a more complicated barrier. For people at low risk who may already be leading anxious lives, fearful of HIV, this may be unhelpful. And for someone who wants to reduce their risk of HIV while having sex that DOES NOT involve condoms (and when neither pregnancy nor STIs are a concern), the data support clearly stating throughout the guidelines, that PrEP is a highly effective stand-alone option.
3. **Although a discussion on stopping PrEP is included, periodic use is not. There are many people who might choose to use PrEP during high risk periods and stop for months if their circumstances change. The iPrEX study reported that most high risk men in were only periodically high risk, for example, when between relationships. Expanding on this in future updates to the guidelines might therefore be useful. [9]**
4. **Finally, the inclusion as a criteria for PrEP of having a sexual partner who is HIV positive does not include a discussion on the role of HIV viral load as a risk factor, and the dramatically reduce risk from someone on treatment.**

In Europe, although Truvada has not been submitted to the European Medicines Agency for a PrEP indication, it can be prescribed if a doctor believes this is appropriate. However, funding for PrEP in the UK has been complicated by the recent decision to separate commissioning of prevention and treatment services.

This is likely to make results from the ongoing PROUD study especially important in determining whether access to PrEP is broadened in the for people at high risk of HIV. Broader NHS access should be a community demand for activists involved in HIV prevention. [10]

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BASIC SCIENCE AND CURE RESEARCH

Incidence of HIV dual infections in US men who have sex with men

Gareth Hardy, HIV i-Base

A new study published in the Journal of Infectious Diseases confirms that HIV dual infection and HIV reinfection are common.

Researchers at University of California in San Diego and colleagues used new sequencing technology and phylogenetic analyses to determine the incidence and prevalence of dual infection by more than one strain of HIV in the same individual. [1]

Dual infection can include either:

- Co-infection, in which infection with a second viral strain occurred simultaneously or very soon after primary infection; or
- Superinfection, in which a second viral strain is acquired after immune responses to the first strain have been established.

These dual infections can either be intra-subtype, where both strains are from the same viral clade, or inter-subtype, where the dual infections are established by different clades. Dual infection has previously been associated with faster rates of CD4 count decline more rapid rises in viral load and more rapid disease progression. [2]

The recent development of next generation sequencing technology enables the more accurate and efficient detection of dual infection, with the ability to detect circulating minority variants that are as low as 0.25% of the viral population. This could help reveal valuable information about the impact of dual infection on disease progression as well as potential correlates of protection against superinfection.

In this longitudinal study, plasma samples were collected at regular time points between January 1998 and January 2007 from 118 treatment-naïve participants with recent HIV infection in the San Diego Primary Infection Cohort. Those patients that initiated ART were followed until their viral load became undetectable (<50 copies/mL). The median time from the estimated date of infection to the baseline time point in these subjects was 71 days (IQR: 70–133).

Seven cases of co-infection were detected at baseline using this technique. The median time from the estimated date of infection for the detection of co-infection was 2.8 months (IQR: 2.3–3.2). This result translated to a coinfection prevalence of 5.9% (95% CI, 2.4–11.8%). Over a total of 201 person-years of follow up (PYFU), 10 subjects were found to have acquired superinfection. The incidence of superinfection was 4.96 per 100 PY (95% CI, 2.67 – 9.22).

Six of these infections occurred within the first year of the estimated date of infection, and four of those within the first six months. The incidence rate of superinfection in the first year was 2.92 (95% CI, 1.31–6.50) per 100 PYFU. In the second year, in which 4 infections occurred, the incidence rate was 9.47 (95% CI, 3.56–25.23) per 100 PYFU. The median time from the estimated date of infection to superinfection was 10.5 months. Taking these results together, the cumulative prevalence of dual infection (both co-infection and superinfection) was 14.4% (95% CI, 8.6% - 22.1%). In all cases, dual infections had occurred with subtype B clade viruses. In contrast the prevalence of new HIV infections in a related Early Test Program cohort, was 4.37 per 100 PYFU (95% CI, 3.56- 5.36).

The prevalence of dual-infection identified in this study was high, at 14.4%. Interestingly the incidence of superinfection in the first year of infection was comparable to that of initial HIV infection (4.96 versus 4.37 per 100 PYFU respectively), but this rate of superinfection seemed to decline rapidly afterwards, suggesting that the establishment of HIV-specific immune responses may protect against subsequent infection. A different theory might be that potential host central memory T cells are already saturated with virus to the extent that superinfecting viral strains are unable to gain sufficient foot-hold. The small number of cases in this study together with shorter follow up from access to ART could mean that the apparent decline in incidence of superinfection may be the result of bias.

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Reassessing the role of HDAC inhibitors in cure research

Gareth Hardy, HIV i-Base

Two recent papers present conflicting data on the efficacy of the histone deacteylase (HDAC) inhibitors, the leading class of latency reversing agents (LRAs).

Korin Bullen, from Robert Siliciano's group at Johns Hopkins University in Baltimore, USA and Datsen Wei, from Gilead and working with John Mellor's group at University of Pittsburgh, tested a panel of HDAC inhibitors and other LRAs for their ability to induce activation of latently infected CD4 T cells from patients on ART. The two groups report contradictory findings.

HDACs are enzymes involved in repression of gene expression and are thought to actively repress HIV expression during viral latency. Clinical trials have suggested that the HDAC inhibitor vorinostat increases HIV RNA expression in CD4 T cells by an average of 4.8 fold, when used in people on ART [1]. Despite this, it is not known if HDAC inhibitors can induce replication-competent virus from patients' CD4 T cells, leading to an increased decay-rate of the latent-reservoir.

Bullen et al, describe their results in Nature Medicine [2]. Using clinically relevant concentrations of each agent, they assessed the HDAC inhibitors vorinostat, romidepsin and panobinostat, as well as agents from other classes of LRAs: disulfiram; JQ1 and; bryostatin-1. In order to allow reactivated HIV to sufficiently grow from cultures of patient CD4 T cells, they first treated resting CD4 T cells from 13 ART-treated patients with LRAs for 18 hours and then added lab-grown T cells for a further 14 days to allow viral propagation. In previous versions of this assay, the use of T cell blasts for propogation may have caused mixed lymphocyte reactions leading to background T cell activation, which could have caused a false positive signal for viral induction by LRAs. To prevent this they used the lab-adapted T cell line, MOLT-4. Surprisingly, using this new assay, HDAC inhibitors did not induce latent HIV as measured by p24 ELISA of supernatants. These results were confirmed by assessment of supernatant HIV mRNA in five of these patients, for which one demonstrated induced virus, in response to bryostatin-1. The PMA/I positive control induced HIV p24 expression in CD4 T cells of 11 of 13 patients.

Most HIV mRNA PCR assays target gag or gag and LTR together. Bullen and colleagues considered that the sequences detected by these assays may not represent bona fide HIV RNA, as "HIV integrates into host genes that are actively transcribed in resting CD4 T cells, allowing for the production of chimeric host-HIV transcripts". These viral transcripts will not lead to production of functional virus but would contain sequences of HIV gag and be indistinguishable from HIV-LTR-initiated transcripts when using conventional HIV PCR assays. In order to address this, Bullen and colleagues designed a PCR assay to detect a portion of the HIV LTR gene that should not be present in LTR-initiated transcripts, but would be present in host gene-initiated HIV 'readthroughs'.

Using their new PCR assay they treated resting CD4 T cells from five HIV infected patients receiving ART, with vorinostat and determined that while vorinostat did not induce complete HIV RNA, it did induce a two fold increase in host-initiated 'readthrough' transcripts, which were comparable to the induction of gag-containing transcripts. The authors conclude: "although not every potential LRA will induce readthrough transcription by activating a host gene, our data show that chimeric host-HIV transcripts can have a confounding effect on the RT-qPCR signal obtained using standard gag primers. Such an effect should be taken into consideration when evaluating LRAs using conventional gag RT-qPCR assays".

These results have two implications. Firstly, HDAC-inhibitors may not be effective at inducing latent HIV in vivo; and secondly, the mechanisms by which HIV latency naturally occurs, are not captured by laboratory latency models.

In contrast to these results, Wei at al describe their findings in PLoS Pathogens [3], showing that vorinostat and romidepsin induce expression of latent HIV from CD4 T cells of patients receiving ART. Using an in vitro latency model, they screened the activity of the clinically tested HDAC inhibitors: vorinostat, romidepsin, panobinostat, givinostat, mocetinostat, and pracinostat. Wei et al showed dose-dependent increases in activity for all HDAC inhibitors, with superior activity for romidepsin. Wei et al then assessed the ability of each of the HDAC inhibitors to induce expression of HIV from purified resting CD4 T cells of HIV infected patients receiving ART. Unlike the viral outgrowth approach taken by Bullen et al, described above, Wei and colleagues treated purified resting CD4 T cells from patients with vorinostat or romidepsin and then assessed HIV RNA expression by PCR using the Roche COBAS HIV test after 6, 12, 24 and 48 hours of culture. This assay would not be as dependent on production of replication-competent HIV as that used by Bullen. Using this method Wei et al found that vorinostat induced 2- to 4- fold increases in HIV RNA expression, which peaked at 6 hours and the more potent romidepsin induced 5- to 6- fold increases that peaked after 24 – 48 hours.

In order to demonstrate that vorinostat or romidepsin could induce extracellular virions from resting CD4 T cells, supernatants were tested for HIV RNA after 6 days culture. HIV RNA could be detected in the supernatants of romidepsin-treated cells, but not vorinostat-treated cells. The authors add that HIV RNA released into supernatants following treatment with romidepsin, could be pelleted by high-speed centrifugation, suggesting that the RNA must be encapsulated in virions, rather than having been released during cell death potentially caused by HDAC inhibitor toxicity.

The authors conclude: "We observed reproducible ex vivo activation of HIV by romidepsin... Given these results… clinical testing is warranted to assess whether romidepsin can activate latent HIV and potentially reduce the size of the latent reservoir in HIV-infected patients on suppressive ART".

There are two key differences in the approaches taken by the Bullen and Wei groups that could explain their discrepant results. First, Bullen used a viral outgrowth assay that depended on propogation of infectious virus (over 14 days), whereas Wei measured shorter-term viral RNA expression (24 hours – 7 days) that may have represented a partial phase of the viral life cycle. The former method used by Bullen is likely to be more sensitive to the production of replication-competent virus, yet only Wei showed viral induction by HDAC inhibitors. The inability of the more robust method used by Bullen to detect HIV activation would suggest that the viral expression detected by Wei may not have been replication competent.

The second important difference was Bullen's PCR assay for host-initiated HIV readthrough transcripts. Conventional HIV PCR assays that target gag and LTR are likely to measure viral transcripts initiated by host genes. These will not reflect properly spliced viral transcripts, required for functional virions. This is another important difference between the approaches taken by the two groups. Wei's detection of an effect of HDAC inhibitors, relies on Roche's COBAS HIV PCR assay. According to Roche [4], this assay uses primers for gag and LTR that would also, presumably, measure HIV transcripts initiated by host genes. As the mechanism of action of HDAC inhibitors is to release genes from a silent state, enabling their expression, HDAC inhibitors will activate host genes. Therefore HDAC-inhibitors are liable to initiate HIV transcription by activating the promotors of host genes, into which HIV has integrated. The implication of this is that Wei's detection of HIV mRNA sequences in HDAC-treated cells could conceivably be a false signal.

Wei et al say that HIV virions from the supernatants of HDAC-inhibitor treated CD4 cells can be pelleted by centrifugation, as further evidence that supernatant HIV RNA is encapsulated in virions (rather than RNA released from dying cells due to HDAC inhibitor toxicity). However, host cell-derived extracellular RNA occurs in normal biology, in the form of extracellular vesicles. These can be the same size and density as HIV virions and so very hard to distinguish by centrifugation. If the centrifuged particles are extracellular vesicles or cell debris containing host-initiated viral read-through RNA, it is possible that Wei's data does not confirm viral induction by HDAC inhibitors and Bullen's conclusion that HDAC inhibitors do not induce latent HIV may stand. Some of these questions could be resolved by the use of Bullen's readthrough PCR assay, to measure the RNA in the cells and supernatants that Wei et al have generated.

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More on the links between the CD4/CD8 ratio, immunological perturbations, and risk of illness and death

Richard Jefferys, TAG

Since the review in the last issue of HTB of studies investigating the relevance of the CD4/CD8 ratio in the antiretroviral therapy era, [1] several new papers and presentations have provided more information on the topic.

In the open access journal PLoS Pathogens, Sergio Serrano-Villar and colleagues reported evidence that a low CD4/CD8 ratio (less than or equal to 0.4)—despite CD4 T cell recovery to a count above 500 on ART—is associated with low naïve CD8 T cells, elevated levels of activated and senescent CD8 T cells, increased innate immune activation, and a greater risk of non-AIDS events. [2]

After controlling for age, gender, ART duration and both nadir and proximal CD4 count, each 10% decrease in the CD4/CD8 ratio was associated with 48% higher odds of serious non-AIDS events.

In a separate cohort that started ART with advanced disease, a significant correlation between the CD4/CD8 ratio and the risk of mortality was documented. In this analysis, the researchers report that for each 10% increase in the CD4/CD8 ratio on ART there was a 15% decrease in the risk of death. Individuals initiating ART earlier in the course of HIV infection exhibited greater and more rapid improvements in the CD4/CD8 ratio compared to those starting late.

A poster at CROI 2014 presented similar findings. Cristina Mussini and colleagues assessed whether the CD4/CD8 ratio predicted clinical progression in the Icona cohort in Italy. The CD4/CD8 ratio was a significant predictor of the risk of serious non-AIDS events and death, independent of CD4 T cell counts. Normalization of the CD4/CD8 ratio (to greater than or equal to 1) only occurred in a minority of participants, and was more common among younger individuals, those with higher CD4/CD8 ratios at ART initiation, and those starting ART in more recent periods at higher CD4 T cell counts. [3]

Another poster at CROI from Talia Sainz et al described the role of CMV infection in lowering CD4/CD8 ratios in HIV-positive people, as is also known to occur in the HIV negative elderly. [4]

Lastly, a recent paper in PLoS One published by Willard Tinago and colleagues from the laboratory of Paddy Mallon in Dublin looked at the links between the CD4/CD8 ratio and other immunological perturbations, with results that appear consistent with those reported by Sergio Serrano-Villar's group. [5]

The discussion section of the Serrano-Villar paper notes that the data imply that the CD4/CD8 ratio could be useful for monitoring responses to therapies that aim to reduce residual immune activation.

Additionally, HIV positive individuals on suppressive ART who do not experience an increase in the CD4/CD8 ratio "might benefit from screening programmes or aggressive management of concomitant risk factors for ageing-associated disease."

Source

TAG Basic Science Blog. Update published on the first Berlin patient. (21 May 2014).

http://tagbasicscienceproject.typepad.com

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HEPATITIS C

EMA fast-track sofosbuvir/ledipasvir FDC for hepatitis C

Gilead press statement

On 27 March 2014, Gilead announced that the European Medicines Agency (EMA) has agreed to an accelerated assessment for a once-daily fixed-dose combination of sofosbuvir plus ledipasvir.

Sofosbuvir is a nucleotide analogue polymerase inhibitor and ledipasvir is an NS5A inhibitor, that together are indicated as a treatment of chronic hepatitis C genotype 1.

The data included in the application, which was submitted on February 27, 2014, supports the use of LDV/SOF among adult patients with genotype 1 HCV infection for eight or 12 weeks, (depending on their prior treatment history and whether they have cirrhosis).

The Marketing Authorisation Application (MAA) is supported by three Phase 3 studies, ION-1, ION-2 and ION-3, in which nearly 2,000 patients were randomised to receive the fixed-dose combination, with or without ribavirin, for treatment durations of 8, 12 or 24 weeks.

Accelerated assessment reduces the review period by approximately two months.

Source:

Gilead press statement. European Medicine's Agency validates Gilead's marketing application for ledfipasvir/sofosbuvir fixed-dose combinationtablet for genotype 1 chronic hepatitis C infection. (27 March 2014).

UK RESEARCH STUDIES

Partner 2 study extended for gay couples

Simon Collins, HIV i-Base

The second phase of the PARTNER Study aims to estimate the risk of HIV transmission in gay sero-discordant couples. [1]

To enrol, the HIV positive partner needs to be on ART with an undectectable viral load and the couple need to be sexually active and not always using condoms.

A total of 950 gay male (MSM) couples are needed for PARTNER 2 and currently 470 MSM couples are already participating in the first phase of the PARTNER study.

MSM couples already participating in PARTNER 1 will be encouraged to continue follow-up in PARTNER 2 until 2017.

Interim results presented at CROI 2014 reported no linked transmissions after 894 eligible couple-years of follow up and more than 44,500 exposures (half of which involved anal sex without a condom). [2]

The additional follow-up will provide similar confidence levels for the residual risk of HIV transmission for gay men compared to heterosexual couples.

UK sites for PARTNER 2

- Chelsea and Westminster, London
- Mortimer Market Centre, London
- Royal Free Hospital, London

- St. Thomas's London
- Western General Hospital, Edinburgh
- Royal Sussex County Hospital, Brighton
- Southmead Hospital, Bristol

New sites are still being sought for this second phase. For further information, please contact the study coordinator Tina Bruun:

tbr@cphiv.dk

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TAILoR Study: telmisartan to reduce risk of insulin resistance: potential role for lipodystrophy

Simon Collins, HIV i-Base

The UK TAILOR study plans to enrol almost 400 HIV positive people who are already on stable HIV treatment. [1]

Participants will be randomised to use different doses of telmisartan (20 mg, 40 mg or 80 mg) to see whether this reduces the risks of developing diabetes or heart disease.

The 48 week study involves taking one (small) pill daily. People taking the 80 mg dose may use a formulation that involves either one or two daily pills.

Of interest, two small studies have looked at whether telmisartan might have a benefit against HIV-related lipodystrophy, especially for central fat accumulation.

One looked at whether telmisartan (40 mg daily) could help reduce central fat accumulation (visceral fat – a symptom of lipodystrophy) in 35 people. There was a range of responses after 24 weeks. No benefit was reported for visceral fat but reductions were seen for total body fat and subcutaneous fat. [1]

Another small study (n=18) used a higher dose of telmisartan (80 mg daily) for HIV positive people who already had high blood pressure. As well as reducing blood pressure, there were benefits in insulin sensitivity and blood lipids (triglycerides and cholesterol). [2]

This TAILOR study has 11 UK sites:

- Royal Liverpool Hospital, Merseyside
- Royal Free Hospital, London
- Guys and St Thomas' Hospital, London
- Kings College Hospital, London
- Royal Bournemouth Hospital, Dorset
- Western General Hospital, Edinburgh
- St. James' Hospital, Leeds
- City of Coventry Health Centre, Coventry
- Brighton and Sussex University Hospitals
- James Cook University Hospital, Middlesbrough
- York Clinic, York

By April 2014, over 110 people have already been enrolled.

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SCART study: selumetinib as potential treatment for HIV-related KS

Simon Collins, HIV i-Base

SCART is a UK phase 2 study using selumetinib to treat HIV-related Kaposi's Sarcoma (KS) in people on ART with progressive KS.

Selumetinib is a mitogen-activated protein kinase (MEK) inhibitor currently in phase 3 studies to treat other types of cancer. MEK is a protein involved in signaling for cell division.

SCART is a phase 2 study because there is less information on the use to treat KS. Phase 1 of the study was used to decide the best dose and to check for any early safety concerns in HIV positive people.

Phase 2 is now looking at how effectively KS responds to treatment in 25 people with HIV-related KS that has become worse during the last six months. Selumetinib is dosed at 75 mg twice-daily (2 x 3 tablets per day, total 6 tablets per day). The study involves safety and monitoring visits to the hospital every 21 days.

Study sites

The SCART study is being run at five UK hospitals.

- Weston Park Hospital, Sheffield
- Chelsea and Westminster Hospital, London
- Royal Sussex County Hospital, Brighton
- The Beatson West of Scotland Cancer Centre, Glasgow
- Christie Hospital, Manchester

More detailed information:

http://clinicaltrials.gov/show/NCT01752569

http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=11876

For further information or enquiries about the SCART trial please contact:

SCART@contacts.bham.ac.uk

The Coordinating Centre for SCART is the Cancer Research Clinical Trials Unit (CRCTU), University of Birmingham.

This trial is supported by AstraZeneca, Cancer Research UK, Experimental Cancer Medicine Centre (ECMC), National Institute for Health Research Cancer Research Network (NCRN), Sheffield Teaching Hospitals NHS Foundation Trust and the University of Birmingham.

OTHER NEWS

Scotland agrees to free HIV treatment, regardless of residency status

NAT press statement

Changes to the NHS in Scotland now mean that HIV will be exempt from charging rules, irrespective of residency status. [1]

This brings HIV treatment inline with TB, sexual health services (including HIV testing) and infectious diseases.

Similar changes were introduced in England in 2012.

Yusef Azad, director of policy and campaigns at National AIDS Trust, said: "This change will ensure destitute asylum seekers and vulnerable migrants are able to get the essential healthcare needed while living in Scotland. It is also a step to safeguard the public health of communities, as HIV treatment has been shown, when successful, to make it practically impossible for someone to pass HIV on to others." [2]

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FUTURE MEETINGS

Conference listing 2014/15

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.

International Workshop on Antiviral Drug Resistance

3-7June 2014, Berlin, Germany

http://www.informedhorizons.com/resistance2014

10th HIV and Hepatitis Coinfection Workshop

12 - 13 June 2014, Paris, France

http://www.virology-education.com

6th International Workshop on HIV Paediatrics

18-19 July 2014, Melbourne

http://www.virology-education.com

20th IAS World AIDS Conference

20-25 July 2014, Melbourne, Australia

http://www.aids2014.org

16th International Workshop on Comorbidities and Adverse Drug Reactions in HIV

6 - 8 October 2014, Philadelphia, USA

http://www.intmedpress.com

5th International Workshop on HIV & Ageing

20 - 21 October 2014, Baltimore, USA

http://www.virology-education.com

9th International Workshop on HIV Transmission Principles of Intervention

25 - 26 October 2014, Cape Town, South Africa

http://www.virology-education.com

12th International Congress on Drug Therapy in HIV Infection

2-6 November 2014, Glasgow

http://www.hiv11.com

22nd Conference on Retroviruses and Opportunistic Infections (CROI 2015)

23 - 26 February 2015, Seattle

http://www.croi2014.org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website: updates for PDA access

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

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

http://www.i-Base.info

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

Publications and regular subscriptions can be ordered online.

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

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

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

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

Non-technical treatment guides

i-Base treatment guides

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

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

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

Publications and reports

HIV Treatment Bulletin (HTB)

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

HTB South

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

HTB Turkey

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

HTB West Balkans

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

Why we must provide HIV treatment information

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

Translations of i-Base publications

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

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

Advocacy resources

Online treatment training for advocates

http://i-base.info/ttfa

Entry-level curriculum relating to HIV and treatment.

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

UK CAB: reports and presentations

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http://www.ukcab.net

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Editor: Simon Collins
Contributing Editor: Polly Clayden

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

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

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