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EDITORIAL

Given the dramatic developments during 2015 – including START, PrEP and earlier treatment – the final issue of HTB includes an appropriately exciting range of articles and news.

Reports from EACS 2015 include those from several START sub-studies with unexpected results – and later in HTB (in an opinion article) the case for extending follow up in START beyond 2017. Two other reports from EACS look at reducing the cost of generic drugs for treating hepatitis C and MDR-TB in low- and middle-income countries.

EACS had surprising news from several independent research groups using dolutegravir as monotherapy (and dual therapy with 3TC) that hint at applications for dolutegravir's unique drug resistance profile. While the early results generated some discussion at this conference, most people are waiting for more data before commenting.

We think the results are sufficiently important to discuss – in another opinion article – the implications of these early results for HIV positive people, including using dolutegravir monotherapy to revisit the concept of “drug holidays”. For people on complex multidrug combinations, reducing to a single small 50 mg pill each day that has minimal drug interactions or side effects – might improve quality of life, even for six months each year.

New European treatment guidelines were launched at EACS that include ART at any CD4 count and the importance of PrEP. And other new guidelines include the UK recommendations on vaccinations in HIV positive people and the annual update to the drug resistance tables from IAS-USA.

Reports from the paediatric workshop earlier in the year describe new several antiretroviral studies in children, including switching to efavirenz and management of TB coinfection.

And as we went to press, a new four-in-one fixed dose combination was approved in both Europe and the US. Tradename Genvoya, this is Stribild with tenofovir alafenamide (TAF) – a compound whose development we have reported over the last three years – substituted for tenofovir DF.

We review the latest Market Report from the Clinton Health Access Initiative (CHAI) that predicts that TAF will replace tenofovir DF globally once a generic version is available from 2018. Also that dolutegravir and 400 mg efavirenz are likely to dramatically reduce the cost of treatment (and improve standard of care) in low- and middle-income countries.

HIV prevention news in this issue is set against the latest HIV report from Public Health England showing increased rates of new infections – especially in gay men. We include new data supporting the use of PrEP and the news that France has just approved PrEP as part of its national health service for people at high risk of HIV infection.

PrEP is not expensive and the NHS should make similar provision. Tenofovir will then be off-patent in a year and potential 6000 might not become HIV positive. **Doctors are smart people, they should be trusted to prescribe PrEP to people at highest risk of HIV who are not able to buy generic PrEP online.**

Finally, with all this potential for change, i-Base would like to thank all contributors and partners who helped us produce HTB this year. We would also like to wish all readers our seasonal best wishes for the New Year ahead.

SUPPLEMENT IN THIS ISSUE

Three supplements are included with this issue of HTB – two new pocket leaflets and an update to the i-Base booklet about HIV, pregnancy and women's health.

New pocket guides

i-Base are producing a series of new small pocket-size leaflets to summarise the A5 treatment booklets.

The first three pocket leaflets are:

- Side effects and Quality of Life
- HIV and pregnancy
- ART (included with the Sept/Oct HTB)

The leaflets use simple statements and quotes, with short URL links to web pages that have additional information in a similar easy format.

All with all i-Base material, these leaflets are free in the UK.

Please order online or use the fax-back form on the back cover of HTB.



HIV, pregnancy and women's health

This comprehensive 48-page A5 booklet has been updated from the 2013 guide.

Changes to this edition include greater emphasis on using ART to conceive when one partner is positive and the other is negative.

These booklets are free to order for individual and clinic use in the UK.

<http://www.i-Base.info/order>

CONFERENCE REPORTS

15th European AIDS Conference (EACS)

21-24 October 2015, Barcelona

Introduction

The 2015 European AIDS Conference (EACS) was held this year from 21-24 October in Barcelona.

This biannual conference organised by the European AIDS Clinical Society always produces a diverse range of new and important research and this year was no exception.

The full programme is available on the conference website. Individual abstracts are currently only available by searching the programme.

<http://www.professionalabstracts.com/eacs2015/iplanner>

More than 400 posters are now online as PDF files.

<http://www.abstractstosubmit.com/eacs2015/eposter>

Webcasts are available by following links from the conference website, although these seem to only be accessible via an App called Talks On The Go.

Reports in this issue of HTB are:

- Remarkable results with dolutegravir monotherapy
- First-line ART with dolutegravir plus 3TC: 24-week early results
- New European HIV guidelines (October 2015): universal ART, first-line integrase and PrEP
- Impact of early ART on lung function: important results on ART and COPD from START substudy
- No difference in neuropsychological test results between early and delayed ART in START substudy
- Immediate ART in START linked to greater bone loss over three years
- Price of MDR TB drugs could be greatly reduced with competitive generic manufacture
- Potential for generic prices for 12 weeks sofosbuvir treatment to drop below US \$300 and daclatasvir to US \$ 23
- Achieving viral suppression with HIV multi-drug resistance: Peg-interferon and valaciclovir as part of rescue therapy
- French cohort of HIV transgender women highlights issues relating to HIV management

EACS 2015: ANTIRETROVIRALS

Remarkable results with dolutegravir monotherapy

Simon Collins, HIV i-Base

EACS 2015 presented the first evidence that dolutegravir, the most recently approved integrase inhibitor, might have a resistance profile that enables monotherapy.

More surprisingly, several research groups reported similar results, with people maintaining viral suppression for up to six months without evidence of low level blips that were seen with boosted PI monotherapy. Something special was reported: these results would not happen with any other HIV drug.

Two small, uncontrolled, open label studies were presented as oral abstracts, using dolutegravir as a single drug monotherapy in similar groups of treatment-experienced patients.

The first study was presented by Esteban Martinez from University of Barcelona. [1] It included 33 people who had been diagnosed for a median of 19 years and who had been on suppressive HIV treatment for a median of 8 years (IQR 4 to 13 years).

Median age was 56 years (IQR 50-62), 40% had a history of AIDS-related complications, and half the group were women. At the start of the study, 11 people were using PI-based treatment, 9 were using NNTRI-based treatment and two people were already using an integrase inhibitor (one on raltegravir and one on elvitegravir).

After 24 weeks of dolutegravir monotherapy, 32/33 study participants still had an undetectable viral load (using a test sensitive to <37 copies/mL).

The single case of viral load rebound was in a person with a history of viral failure on a previous integrase inhibitor-based combination. This occurred at week 4, with a viral rebound to 88 copies/mL (and confirmed at 155 copies/mL). This person reported low adherence, including to the subsequent dose increase to twice-daily dolutegravir. At week 24, viral load remained detectable at 101 copies/mL with evidence of dolutegravir resistance (118R was detected in integrated DNA in 7% PBMCs, but not in blood).

There was no indication that reduction to dolutegravir monotherapy was associated with reduced viral pressure or potency. A post-hoc analysis of viral dynamics below the 37 copy/mL cut-off showed that at baseline 11/33 people had a positive signal of viral replication that was unquantifiable below 37 copies/mL. Of these 11 people, 6 became PCR negative at week 24 and 5 remained with a positive signal. Of the 22 people with negative PCR results at baseline, 20 remained negative at week 24 and 2 became positive but were unquantifiable <37 copies/mL.

The second dolutegravir monotherapy study was reported by Christine Katlama from Pitié-Salpêtrière Hospital in Paris as a single arm observational study in 28 people with a similar HIV and history and level of treatment experience as the Spanish study. [2] Median time since diagnosis was 20 years (IQR 15-21) with median viral suppression of 6.6 years (IQR 3.5 to 7.9 years). Median age was also similar at 48 (IQR 43 to 57) with equal balance of men and women (15/13).

After 24 weeks of dolutegravir monotherapy, 25/28 people still had undetectable viral load using a <50 copy/mL test and 24/25 were undetectable using a <20 copy/mL test, with one result at 37 copies/mL.

However, three participants had viral failure. One person had early viral rebound to 138 copies/mL at week 1 (confirmed at 469 copies/mL) and two cases of late rebound at week 24, to 2220 copies/mL and 291 copies/mL, respectively. These three cases were all in people who had previously used integrase inhibitors. The clinical implications for these cases were serious because they occurred under good adherence (optimal dolutegravir drug levels were confirmed in all three) and because resistance to dolutegravir developed that was not detectable when baseline samples were subsequently tested.

One person who experienced viral rebound to 300 copies/mL at week 12 still had low level but detectable viral load (at 41 copies/mL) 14 weeks after switching back to triple therapy with rilpivirine/tenofovir/FTC. With longer follow-up this person has since become detectable. [3]

A poster from a second French group reported similarly impressive results for 52 treatment-experienced patients using either dolutegravir monotherapy (n=21) or dual therapy with another drug (n=31). [4]

This cohort included 9 people with previous integrase-inhibitor experience. Over a median follow-up of 27 weeks (IQR 24 to 40) and 45 weeks (IQR 25 to 70), in the mono and dual therapy groups respectively, all except one participant maintained viral suppression to less than 50 copies/mL (with 96% of viral load results <20 copies/mL). The single case of viral rebound was in a patient with low adherence who was using dolutegravir plus maraviroc dual therapy.

The strategy of using dolutegravir with 3TC as initial dual therapy was presented in the same session at EACS and these dual therapy studies are reported later in a separate HTB article below. [5, 6]

C O M M E N T

Although these results are from small, uncontrolled studies, maintaining such low levels of viraemia for 24 weeks in people naive to integrase inhibitors has not been seen with any other single drug.

The results are preliminary because the data is still short-term, but the expected dynamics of viral replication – basically how quickly HIV would be expected to respond under similar circumstances with other drugs – mean that something appears to be special about dolutegravir in terms of both potency and the lack of drug resistance.

Just as importantly – and fortunately – dolutegravir has fewer side effects and drug interactions than many other commonly used HIV drugs. So simplifying treatment has the potential to reduce underlying side effects and laboratory abnormalities (including impact on lipids and renal function).

Looking even further forward, cabotegravir, the follow up compound to dolutegravir, has a long-acting injectable formulation in development that might only require quarterly injections.

If the 24-week results are sustained out to 48 weeks, treatment simplification might become an option for many, questioning the future role of the three most widely used drug classes: nukes (NRTIs), non-nukes (NNRTIs) and protease inhibitors (PIs).

However, simplification to dolutegravir monotherapy failed in 3 out of 28 people, perhaps because of earlier use of integrase inhibitors. In these cases, viral rebound occurred in people who had otherwise been stable on treatment with an undetectable viral load for more than six years. These three people developed resistance to dolutegravir.

Until the longer term risk of viral rebound is understood, together with the mechanism for control and any impact this has on the structure of HIV, the caution to study simplification as dual therapy with 3TC is probably warranted. This should involve larger, well designed, controlled studies.

The registry at clinicaltrials.gov already lists at least five studies using dolutegravir monotherapy or in dual therapy with 3TC that are either already ongoing or due to start shortly.

One of these studies is from a Dutch group that reported using dolutegravir monotherapy at a meeting the day before EACS. This included a case of clinically significant viral rebound on dolutegravir monotherapy that might have involved an interaction with multivitamins. [7] This larger study is already now enrolled. [8]

Although the results only generated limited, Professor Mark Wainberg, who has reported on the resistance profile of dolutegravir for several years, is more optimistic for the potential role in overlapping strategies for remission and a cure. [9]

Several mechanisms have been suggested for the why resistance to dolutegravir is difficult. One hypothesis is that dolutegravir remains bound to the viral integrase for longer than first-line integrase inhibitors (8 x longer than raltegravir and 26 x longer than elvitegravir). Also, any resulting changes must dramatically impair viral fitness. However, in the continued presence of drugs that bind for shorter periods - ie with good adherence - the binding site would not be unoccupied for long and yet resistance to both raltegravir and elvitegravir easily occurs in conditions of suboptimal viral suppression (>50 copies/mL) on treatment. [10]

Another explanation, perhaps more likely, is that dolutegravir specifically targets a highly conserved section of viral integrase that remains constant even when mutational changes occur elsewhere. Integrase is critical for survival and would be unable to function after structural changes of the responsible proteins. Any mutations involving conserved sequences would result in either non-viable virus, or one with reduced replicative capacity. [11]

Theoretically, resistance is unlikely to develop to any drug that targets a highly-conserved sequence including in other regions than integrase (ie RT and protease). [12] Dolutegravir is just the first antiretroviral that has this profile that is supported by clinical data.

These dolutegravir studies appear to be a proof of concept – at least in integrase-naive people – that such regions can not only be effectively targeted, but that this prevents the development of drug resistance.

Resistance to dolutegravir can develop with prior use of raltegravir or elvitegravir and this is a critical caution for future studies. [13] Some of the many ongoing research questions might also be able to be answered in animal studies. [14]

Thanks to Joseph Sonnabend for additional comments.

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Unless stated otherwise, references are to the programme and abstracts of the 15th European AIDS Conference (EACS), 21-24 October 2015, Barcelona. <http://www.professionalabstracts.com/eacs2015/iplanner>

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First-line ART with dolutegravir plus 3TC: 24-week early results

Simon Collins, HIV i-Base

EACS 2105 also included studies of dolutegravir-based dual therapy.

Early results were presented from an ongoing pilot study using dolutegravir plus lamivudine (3TC) as first-line ART. Participants became undetectable within four weeks and remained suppressed for six months. [1]

These early results from a pre-planned analysis of a secondary endpoint were presented at EACS 2015 by Pedro Cahn from Fundacion HUESPED, Buenos Aires.

This was a single arm, open label study in 20 HIV positive treatment-naive adults. Entry criteria included CD4 count >200 cells/mm³ and viral load <100,000 copies/mL and being HB(s)Ag negative. Dolutegravir (50 mg) and 3TC (300 mg) were taken together, once daily.

Given the preliminary nature of this strategy, the study was carefully designed to ensure that intensive viral monitoring would detect any early signal of sub-optimal therapy.

Viral load was monitored at baseline, at days 2, 4, 7, 19 and 14 and then at weeks 4, 8, 12 and 24. The primary endpoint was viral suppression <50 copies/mL at week 48 (by FDA snapshot ITT analysis). Enrolment was in two stages, dependent on successful viral outcomes at week 8 for the first ten participants, with predetermined discontinuation rules for the study based on suboptimal viral responses.

Median (IQR) approximate baseline characteristics of the 19 men and one woman included age 34 years (IQR: 31 to 43), CD4 count 507 cells/mm³ (IQR: 296 to 517) and viral load 24,000 copies/mL (IQR: 12,000 to 37,000).

By day 14, mean (+/- SD) viral load dropped by 2.54 log/copies/mL (+/- 0.27).

All participants had viral load <50 copies/mL by week 12 that was sustained to week 24.

Although the entry criteria excluded high baseline viral load, four participants had viral load increases to >100,000 copies/mL (range 105,000 to 273,000) between screening and baseline. Although these four people took slightly longer to suppress viral load, 3/4 reached <50 copies by week 4 and the fourth by week 8.

CD4 changes were reported as mean increase of 194 cells/mm³ (+/- 160) by week 12 that remained stable out to week 24.

The only side effects were generally mild with single reports of somnolence, epigastric pain, headache, diarrhoea and nausea (all grade 1) and one report of grade 2 headache. There were no serious side effects or grade 3/4 laboratory abnormalities.

Planned follow up will continue until week 96.

C O M M E N T

The inclusion of 20% people during likely primary infection in this otherwise very well-designed study could perhaps have been detected with exposure risk history, with or without symptoms.

However, in a question after the presentation, the results from the four cases >100,000 copies/mL were used to suggest that future studies might not require an upper viral load exclusion criteria.

Clearly these results need to be confirmed in larger randomised studies, several of which are either ongoing or due to start shortly. [2, 3, 4, 5]

Several switch studies in treatment-experienced participants were also presented at EACS with similar virological results using dolutegravir as monotherapy. [6, 7]

The low toxicity and cost of 3TC has also been used in dual therapy to overcome the lower rates of virological efficacy from studies of boosted-PI monotherapy. The 96-week results of the GARDEL study showed that dual therapy with lopinavir/r plus 3TC was non-inferior to lopinavir/r plus two NRTIs were also reported by Pedro Cahn at EACS 2015. [8]

The data supporting safety for a French study switching people to maintenance therapy with only tenofovir DF/FTC is unclear given the history of early dual-NRTI being suboptimal treatment. [9]

References

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<http://www.professionalabstracts.com/eacs2015/iplanner>

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EACS 2015: GUIDELINES

New European HIV guidelines (October 2015): universal ART, first-line integrase and PrEP

Simon Collins, HIV i-Base

The 8th edition of the European HIV Treatment Guidelines was launched at EACS 2015.

The guidelines are organised into five key sections, and regularly updated by specialist panels for each one.

These sections are:

- Assessment at initial & subsequent visits
- ART
- Prevention and management of comorbidities
- HBV and HCV coinfection
- Opportunistic infections

The recommendations are mostly structured by easy-to-view reference tables that extensively cover the increasing diversity of medical issues that are important for management of HIV infection. This makes the guidelines simple to use and the electronic version includes a large range of additional material that is not included in the printed booklet.

Key changes in the 2015 guidelines include:

- When to start: ART is now recommended for all HIV positive people, irrespective of CD4 count
- What to start with: There are now four rather than 16 combinations recommended for first-line ART. Combinations based on integrase inhibitors are now largely preferred, with darunavir as a boosted PI option and rilpivirine as an NNRTI option (if viral load is <100,000 copies/mL). Efavirenz is no longer recommended as preferred first-line ART.
- In a new section, preexposure prophylaxis (PrEP) is now strongly recommended for HIV negative people who are at high risk of becoming HIV positive. Based on the results on the PROUD and IPERGAY studies both daily- and event-based PrEP are recommended.
- Post-exposure prophylaxis (PEP) is no longer recommended if the HIV positive partner is on ART with an undetectable viral load - whatever the sexual risk. New recommendations for choice of drugs for PEP are tenofovir/FTC plus either raltegravir or darunavir/ritonavir.
- Older age is a key focus in the comorbidities section that emphasises the increasing importance of multidisciplinary care. This section includes renal, liver and cardiovascular monitoring and risk, and related lifestyle interventions.
- Drug interaction tables have been extensively revised, including between ART and corticosteroids, contraceptive drugs and hepatitis C medications.
- ART is now routinely recommended for anyone with HBV coinfection.
- Earlier HCV treatment and new oral hepatitis C drugs are emphasised more strongly.
- The OI section has been restructured with new tables added for PML, histoplasmosis, cryptosporidiosis and cystoisosporiasis, and there is a new section on preemptive therapy for cryptococcosis.

The European guidelines are produced by the European AIDS Clinical Society who also organise the main conference.

Simon Collins is a member of the writing committee for the comorbidities panel for the EACS guidelines.

C O M M E N T

The major change to recommend earlier ART is now in line with UK (BHIVA), US (DHHS), and WHO guidelines. Latest UK and US guidelines also have preferential use of integrase inhibitors instead of efavirenz and WHO and the US guidelines recommend wider use of PrEP.

These European guidelines are particularly useful for using a simple table format, with annotated notes.

A small proof error on management of cryptococcal meningitis in the print edition has been corrected for the online and PDF editions: the guidelines now recommend secondary prophylaxis for at least 12 months until the CD4 count is >100 cells/mm³ for at least three months, rather than the previously more cautious need to reach >200 cells/mm³ for at least six months.

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EACS 2015: SIDE EFFECTS & COMPLICATIONS

Impact of early ART on lung function: results on ART and COPD from START substudy

Simon Collins, HIV i-Base

Chronic obstructive pulmonary disease (COPD) is the third highest cause of global mortality, and prevalence is higher in HIV positive compared to general population cohorts, even after adjusting for cigarette smoking, a major risk.

Conflicting data relating to the impact of ART on reducing or increasing the risk of COPD made the importance of further research in a randomised study essential.

Ken Kunisak from University of Minnesota and the Minneapolis VA Health Care System, reported results from the START COPD sub study at EACS 2015.

The main START study randomised 4685 participants with CD4 counts above 500 cells/mm³ to either immediate ART or to or defer until the CD4 reached 350 cells/mm³. This substudy included 1026 people from 20 countries. The primary outcome on lung function was change in FEV1 (the annual slope of forced expiratory volume in 1 second), measured by spirometry and stratified by smoking status. Expected drop in FEV1 is 25-30 mL/year with double this rate expected in people at higher risk of COPD progression.

Participants were median age of 36 years, with high CD4 count and low viral load (median 648 cells/mm³ and 4.2 log copies/mL respectively). Almost a third were women (29%); 28% were current smokers and 11% former smokers.

Over a median follow-up of 2.0 years, there were no significant differences in FEV1 decline between the early vs deferred arms, for either smokers, non-smokers or in the pooled analysis, see Table 1.

Differences of -4 (-24 to +16), -4 (-39 to +34) and -5 (-29 to +20) were all non-significant with p-values of 0.67, 0.84 and 0.69 respectively.

Secondary analyses restricted to only high-quality spirometry results (95% of tests were this standard), after adjustment for smoking status and with data from the deferred arm censored on start of ART all found similar results.

Table 1: Change (95%CI) in FEV1 (mL/yr) in early vs deferred arms START COPD substudy

	Early ART	Deferred ART	Difference	p-value
Pooled analysis	-29 -43 to -15 n=518	-25 -39 to -11 n=508	-4 -24 to +16	0.67
Smokers	-34 -59 to -9 n=138	-3 -55 to -6 n=158	-4 -39 to +34	0.84
Non-smokers	-28 -44 to -11 n=380	-23 -40 to -5 n=350	-5 -29 to +20	0.69

C O M M E N T

With over 1000 participants and >2000 patient-years of follow-up this is the largest prospective HIV study of COPD and the results will immediately inform care.

Although early ART produced no benefit on lung function, the results are just as important for showing that treatment did not worsen lung function.

The recommendation from the main START study that the benefits of early ART outweigh the risks in patients with CD4 counts >500 cells/mm³ can therefore be applied to people irrespective of their risk of COPD.

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Ken Kunisaki K et al. Lung function decline in HIV: effects of immediate versus deferred ART treatment on lung function decline in a multi-site, international, randomized controlled trial. 15th EACS, 21-24 October 2015, Barcelona. Oral abstract PS1/2.

No difference in neuropsychological test results between early and delayed ART in START substudy

Mark Mascolini, natap.org

Through 3.3 years of follow-up, people randomised to immediate antiretroviral therapy (ART) in the international START trial had neuropsychological (NP) test results similar to people in the delayed-ART arm. [1]

Everyone in this young study group entered the trial with a CD4 count above 500 cells/mm³, and the percentage of time on ART was 93% in the early arm versus 34% in the delayed arm.

START randomised more than 4600 asymptomatic antiretroviral-naive people with a CD4 count above 500 cells/mm³ to either immediate ART or to defer treatment until the CD4 count fell to 350 cells/mm³ or clinical AIDS developed [2].

After three years of follow-up, researchers unblinded the trial when significantly more people in the deferred arm met the composite primary endpoint of any serious AIDS or non-AIDS disease or death from any cause.

A neurology substudy aimed to compare NP test results in the immediate and deferred arms over the course of the study. START investigators proposed that early ART may have a neurocognitive impact because HIV enters the central nervous system (CNS) early in the course of infection, overt CNS disease has been reported during primary HIV infection, and cognitive impairment reaches a high prevalence during chronic infection. On the other hand, ART may be neurotoxic.

Neurology substudy participants completed eight NP tests when entering the study then after 4, 8, and 12 months and annually after that. Researchers standardised test scores to Z scores and figured the average of eight Z scores, or QNPZ-8. The analysis involved 291 people in the early ART arm and 301 in the deferred arm with follow-up data.

The neurology substudy group had a young median age of 34 years (IQR: 27 to 42), and 11% were women. While 47% were white, 16% were Asian, 16% Hispanic, and 15% black. The highest proportion of participants came from Brazil (28%), followed by European countries (17%), Thailand (15%), the United States (15%), Argentina or Chile (14%), and the UK or Australia (11%).

More than half (55%) had at least some college education, and three quarters had a job. The two treatment arms did not differ significantly by any of these measures. Nor did they differ by known duration of HIV infection (median 0.9 year), CD4 count (629), or viral load (about 16,000 copies). Fewer than 1% of participants injected drugs. While 8.3% had a psychiatric diagnosis, 5.2% reported alcohol or substance dependence.

The early ART group spent 93% of follow-up time on treatment, compared with 34% in the deferred arm. Half of deferred arm participants started ART by follow-up year three. Three years after randomisation, the average CD4 count rose by about 200 cells/mm³ in the early ART arm while remaining unchanged in the deferred arm.

Through an average 3.3 years of follow-up, QNPZ-8 rose to similar degrees in the two study arms. Estimated difference between the immediate and deferred arms at the end of follow-up was negligible (-0.01, 95%CI: -0.06 to 0.03, p = 0.63). Statistical adjustment for age, race, sex, education, geographic region, viral load, CD4 count, and CD4/CD8 ratio had little impact on this outcome.

The START team concluded that there is "no overall neurocognitive advantage (or disadvantage) for immediate ART initiation in asymptomatic treatment-naive individuals with high CD4 counts."

The researchers believe their results suggest low prevalence of early neurocognitive impairment that ART can reverse and low incidence of neurocognitive decline that ART can prevent. At the same time, the young age, good health, and high educational attainment of the study group may explain why early ART had no neurocognitive advantage.

C O M M E N T

Based on the hypothesis that reducing inflammation associated with untreated HIV might have other clinical benefits, many people expected to see neurological benefits from earlier use of ART.

This highlights the importance of prospective randomised data including from START sub-studies for other critical questions relating to HIV management.

Source: www.natap.org

http://www.natap.org/2015/EACS/EACS_29.htm

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Immediate ART in START linked to greater bone loss over three years

Mark Mascolini, [natap.org](http://www.natap.org)

People randomised to begin antiretroviral therapy (ART) immediately in the international START trial had steeper declines in bone mineral density (BMD) than people randomised to delayed therapy. [1]

Hip BMD kept falling through three years of follow-up in the immediate ART group, but dwindling spine BMD stabilised after 1 year.

Waning BMD with ART remains a concern in HIV care, especially among people with other risk factors for osteoporosis and fracture. An international team that offered recommendations for managing bone disease with HIV noted that BMD drops 2% to 6% in the first two years of ART, depending on the antiretrovirals used. [2]

START randomised more than 4600 antiretroviral-naïve people with a CD4 count above 500 cells/mm³ to begin ART immediately or to wait until the CD4 count dropped to 350 cells/mm³ or AIDS developed [3]. The bone substudy focused on 193 people randomised to early ART and 204 randomised to deferred ART. All participants had hip and spine BMD determined by DXA scan at baseline then every year. Follow-up ended in May 2015, when START results were unblinded.

The bone substudy group had a median age of 32 years (IQR: 26 to 41), very young for an antiretroviral trial. While 26% of participants were women (only 13% of whom had reached menopause), 32% were Asian, 24% Latino/Hispanic, 20% white, and 19% black. Median known HIV duration measured only 0.7 years (IQR 0.3 to 2.8), median CD4 count stood at 641, and median viral load at 4.2 log₁₀ copies/mL (about 16,000 copies). Only 19% of the study group currently smoked. Median body mass index lay in the high normal range at 24 kg/m² (IQR 21 to 27). A little more than one third of the group (38.3%) had low BMD at the baseline visit (T score at or below -1 at spine, total hip, or femoral neck), and 3.3% had osteoporosis.

The early ART group used tenofovir during 79% of follow-up, compared with 15% in the deferred group. Respective proportions of follow-up time on efavirenz were 65% and 11%, and on protease inhibitors 19% and 3%. Among treated people, more than 80% in both study arms used tenofovir. Decline from baseline in total spine BMD was significantly greater in the early ART group than the deferred ART group at 12 months (about 2% versus less than 1%, $p < 0.001$) and at 36 months (more than 2% versus less than 1%, $p = 0.001$). Decline from baseline in total spine BMD was also greater in the early group at 12 months (about 2% versus less than 1%, $p < 0.001$) and 36 months (more than 3% versus 2%, nearly significant at $p = 0.06$).

Through an average follow-up of 2.2 years, estimated average difference in total spine BMD was 1.6% lower in the early ART group (95% confidence interval [CI] -2.2% to -1.0%, $p < 0.001$). At that point, estimated average difference in total hip BMD was 1.5% lower in the early ART group (95% CI -2.3% to -0.8%, $p < 0.001$). When START statisticians limited the analysis to people actually on ART and off ART, estimated mean difference in total spine BMD became 2.2% lower in the early ART group (95% CI -2.8% to -1.6%, $p < 0.001$) and estimated mean difference for total hip BMD became 2.1% lower in the early group (95% CI -2.8% to -1.4%, $p < 0.001$).

During follow-up, osteoporosis developed at a nonsignificantly greater rate in the immediate ART arm of this young study group (1.72 versus 0.90 per 100 person-years, $p = 0.27$). Incidence of any fracture was similar in the two groups (0.81 and 0.71 per 100 person-years, $p = 0.45$), while incidence of minimal-trauma fracture was nonsignificantly lower in the early ART group (0.18 versus 0.32 per 100 person-years, $p = 0.11$).

The START team concluded that people randomised to immediate ART had greater BMD loss at both the hip and spine. Spine BMD dropped steeply in the first year of ART then stabilised, while hip BMD loss continued through three years of follow-up.

C O M M E N T

The likelihood of greater reductions in BMD from earlier use of ART was expected, based on results of the earlier SMART study.

The results from the START sub-study emphasise the importance of individualising HIV management, especially for people at higher risk of bone disease.

Source: www.natap.org
http://www.natap.org/2015/EACS/EACS_07.htm

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EACS 2015: TREATMENT ACCESS

Price of MDR TB drugs could be greatly reduced with competitive generic manufacture

Polly Clayden, HIV i-Base

Competitive large-scale generic manufacture could mean that at least 10 times more multi-drug resistant TB (MDR-TB) cases could be treated within current procurement costs, according to an analysis presented at EACS 2015. [1]

Andrew Hill and colleagues from Imperial College London, Howard University, Washington, Chelsea and Westminster Hospital, and Liverpool University, performed the study. The authors used methodology previously developed to calculate the cost of antiretrovirals and hepatitis C and B drugs.

New TB drugs are being developed for shorter course treatment and MDR-TB. Current MDR-TB treatment can cost more than \$1000 per course in low-income countries with far higher prices elsewhere. The authors noted that such prices strain health budgets. The study calculated target generic prices for novel TB treatments.

Key TB drugs were categorised as:

- Group 1-3, already generic – clofazimine (although patent expired, only one manufacturer)
- Group 4, basic use patent expiring from 2014 (moxifloxacin, linezolid, sutezolid)
- Group 5, patent expiry 2016-2013 (pretomanid, delamanid, bedaquiline)

The authors obtained costs of active pharmaceutical ingredients (API) for all group 1-4 drugs using an online database reporting cost per kilogram (kg) of exported API. [2] They also collected prices by country and from the Global Drug Facility (GDF).

They estimated prices for linezolid, moxifloxacin, and clofazimine using algorithms combining dosage with per-kg prices of API and excipients and adding on formulation, packaging and a typical generic profit margin.

Estimates for sutezolid and posizolid synthesis were projected from those for linezolid. Sutezolid is structurally similar to linezolid and has similar costs of production. Posizolid is structurally similar but has production costs three times higher than linezolid.

Target prices for bedaquiline and delamanid were calculated by analysing chemical synthesis, costs of raw materials and production. The authors assumed production costs of pretomanid to be four times that of delamanid, based on its chemical structure.

They projected lower and higher target prices for each of the drugs. The lower price was estimated using: 1 cent per pill for formulation; 10 cents per month for packaging; and 10% profit margin. The higher target price used: 4 cents per pill for formulation; 35 cents for packaging; and 50% profit margin.

Volume demand assumptions for the lower and higher target prices respectively were: greater than one million treatment courses per year (validated from GDF price comparisons) and greater than 100,000 treatment courses per year (validated from hepatitis C analysis).

The analysis revealed current GDF prices of group 1-4 drugs that mostly fell within calculated target prices with the exception of moxifloxacin (GDF price \$18.1/month compared with target price \$3.5-9.4).

The price of moxifloxacin varied enormously from \$806/month (Bayer) and \$232 (generic) in the US to \$19 in Russia.

Group 5 drugs that are still patent protected or not yet approved for use in TB treatment had the highest current prices and the greatest potential for reduction. See Table 1.

The price of linezolid ranged from \$4,298/month for the Pfizer drug in the US to \$70 for an approved generic version in India (and \$17 for a non-approved generic).

Bedaquiline has tiered pricing of US\$4,532, US\$453 and \$136 for high-, middle- and low-income countries respectively – compared with the high and low target prices (\$8.8-16.4).

Prices for delamanid were available for the US, Germany and Japan, US\$4,510, US\$4,258 and US\$3,108 respectively – compared with generic high and low prices (\$3.5-8.6).

Using these prices, the cost of treatment courses containing bedaquiline in two arms the STREAM study, [3] could be fall from \$871-1834 to \$176-422 per course. For three drug regimens the generic price could be \$86-389.

The authors explained that the analysis assumes that MDR-TB drugs can be ordered centrally at low prices. Currently multiple drugs are ordered in small quantities nationally. Achieving low prices will need a simplified market, with fewer

drugs (purchased at higher volume) or standardised treatment courses.

They note that there might be secondary patents on some TB drugs even after the basic patents have expired that will need to be resolved before generic companies can produce them.

They conclude that competitive large-scale generic manufacture could allow treatment of at least 10 times more MDR-TB cases while still operating within the procurement costs of current budgets. But such this would depend on overcoming patent barriers, competitive pricing, and scaling-up surveillance and case detection to increase demand for treatment.

Table 1: Group 5 drugs predicted production costs

Drug	Patent expiry	Target price/month	GDF price/month
Clofazimine	Expired	\$6.2-16.4	\$99
Linezolid	2014	\$4.9-12.8	\$193
Sutezolid	2014	\$4.9-12.8	No prices
Pretomanid	2016	\$8.2-21.2	No prices
Posizolid	2019	\$11.4-13.4	No prices
Delaminid	2023	\$3.5-8.6	\$3,108*
Bedaquiline	2023	\$8.8-16.4	\$136

*Little information available on pricing of delaminid – price in Japan quoted.

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Potential for generic prices for 12 weeks sofosbuvir treatment to drop below US \$300 and daclatasvir to US \$ 23

Simon Collins, HIV i-Base

The potential for even lower prices for generic formulations of new oral hepatitis C drugs was presented as a poster by Andrew Hill from Liverpool University. [1]

This study used the falling costs of active pharmaceutical ingredients (API) during 2015 related to production efficiency and greater demand in order to model future potential lower target prices.

Currently, sofosbuvir costs US \$50,000 - 84,000 in high-income countries for 12 weeks treatment compared to less than \$1000 for generic versions in low- and middle-income countries (produced under license from Gilead). Daclatasvir costs approximately US\$ 35,000 for 12 weeks, but information on generic access and prices have not yet been announced by Bristol Myers-Squibb.

The model included a 40% markup for formulation costs, \$0.35 per month for packaging, and a 50% profit margin.

The model predicted that if API price reductions continue at the current rate, then by the end of 2015 target prices would reach US \$281 for sofosbuvir and US \$23 daclatasvir.

C O M M E N T

The potential to dramatically reduce the price of hepatitis C drugs in low- and middle-income countries is essential given that most people with hepatitis C live in these countries.

It is therefore reassuring that prices for generic sofosbuvir have already fallen in line with this model to less than US\$ 400. [2]

This study further highlights the indefensible pricing structure for sofosbuvir and daclatasvir in high-income countries, putting the drugs beyond the reach of health systems to enable universal treatment for people with hepatitis C.

It is perfectly legal in many countries, including the UK, to use an online pharmacy to import 12 weeks of generic medication for personal use.

The Australian HIV medical association (ASHM) has published online guidance for how to do this, that could be used by people in the UK. [3]

Prices for other new hepatitis C drugs were included in an earlier presentation by this group at the IAS 2013 conference two years ago. [4]

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EACS 2015: CLINICAL MANAGEMENT

Achieving viral suppression with HIV multi-drug resistance: peg-interferon and valaciclovir as part of rescue therapy

Simon Collins, HIV i-Base

An important case was presented at EACS as a poster, where highly individualised care achieved sustained viral suppression for a person with extensive resistance to antiretroviral therapy (ART).

This success was due both to very careful management that minimised the risk of drug resistance and the strategic use of novel drugs that are often overlooked for their antiretroviral potential.

The lead author was Dr Markus Bickel from Goethe University Frankfurt who reported on a case of a 26 year old man who was diagnosed HIV positive when a child (age 4) and who, despite complex sequences of different combinations since the age of 6, was unable to get undetectable viral load.

By 2009, he had extensive drug resistance to five ARV classes having used all approved HIV drugs including tipranavir, T-20 and raltegravir. Viral load was >160,000 copies/mL and risk of clinical progression was severe with a CD4 count of 10 copies/mL.

From May 2009 to April 2013, he received a dual-boosted-PI "holding strategy" using darunavir/atazanavir/ritonavir to limit further drug resistance. Despite the lack of a CD4 recovery and viral load that at it's highest points fluctuated between 3 to 5 million copies/mL this person was lucky to remain clinically stable.

In April 2013, due to serious opportunistic infections (meningitis and MAC), he switched to a six-drug combination of AZT, tenofovir DF, FTC, darunavir/r, maraviroc and dolutegravir. Although this multi-drug combination reduced viral load by one log from about 3 million copies/mL to 330,00 copies/mL, in June 2013, T-20 and dolutegravir were discontinued in order to hold on to these drugs for future options - resistance being a likely outcome in someone with such high viraemia.

In October 2013, due to severe herpes encephalitis, aciclovir and later valaciclovir, were added to his ART, and which steadily reduced viral load to 60,000 copies/mL by March 2014.

In March 2014, dolutegravir and T-20 were added back to his combination, reducing viral load to 5,000 copies. Adding pegylated interferon and increasing the darunavir/r dose (to 1000/100 mg twice-daily) led to continued viral decline, dropping to below 50 copies/mL by August 2014.

From November 2014 to June 2015, his treatment was steadily simplified, dropping AZT, FTC, tenofovir DF and T-20 while maintaining viral load at <20 copies/mL

Once his viral load was suppressed, his CD4 count steadily increased to the point where OI prophylaxis drugs were also stopped and by June 2015 his CD4 count was around 500 copies/mL.

C O M M E N T

Two recent studies have reported direct antiretroviral impact of aciclovir and valaciclovir, independent of HSV activity. [2, 3]
In the encouraging and impressive case reported by Bickel et al, finding a way to overcome multidrug HIV resistance was dependent on a several stages.

- **Firstly finding a combination with sufficient antiretroviral pressure - or potency - to drive viral load to <50 copies/mL in blood. This cut-off seems sufficient to limit the greatest risk for the development of additional new mutations, including to any drugs in the new combination to which someone is still fully sensitive.**
- **Maintaining this drug combination (likely to include more rather than fewer drugs) for several months (minimum 3 to 6 months) in order to reduce viral load in lymph and other compartments.**
- **Steadily reviewing treatment to discontinue drugs that are least likely to be contributing to continued antiviral pressure, in order to improve tolerability.**

This case was also important for the prompt decision to discontinue drugs that were likely to be vulnerable to developing resistance in the presence of high viral load, in order to reserve these for later use.

Luckily, the availability of five classes of antiretroviral drugs has dramatically reduced the number of people with extensive drug resistance. The development of new medications is desperately needed as life-saving treatment for people who are in this situation. Two promising pipeline compounds include the attachment inhibitor (BMS-663068) and maturation inhibitor (BMS-955176), both in development by BMS. [4]

Many people with multi drug resistance are likely to also have complex HIV histories, perhaps involving decades of ART.

i-Base publishes a community guide to treating drug resistance. [5]

The online version has always included the option to use other drugs with anti-HIV activity but that are only used in difficult cases because of a poorer tolerability profile compared to widely recommended drugs. [6]

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French cohort of HIV transgender women highlights issues relating to HIV management

Simon Collins, HIV i-Base

In the UK there are currently no national data on the number of transgender people who are also HIV positive.

In fact, there are little data on any aspect of transgender health due to the lack of non-binary options on health records. But during 2016, a new NHS policy that will ask patients to include their current gender and their birth gender in medical records and to specify how they currently identify, is hoped to improve this.

Even with these policy changes, compiling data is complicated as it is dependent on self-identity and many transgender people no longer associate with their birth gender. In countries where data exist, the incidence of HIV in transgender people is often very high and engagement in care is often more complex. Although HIV treatment and management of transgender people is largely similar to people who retain the same gender in life as their birth gender (cis-gender people), there are a few important differences.

These include potential drug interactions between ART and hormone treatment (including non-prescribed steroids), complications from surgery and health issues that relate to birth gender (ie cervical screening for trans men and AIN screening for trans women).

A poster at EACS 2015 presented data from a multicentre retrospective descriptive study of 47 transgender women in four university hospitals in northern France. Data was collected from a single anonymous questionnaire.

Mean age was 40 years (25 to 62). All respondents had a current or past history of sex work and 43/47 had been born in South America (32% said they did not speak French). All participants were on ART (more than half using a boosted PI) with a mean CD4 count of 608 cells/mm³ (60 to 1908) and approximately 70% had viral load <40 copies/mL.

All participants had a history of surgery, mainly mammoplasty, rhinoplasty and silicone injections, with 10/47 (21%) having undergone sex reassignment surgery. Just under half (46%) of the participants had current or previous use of hormone treatment.

The low rate of treatment for STIs compared to earlier French studies was explained by likely missing data. The study reported that only eight people had been treated for syphilis and three for urethritis. However, anal Pap smear results for 68% of the cohort included abnormalities in 70% of those tested, with one case of anal carcinoma.

A high incidence of comorbidities was similar to HIV cohorts. Cardiovascular risks included half being current smokers and half had dyslipidaemia (details not presented) and 22/39 had BMI >25.

The poster noted multiple social and psychological issues including migrant status, multiple addiction and violence, in addition to gender identity and HIV. Hormone therapy was inconsistent in almost half the respondents. Two previous French studies were referenced for having reported good immunological and virological response to ART.

C O M M E N T

Having accurate data on transgender people is an essential step towards knowing whether the health needs and services for this population are being effectively delivered and met. The new NHS proposed policy that broadens information about gender options when accessing care is strongly welcomed. Sexual health centres are expected to introduce this policy from spring 2016.

Last year the BHIVA conference included an overview talk on HIV and transgender patients that is available online as a webcast. [2] A review of transgender studies from the IAS 2014 conference is still relevant for many of the issues it covered. [3]

cliniQ is the UK's only comprehensive sexual health and well-being clinic run by and for transgender people. cliniQ is a community service and is in Partnership with 56 Dean Street. [4]

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CONFERENCE REPORTS

7th International Workshop on HIV Paediatrics

17-18 July, Vancouver, Canada.

Introduction

The three reports from this annual workshop are:

- Substituting lopinavir/ritonavir with efavirenz in children on stable ART
- The effects of systemic efavirenz exposure, sex and age on risk of viral non-suppression
- Pharmacokinetics of lopinavir/ritonavir super-boosting in infants and young children co-infected with HIV and TB

Substituting lopinavir/ritonavir with efavirenz in children on stable ART

Polly Clayden, HIV i-Base

Virologic outcomes in children who were suppressed on lopinavir/ritonavir (LPV/r)-based ART and switched to efavirenz (EFV) were no worse than for those who remained on LPV/r, in a South African retrospective cohort study.

These findings from the leDEA cohort were presented at the 7th International Workshop on HIV Pediatrics in Vancouver.

In 2013 World Health Organisation (WHO) guidelines added the option to substitute LPV/r with EFV in children who had started with LPV/r-based ART and had sustained virologic suppression. The evidence for this recommendation was mainly from the NEVEREST studies.

The leDEA study compared outcomes between virologically suppressed children aged three years and above who switched to EFV or stayed on LPV/r in a routine clinical setting.

Of 690 children, 36 substituted EFV at a median of 44.1 months old. The median follow up time was 25.8 months (15 to 34.2) and 24.4 months (18.1 to 31.7) in the substitution and stay groups respectively.

At ART initiation, the children in the two groups were well matched, for age, CD4 percentage, weight-for-age z-score, WHO stage and viral load and at 42 months.

Remaining on LPV/r (stay group) was negatively associated with viral blip (an isolated viral load result >1000 copies/mL that returned to <400 copies/mL at next measurement) at 42 months. Blips occurred in 318 (48.6%) children in the stay group compared with 10 (27.8%) in the substitution group, $p=0.015$.

Factors associated with EFV substitution included: favourable clinical response to ART, adjusted OR per 1 weight-for-age z-score increase 1.34 (95% CI: 0.96 to 1.80); and viral blips adjusted OR 0.34 (95% CI: 0.15 to 0.79).

C O M M E N T

Clearly the success of this strategy depends on access to viral load testing for widespread implementation.

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The effects of systemic efavirenz exposure, sex and age on risk of viral non-suppression

Polly Clayden, HIV i-Base

Pharmacokinetic (PK) sub study from CHAPAS-3 suggests new paediatric target minimum concentrations for efavirenz (EFV) – according to data presented at the 7th International Workshop on HIV Pediatrics.

CHAPAS-3 (Children with HIV 1 in Africa, Pharmacokinetics and Adherence/Acceptability of Simple Antiretroviral Regimens) was an open-label, randomised, phase 2/3 trial, conducted in Zambia and Uganda to evaluate new solid, dispersible, scored, antiretroviral fixed-dose combination and single drugs in African children.

The sub study was conducted to describe the effect of systematic EFV exposure on viral suppression and determine the minimum exposure predictive of reduced risk of non-suppression.

The investigators used Cox proportional hazards regression models to estimate the risk of viral non-suppression (>100 copies/mL) associated with EFV exposure and other factors as hazard ratio.

They analysed 590 matched PK/viral load samples from 118 children 1.7 to 13.5 years of age.

They found the risk of non-suppression was best described using a non-linear model that showed risk of non viral suppression decreased by 40% for every 2-fold increase in mid dose concentrations (95% CI: 24 to 51%) $p<0.0001$. The risk reached a plateau around values of 8mg/L (\log_2 C12h).

Multivariate analysis found male sex and older age to be other risk factors for viral non-suppression. See table 1.

Table 1: Multivariate analysis risk factors for non-suppression

Group	Relative hazard	95% CI	p-value
Girls <8	Reference		
Boys <8	5.55	1.97 to 15.5	0.001
Girls>8	12.72	4.89 to 33.07	<0.001
Boys>8	11.23	2.64 to 47.76	0.001

The most predictive C12h cut off value for risk of viral non-suppression was 1.2mg/L, p<0.001. Based on their results the investigators suggested that mid-dose mid dose interval concentrations of 1.2 mg/L should be used as the new EFV paediatric target minimum concentrations.

References

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Pharmacokinetics of lopinavir/ritonavir super-boosting in infants and young children co-infected with HIV and TB

Polly Clayden, HIV i-Base

Lopinavir/ritonavir (LPV/r) dosed at 1:1 ratio in the presence of rifampicin (RIF) was not inferior to LPV/r 4:1 ratio without rifampicin in HIV positive children in an interim pharmacokinetics (PK) analysis presented at the 7th International Workshop on HIV Paediatrics.

The analysis was from a multicentre, open label sequential, non-randomised, prospective PK study conducted by Mark Cotton and colleagues from South Africa in collaboration with Drugs for Neglected Diseases Initiative (DNDI).

RIF causes drug-drug interactions by cytochrome (CYP) p450 induction and reduces LPV/r exposure by approximately 90%. Doubling LPV/r works in adults receiving concomitant RIF-containing TB treatment but does not in children. A ritonavir (RTV) super-boosting strategy to LPV/r 1:1 ratio in order to overcome the effect of RIF is recommended for children. Evidence to support this is limited and mainly from older children.

The study used two strategies: in the first children started TB treatment before starting ART and in the second ART first before TB treatment. The investigators performed PK evaluations during the periods of concomitant TB treatment and LPV/r 1:1 dosing and ART alone with LPV/r 4:1 dosing.

The primary objective was to demonstrate that the proportion of participants achieving modelled LPV/r0/morning trough >1 mg during RTV super-boosting on RIF-based anti-TB treatment is non-inferior to LPV/r 4:1 without RIF.

Children >42 weeks post-conception, weighing >3 to <15 kg at enrolment were eligible. Dosing was according to standard World Health Organisation (WHO) weight bands for ART and TB treatment using liquid LPV/r and RTV.

Six PK samples were taken over 10 hours: pre-dose then 1,2, 4, 6 and 10 hours post-dose:

- PK 1 – RIF X 4 weeks + super-boosted LPV/r (1:1) > 1 week.
- PK2 – RIF + super-boosted LPV/r (1:1) month 6 for TB treatment
- PK3 – LPV/r (4:1) 4-6 weeks post RIF + super-boosting
- PK4 – LPV/r (4:1) 3 months after TB treatment

The investigators used PK1 data to develop model, which they applied to PK2 and PK3 data.

The study sample size was calculated for 80% power to compare the predicted number of children with C0/morning trough <1mg/L between PK3 and PK2 for non-inferiority – defined as upper limit of 95% CI of the difference PK3-PK2 below 10%.

At the request of WHO – to inform the 2015 guidelines – the investigators performed an interim analysis (to May 2015 before required sample size reached).

At this time point: 256 children had been screened, 89 enrolled, 22 were on study, 59 had completed, 3 died, 3 were lost to follow up and 4 withdrew. Two thirds (66) of the children started TB treatment first, 21 ART first and two started TB treatment and ART together. The investigators had performed 217 intensive PK evaluations across groups (154 on RIF).

Table 1: Basic data at interim analysis

	Enrol	PK1 (n=80)	PK2 (n=68)	PK3 (n=56)
Age (months) *	18.2 (9.1 to 26.8)	19.1 (10.0 to 28.8)	22.9 (3.5 to 33.4)	23.7 (15.2 to 33.5)
Age <1 year	29 (33%)	26 (31%)	14 (20%)	7 (11%)
Weight (kg) *	8.4 (6.9 to 10.7)	8.8 (7.2 to 11.1)	9.8 (8.7 to 12.2)	10.1 (9.1 to 12.3)
CD4% CD4 cells/mm ³	19 (11.2 to 25.5) 880 (459 to 1710)			
Viral load (log)	5.8 (4.7 to 6.3)			

* Median +IQR

The percentage of modelled LPV/r C0/morning trough below target: 10.7% (95% CI: 3.3-19.6) and 15.1% (95% CI: 5.1-27.7%) for the super-boosting plus RIF and standard dosing respectively. This gave a difference of 4.4% (95% CI: -12.1 to 1.4%), which met the criteria for non inferiority. There was a smaller percentage of C0/morning trough below target with super-boosting compared with standard LPV/r dosing.

At the end of the study (24-36 weeks) for which there were data available for 30 children, 24 (80%) had viral load <1000 copies/mL; 22 (73%) <400 copies/mL and only 6 (20%) <50 copies/mL. The investigators noted that there were no major PI mutations in the unsuppressed children or safety concerns at this stage.

Enrollment to this PK study continues. The study was complicated and had both logistical and tolerability obstacles associated with the liquid formulation. The investigators expect that the LPV/r pellets and granules and RTV granules might help.

Reference

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TREATMENT ACCESS

CHAI's ARV market report predicts that new drugs and formulations will drive the next major drop in treatment costs

Polly Clayden, HIV i-Base

Lower dose efavirenz (EFV), dolutegravir (DTG) and tenofovir alafenamide fumarate (TAF) are expected to make up a large chunk of the adult first-line market over the next five years, and contribute to treatment cost reductions, according to recent projections by The Clinton Health Access Initiative (CHAI). [1]

CHAI's ARV Market Report – now in its 6th year – provides a global perspective on the antiretroviral (ARV) marketplace in low- and middle-income countries (LMICs) each year and describes CHAI's expectations of the market's evolution over the subsequent five years.

By the end of 2014, 13.5 million people were receiving ART in LMICs. ART coverage grew from 15% in 2009 to 40% in 2014 (including all HIV positive people at all CD4 counts) – coverage rates that year were 29% of children and 41% of adults. CHAI notes that the pace of scale up in 2014 (another 1.8 million additional people on ART since 2013) was similar to that seen in the previous year (2 million more people on ART from 2012 to 2013). By 2018 several countries are projected to approach universal coverage, including Rwanda, Uganda and Swaziland for adults, and Vietnam for children.

The report outlines imminent World Health Organisation (WHO) guideline changes that are likely to increase the overall ARV market size. [2] Most importantly, adoption of test and treat, so that all 36.9 million HIV positive people will be eligible for treatment, but also the recommendation of oral PrEP for people at risk of HIV, that once implemented, will lead to more demand for tenofovir disoproxil fumarate (TDF).

Brazil announced its adoption of test and treat in 2013 and saw a 27% increase in people receiving ART in 2014 (coverage went from 39% to 48% by the end of 2014). CHAI notes that Brazil's domestic manufacturing capacity distinguishes it from other LMICs and might allow faster ART scale up than elsewhere. Other than Brazil, Malawi and Rwanda have announced plans to adopt test and treat – both countries already have relatively high coverage of more than 50%.

CHAI says that the immediate effect of the test and treat recommendation on ART scale up is unclear but as a “conservative” projection 23 million people are likely to be on ART in LMICs by 2019 (95% adults and 5% children).

The report shows how the price of recommended generic ARVs has stabilised and well-established drugs reached the minimum prices at which they can feasibly be produced. Pipeline products are expected to drive the next major drop in ART cost.

Generic accessible (GA) LMICs can look forward to several new drugs and formulations for adults, including DTG, EFV 400 mg and TAF, which are expected to significantly reduce the cost of first-line treatment.

Several generic companies have begun developing fixed dose combinations (FDC) of TDF/3TC/EFV 400 mg and these are expected to be available in mid- to late-2016.

Aurobindo has submitted a generic single DTG to the US FDA in May 2015, which is likely to be available in mid-2016. Generic DTG-based FDCs are likely to be available from 2017.

WHO has indicated that both EFV 400 mg and DTG will be recommended as part of alternative first-line regimens with some restrictions until there is enough evidence to use them in all populations (notably in TB coinfecting people and pregnant women).

CHAI predict that EFV 400 mg and DTG will have a substantial impact on the first-line market by 2019. By this time DTG is expected to gain 37% and EFV 400 mg 19% of the adult first-line NNRTI/INSTI market – respectively 7.2 million and 3.8 million people.

TDF made up 72% of the first-line NRTI market in GA LMICs in 2014 – 8.3 million people received this drug as part of adult first-line regimens by the end of that year.

The US FDA approved TAF as part of an FDC in November 2015, and news is expected about the dual co-formulation TAF/FTC in April 2016. A generic TAF-based FDC is expected mid-2018. With the caveat that various active product ingredient (API) production steps need to be optimised by generic manufacturers, CHAI note that TAF will cost a lot less than TDF as its dose is about 10-fold lower.

Uptake of TAF is likely to begin in the latter half of 2018. In the first year that it is available, TAF is likely to capture up to 22% of the first-line NRTI market in GA LMICs. Eventually TAF is projected to almost entirely replace TDF.

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New trade agreements threaten treatment access in Asia

Simon Collins, HIV i-Base

On 6th October, community activists organisations in south-east Asia issued a press statement expressing concerns that the new Trans-Pacific Partnership Agreement (TPPA) will threaten access to affordable generic medicines and sustainable development goals. [1]

The joint statement from the Asia Pacific Network of People living with HIV/AIDS (APN+), Positive Malaysian Treatment Access & Advocacy Group (MTAAG+) and the Vietnam Network of People living with HIV (VNP+) called for countries and governments to reject ratifications of TPPA.

The TPPA has been led by the United States and includes 11 countries including seven in the Asia-Pacific region including Vietnam, Malaysia, Japan, Australia, New Zealand, Singapore and Brunei. Details of the deal were negotiated in secret and are still unclear but are expected to include extended patent and exclusivity provisions - including for HIV, hepatitis and cancer treatments - that will endanger the lives and health of millions of patients in these countries.

The measures are contrary to the World Trade Organisation's (WTO) Doha Declaration which re-affirmed the right of countries to use flexibilities in the previous Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement that was developed 20 years ago.

The statement included comment from Shiba Phurailatpam of APN+:

“... the reporting around the TPP has focussed only on an exclusivity period for biological medicines with a reported push back on the 12 year period proposed by the US being presented as a victory for developed countries in the TPP like Australia. But even a mandatory 5-year period of exclusivity along with the several other restrictive conditions imposed by the US, will have a massive adverse impact in countries like Malaysia and Vietnam, as will the other damaging provisions in the intellectual property chapter.

The conclusion of this trade deal makes a mockery of the Sustainable Development Goals and the new WHO HIV treatment guidelines that call for immediate initiation of treatment.

We are shocked that the secret deal has been concluded without public consultation or a proper health and human rights review. Even now the text is being kept secret. APN+ members are in 6 of the TPPA countries - Malaysia, Vietnam, Singapore, Australia, New Zealand and Japan - and will be among the first to face the consequences of the TPP on their health and lives.”

Source:

hepcAsia. (6 October 2015). 20 years after the TRIPS agreement, the US government scores massive victory for Big Pharma in TPP deal. (6 October 2015).
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ANTIRETROVIRALS

Tenofovir alafenamide (TAF) approved – but only as part of a fixed dose combination

Simon Collins, HIV i-Base

Within the last two weeks, a fixed-dose combination (FDC) containing a new formulation of tenofovir DF called tenofovir alafenamide (TAF) has been approved in both Europe and the US. [1, 2]

This is the first time that a new antiretroviral HIV drug has been approved that is only available in a coformulation, limiting use for people who want or need the single new drug.

The combination (E/C/F/TAF) is a single pill contains elvitegravir (150 mg), cobicistat (150 mg), emtricitabine/FTC (200 mg) and TAF (10 mg). Although cobicistat is included to boost drug levels of the integrase inhibitor elvitegravir, the combination still needs to be taken with food to achieve optimum drug levels.

The license is for treating HIV-1 in adults and children older than 12 years (who weigh >35 kg).

EMA approval in the EU was on 23 November 2015 and FDA approval in the US was three weeks earlier on 5 November.

The European indication is broader, based on an absence of drug resistance mutations associated with the integrase inhibitor class, emtricitabine or tenofovir.

The US indication is:

1. As initial ART in treatment naive patients; or
2. As switch option in patients who have had:
 - (i) An undetectable viral load for >6 months on their current ART, and
 - (ii) No history of virological treatment failure on previous combinations.

Safety concerns highlighted in the prescribing information include:

- E/C/F/TAF should not be co-administered with other antiretrovirals (ARVs).
- E/C/F/TAF is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious adverse events.
- Patients with chronic hepatitis B/C treated with ARVs are at an increased risk for severe and potentially fatal hepatic adverse reactions.
- The safety and efficacy of E/C/F/TAF in patients co-infected with HIV & HCV/HBV has not been established. It should not be co-administered with medicines containing tenofovir DF, lamivudine (3TCV) or adefovir for treatment of HBV infection.
- Discontinuation of E/C/F/TAF in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.
- E/C/F/TAF should not be used in patients with creatinine clearance (CrCL) < 30 mL/min as no data is available. It should be discontinued in patients with CrCL that declines <30 mL/min during treatment.

For full details please see the full product characteristics. [3]

The combination is manufactured by Gilead and marketed with the tradename Genvoya.

C O M M E N T

This new version of Stribild – with TAF replacing TDF – results in a combination that has reduced impact on laboratory markers of renal and bone toxicity. The better lab results probably also have clinical significance, at least for patients who are already at greatest risk. These people are likely to be older patients or those with reduced renal and bone function.

It is unclear whether the differences between TAF and TDF have clinical significance for people without these risks.

The regulatory decision to approve TAF within a combination but without a stand-alone version has been criticised for two reasons.

Firstly, that this ignores the clinical need for some people, especially those with extensive treatment experience, who would benefit from TAF by who are not able to use - or who do not want to - the other components of the FDC.

Secondly, that this might limit the ability of generic companies to coformulate TAF with other ARVs for use in low- and middle-income countries.

A dual formulation of TAF/FTC was submitted to the EMA for regulatory assessment in May 2015. [4]

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<http://i-base.info/htb/28289>

TREATMENT GUIDELINES

European HIV guidelines updated (October 2015)

Simon Collins, HIV i-Base

In October 2015, the 8th edition of the European HIV Treatment Guidelines was launched at the 15th European AIDS Conference.

The guidelines are organised into five key sections:

Please see the report from the 15th EACS conference earlier in the issue of HTB for a summary on the guidelines and the new changes to the 2015 edition.

Reference

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Direct download (English version)
http://www.eacsociety.org/files/guidelines_8_0-english_web.pdf (PDF)

New UK guidelines on use of vaccines in HIV positive adults (2015)

Simon Collins, HIV i-Base

These comprehensive 94-page guidelines, updated from 2008, provide GRADE-based recommendations on the use of more than 20 vaccines in HIV positive adults.

HIV-specific guidelines are important due to more effective and wider use of ART together with new vaccines and vaccination practices.

Change in the 2015 editions include:

- Use of new vaccines against human papillomavirus (HPV), shingles (herpes zoster) and pneumococcus.

- New recommendations for HIV positive people for hepatitis B, meningococcus and pertussis vaccines.

Reference

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IAS-USA update resistance guidelines and mutation tables (2015)

Simon Collins, HIV i-Base

The 2015 update of mutations associated with resistance to individual HIV drugs produced by the International Antiviral Association (IAS-USA) has been published online.

This updates the figures from 2014 and includes user notes and accompanying text.

The resource is designed to identify key mutations associated with antiretroviral drug resistance and to help guide treatment decisions.

The following mutations have been added to the summary bars for the integrase inhibitors:

- Q148R, N155H and R263K are added as new mutations for dolutegravir
- R263K is added as a new mutation for both elvitegravir and raltegravir.
- G140S for dolutegravir is no longer bold, indicating this is no longer a major mutation.
- Q148H/K mutations for elvitegravir are now highlighted in bold as key mutations.

Reference

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TRANSMISSION & PREVENTION

HIV rates still increasing in gay men: 2015 report

Simon Collins, HIV i-Base

The 2015 report from Public Health England (PHE) on new HIV diagnosis, together with treatment and care based on data from 2014 was published in October.

As with previous years the report provided sober reading.

Key findings from the 2014 data include:

- New diagnosis increased to 6151 in 2014 from 6000 in 2013.
- Gay men are disproportionately affected, with increased to 3360 in 2014 from 3259 in 2013.
- New diagnoses acquired through heterosexual sex has declined (2,490 in 2014), largely due to a reduction in diagnoses among black African men and women (1,044 in 2014).
- Approximately 40% of diagnoses in 2014 were in late stage HIV, defined as a CD4 count below 350. The report notes that this “remains stubbornly and unacceptably high”.
- 613 HIV positive people died, mostly with late diagnoses as a factor.
- There are now 85,489 people diagnosed with HIV in the UK accessing care (compared to 81,500 in 2013). One in 6 are older than 55.
- Of people in care, 90% are on ART, with 95% of those on ART having an undetectable viral load.

- The report notes that even before the 2015 changes in WHO and BHIVA guidelines to recommend ART at CD4 counts >500 cells/mm³, 26% of people started ART while their CD4 count was this high.

C O M M E N T

The report shows a failure by HIV prevention programmes - even though absolute increases in diagnoses are small and might reflect increased uptake of testing rather than new infections.

We should expect effective programmes to be reducing HIV rates, especially given use of earlier ART and some availability of PrEP (in the PROUD study and perhaps even off-label use).

Given the proven clinical and prevention benefits of earlier treatment, it is unacceptable that UK NHS commissioners insist that ART is currently only commissioned for treatment at a CD4 count <350 cells/mm³, and that the timeline for this policy to be changed will not be until 2018.

In the meantime, this anomaly can be easily overcome by prescribing ART to reduce the risk of HIV transmission – which is commissioned irrespective of CD4 count.

References

Public Health England. HIV New Diagnoses, Treatment and Care in the UK 2015 report. (October 2015).

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PrEP to be available free in France from January 2016

Simon Collins, HIV i-Base

France is set to be the first European country to provide free PrEP to people at high risk of HIV infection as part of the public health service.

The announcement was made on 23 November 2015 by Marisol Touraine, the French Minister for Social Affairs, Health and Women's Rights, with free access expected by the beginning of January 2016.

Approval is based on a temporary recommendation (Recommandation Temporaire d'Utilisation, RTU) that covers off-label use for an already approved medicine for up to three years.

The single pill coformulation of tenofovir DF/FTC was approved in the US with an indication for PrEP in July 2012.

The NHS has still to decide when and whether PrEP will be available in the UK. Even if approved, the current timeline for access is unlikely to be until 2017.

This delay has led to increasing use of generic PrEP in the UK, with some NHS clinics now providing the essential support including HIV and HBV testing and renal monitoring. [2]

C O M M E N T

PrEP is not expensive and if prescribed to people at highest risk of HIV it is considerably cheaper than lifelong treatment.

The PROUD study report reported an NNT of only 13 (number needed to treat to prevent one infection) and showed that it is possible in the UK for doctors to accurately identify people whose risk would support this benefit. [3]

Critically, the cost of PrEP to the NHS will dramatically fall when tenofovir comes off patent in 2017.

In the meantime, many community organisations are publicising how to access generic PrEP for less than 90% of the current price to the NHS. [4, 5] This reduces the cost of daily PrEP to about £45 per month – and significantly lower for someone using event-based dosing.

Questions to the i-Base Q&A service cover how and where to buy PrEP online, information on daily dosing and other options and the important of testing and monitoring, preferably at an NHS clinic. [6]

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PrEP efficacy for transgender women: new analysis from iPrEX study

Simon Collins, HIV i-Base

A new analysis from the large international iPrEX study that led to FDA approval of oral PrEP in the US provides additional results on efficacy in transgender participants. [1]

The results are important because even though HIV risk is often very high in transgender women due to a complex range of social factors, most PrEP studies only include a small number of transgender participants. In the paper described, published online in the *Lancet* on 5 November 2015, PrEP refers to oral tenofovir DF/FTC in a single pill.

Previous results from the iPrEX study [2, 3] and the follow-on open label extension (iPrEX-OLE) [4, 5] have been previously reported. The open label phase included additional dry blood spot pharmacokinetic (PK) monitoring for drug levels.

Background and demographics

The new analysis included 339 participants (14%) of the 2499 gay men and trans women enrolled in the randomised placebo-controlled iPrEX study. Of this group, 29 participants (1%) identified as women, 296 identified as trans (12%) and 14 (<1%) identified as men but also reported use of feminising hormones (oestrogen, progestogen or antiandrogen). The open label phase of iPrEX included 192 trans women, of whom 151 (74%) chose to take PrEP.

As background, the mechanism for PrEP efficacy was expected to be similar in transgender compared to cisgender men so long as PrEP is available and adherence is good. However, there is little data on whether hormone treatment changes biological risk or about interactions with drugs used for PrEP.

Transgender participants were from: Peru and Ecuador (n=247; 15% of participants in the region), Thailand (n=43; 38%), Brazil (38; 10%), US (n=6; 3%) and South Africa (n=5; 6%).

At baseline, there were significant social, demographic and HIV risk differences between trans and cisgender groups. Transgender participants had more sexual partners, less condom use for receptive anal sex, more reported sexually transmitted infections, greater use of cocaine or methamphetamines, lower formal education and were more likely to live alone and have a history of transactional sex compared to cis gay men (all $p < 0.0001$).

Use of feminising hormones was reported by 67 (20%) of 339 trans women: 48 (16%) of 296 trans-identified participants, five (17%) of 29 women participants and 14 (0.6%) of 2160 participants who did not identify as either trans or women. Among 163 feminising regimens reported by 67 participants, 60 (37%) contained synthetic oestrogens, 58 (35%) contained natural oestrogens, 121 (74%) contained progestogens and 38 (23%) contained antiandrogens either alone or in combination with other hormones.

Results

In the main iPrEX study, in the transgender group there were 11 new HIV infections in active PrEP arm compared to 10 in the placebo arm (HR 1.1 [95% 0.5 to 2.7], $p=0.77$).

Although the ITT analysis showed no benefit of PrEP, when looking at infections in relation to PrEP use – defined by detection of drug levels – none of the people who seroconverted in the active PrEP arm had detectable drug levels at the time of infection (in either plasma or peripheral blood mononuclear cells). HIV incidence was zero (95%CI not calculable) if drug was detected and 4.9/100 patient years (95%CI 3.0 to 7.7) if not detected.

There were no infections when drug levels were equivalent to taking four or more doses per week. In the two women who became HIV positive during the open label phase, one had no detectable drug levels and one had levels associated with taking less than two doses per week.

The PK results matched drug levels in new infections to controls that remained negative and adjusted for HIV risk factors. During the open label phase, protective drug levels (>4 doses/week) were seen in a smaller percentage of the transgender group compared to gay men (18% vs 34%, $p < 0.003$). This was irrespective of hormone use.

The efficacy results are important for two potential mechanisms where hormones might affect PrEP efficacy, although neither were reported as leading to lower efficacy in the results.

Firstly, although drug interactions with PrEP, might reduce PrEP exposure, the lower drug levels in transgender people compared to gay men in the study could not be separated from adherence.

Although the proportion of people with protective drug levels was lower in the trans vs cisgender groups, and also within the trans group by participants using hormones compared to those who were not, levels associated with 100% protection from taking four or more doses a week were still achieved by all subgroups.

It is important to note that these results provide no direct data on whether there is an interaction between hormones and PrEP because the study reports observed drug levels rather than drugs levels in relation to adherence.

Secondly, although hormones result in biological differences that affect HIV susceptibility in terms of anal and other tissue thickness, the use of these was suggested as a potential protective affect. In the discussion, the authors reported “whereas oestrogens preserve pelvic tissues including anal epithelium and reduce viral susceptibility in an animal model medroxyprogesterone acetate might decrease vaginal thickness and increase HIV susceptibility in non-transgender women its effect on anal epithelium is unknown. To the extent that feminising hormone regimens typically use oestrogens in place of or in addition to progestogens these hormonal effects might decrease HIV susceptibility overall.”

So while neither of this issues could be answered by this sub analysis from iPrEX, both issues should be assess in future prospective studies.

C O M M E N T

While there are many social and economic reasons why transgender people are at high risk of HIV, including reduced access to PrEP and other services as well as social factors that might have an impact on adherence, these results provide data that suggest that in the context of good adherence PrEP was effective in transgender people.

Even though this was an unplanned subgroup analysis that was not powered to be able to show efficacy difference between the transgender and cisgender groups, adherence with more than four doses was not associated with new HIV infections.

As with ART, HIV drugs used as PrEP are effective in both transgender and cisgender people. However, the paper rightly noted the high priority placed on hormone drugs for transgender people. [6]

It is now important to prioritise studies that provide data on the current knowledge gaps.

The research areas with data should not be used to limit access to PrEP for transgender people at risk of HIV infection.

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PrEP in a clinical setting: no infections reported in San Francisco cohort

Simon Collins, HIV i-Base

Experience of PrEP use outside a clinical trial in a high incidence population were presented from a retrospective analysis of people accessing care at the Kaiser Permanente Medical Centre in San Francisco, California.

This analysis described all patients at the centre who were evaluated for and started on PrEP from July 2012 (when PrEP was approved in the US) to February 2015. The results were reported by Jonathan Volk and colleagues and are available as an open access paper in the 1 September edition of *Clinical Infectious Diseases*. [1]

Use was low during the first year (less than 5 to 10 people starting PrEP each month), steadily increasing to approximately 40 people a month at the end of the second year and reaching 50 to 60 for the last six months. Approximately 80% of the 1045 referrals led to an evaluation with at least one clinic visit (n=908) and of these, 657 individuals started PrEP. This cohort was 99% gay men, with one heterosexual women and one transgender man.

During 388 person years of PrEP use, with a mean duration of use of 7.2 months, there were no new HIV diagnoses. This was despite 187 people being diagnosed with at least one STI and 78/178 being diagnosed with multiple STIs (range 2 to 10) indicating likely ongoing HIV exposure and risk.

After 12 months of PrEP use, half the people using PrEP were diagnosed with an STI (95% CI: 43% to 56%), including one-third with a rectal STI, one-third with chlamydia, 28% with gonorrhoea and 5.5% with syphilis.

Although there was no control group or historical data of previous STIs, based on the high rate of rectal STIs, the researchers estimated an expected incidence of HIV without PrEP of 8.9/100 patient years.

An accompanying editorial noted that an increase in STIs among gay men had been reported as predating PrEP and that against a background of zero HIV infections - the key goal - and a lack of control date, that the high rates of STIs might even be "considered a good problem to have".

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New free self-sampling HIV home testing service launched in England

Simon Collins, HIV i-Base

A new self-sampling HIV test service has been launched in the UK, supported by Public Health England (PHE).

This is a nationally commissioned service to provide free test kits to higher risk individuals in England from 1st December 2015 – 1st January 2016. The service is run by a private company (Preventx) working with the community organisation (Yorkshire MESMAC), who were jointly awarded the tender.

The test requires 600 mL of self-sampled blood ("milked" after a finger prick) that is then posted laboratory.

Laboratory testing uses the 4th generation Roche antigen/antibody Elecsys Combi PT test, with 100% sensitivity (for true negative results) and 99.74% specificity (with a small chance of false positive results).

All positive tests require a confirmatory clinic-based test.

45,000 tests have been commissioned, spread across local authorities that have bought into the service. However, more than 10,000 tests had already been ordered during HIV Testing Week from 21 November 2015. [2] If the test limit is reached for one region, further commissioning will be needed to continue the service.

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HEPATITIS COINFECTION

NICE decision on ledipasvir/sofosbuvir for chronic HCV

On 25 November, NICE published guidance for the limited use of sofosbuvir/ledipasvir for chronic hepatitis C (HCV). [1]

As with the NICE approach to other new direct acting antivirals DAAs), the recommendation are categorised both by genotype and treatment experience, see Table 1.

For full details of the guidelines are available online.

NHS treatment with ledipasvir/sofosbuvir should be available within three months of this decision.

The coformulation of ledipasvir/sofosbuvir is manufacture by Gilead Sciences and marketed under the tradename Harvoni.

Table 1: Summary of NICE recommendation for ledipasvir/sofosbuvir

HCV treatment-naïve patients	
G1 without cirrhosis	8 weeks treatment
G1 or G4 with cirrhosis	12 weeks treatment
HCV treatment-experienced patients	
G1 or G4 without cirrhosis	12 weeks treatment
G1 or G4 with cirrhosis	12 weeks treatment, but only if there is a low risk of disease progression

C O M M E N T

A price for ledipasvir/sofosbuvir is approximately £26,000 for 8-weeks and £38,000 for 12-weeks of treatment, both excluding VAT.

The guidance notes that a nationally available price reduction for ledipasvir/sofosbuvir has been agreed with the Commercial Medicines Unit, but also that this was not considered as part of the submission. Not details of the reduced price have been published.

Reference

NICE. Ledipasvir–sofosbuvir for treating chronic hepatitis C. NICE technology appraisals [TA363]. (25 November 2015)
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Sofosbuvir/velpatasvir submitted to US FDA for HCV genotype 1-6

Gilead press statement

On 28 October 2015, Gilead submitted a new drug application to the US FDA for a fixed dose combination of sofosbuvir/velpatasvir.

Sofosbuvir is a nucleotide analog polymerase inhibitor that was approved in the US in December 2013 and velpatasvir is an NS5A inhibitor previously developed as GS-5816.

The application is for treatment for HCV genotypes 1 to 6.

The European application is expected before the end of 2015.

Reference

Gilead press statement. Gilead submits new drug application to U.S. Food and Drug Administration for fixed-dose combination of sofosbuvir/velpatasvir for treatment of all six genotypes of hepatitis C. (28 October 2015).

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US indication for ledipasvir/sofosbuvir expanded

Gilead press release

On 12 November 2015 the US FDA approved an expanded indication for the fixed combination of ledipasvir/sofosbuvir.

The expanded indication now includes treatment for genotype 4, 5 and 6 and for HIV/HCV coinfection

In addition, ledipasvir/sofosbuvir plus ribavirin (RBV) for 12 weeks was approved as an alternate therapy to 24 weeks of ledipasvir/sofosbuvir for treatment-experienced, genotype 1 patients with cirrhosis.

The dual formulation is manufactured by Gilead and marketed under the brand name Harvoni.

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OPINION ARTICLES

Why START would make an excellent long-term cohort

Nathan Geffen, CSSR

Results from the international START study were so important that rapidly changed national and international treatment guidelines for routine management of HIV; antiretroviral treatment (ART) is now routinely recommended even at high CD4 counts.

These results were 18 months earlier than expected, and although everyone in the study now has been recommended to start ART, follow-up with continue for all participants until the end of 2017.

But as a unique cohort - never to be available again in the future - there might be important reasons to follow up these people for longer still in a cohort study.

Long-term cohort groups of people living with HIV have provided useful information on life-expectancy, morbidity and the role of factors such as earlier HIV treatment, smoking and differences in health indicators based on mode of infection. (1-6) Long-term cohort groups do not have the evidential value of clinical trials, but they can provide insight into questions that are too expensive, impractical or unethical to answer in clinical trials.

The Strategic Timing of Antiretroviral Treatment (START) study is a randomized controlled clinical trial that has compared early versus deferred antiretroviral treatment. In May 2015, participants on the deferred arm began to be offered immediate treatment, after the study question was answered, about a year and-a-half before the trial was scheduled to complete. The primary end-point – any serious AIDS related event, serious non-AIDS-related event, or death from any cause – was reached in 42 patients on the immediate arm versus 96 on the deferred one (HR: 0.43; 95%CI: 0.3-0.62; $p < 0.001$). (7)

START has features that collectively would make it a unique long-term follow-up cohort. [7]

- It is large; START has 4,685 participants.
- It is geographically widespread; there are 215 sites in 35 countries.
- The participants are diverse by measures of sex (27% female), sexual orientation (38% reported acquiring HIV from a person of the opposite sex), by self-reported race or ethnic group (9% Asian, 30% Black, 14% Latino or Hispanic, 44% white), reported income (46% high vs 54% moderate or low), smoking status (32% smokers) and mode of acquisition (64 participants acquired HIV through IDU and 5% acquired HIV through blood products or other means, including unknown).
- It has comprehensive patient baseline and monitoring data and excellent follow-up capacity, better than most of the large cohorts.
- Because of the study design the participants were relatively healthy and early in HIV infection when they enrolled, with a median time of one year since infection, a median baseline CD4 count of 651 cells/mm³ [IQR: 584-765] and a median 10 year cardiovascular event risk of just under 2%.
- Participants have been taking ART regimens combinations with negligible risk of lipoatrophy, lipohypertrophy, neuropathy, pancreatitis and lactic acidosis. This was mostly tenofovir/emtricitabine/efavirenz (75% in the immediate arm, with less use over time of efavirenz (approximately 50% of people in the deferred arm),
- Many participants have been placed on newer drug regimens. This provides an opportunity to study possible long-term toxicities.
- The study has already collected an large number of urine and blood samples. Typically five blood vials and a urine sample have been taken from each participant every four months. Use of these as part of a long-term follow-up cohort would require further participant consent.

Potential to learn from START as an observational cohort

The most compelling reason for follow up would be continued comparison of morbidity and mortality between the two arms. This is a randomised cohort that due to the study findings will not be unethical to ever run again.

Rates of drug resistance and treatment failure, as well as the rate at which mutations occur, can be measured. There is also potential to examine long-term outcomes broken down by sex, mode of acquisition, geographical area, income, self-identified race and smoking status. Comparisons of the age/disease profiles that affect the participants could potentially be compared to background populations, albeit that such analyses should be treated with caution.

START would make an ideal long term follow up observational cohort with the potential for important insights in the same

tradition as other cohorts like EuroSIDA, IeDEA, Multicenter AIDS Cohort Study, Danish HIV Cohort Study and Swiss HIV Cohort Study. (8–12)

The study is due to terminate at the end of 2016, and participants are expected to move to other treatment institutions in 2017. It would be unfortunate if in 2017 the opportunity was lost to turn START into a long-term cohort.

Many of the participants might prefer the opportunity to continue getting a high standard of care in a clinical trial environment as well as the opportunity to continue contributing to scientific knowledge, so it is unlikely there will be resistance to turning START into a long-term cohort from most participants.

No doubt there will be some complex logistical and funding requirements to make this work. Nevertheless these challenges should be manageable. The scientific benefits and consequent benefits to people with HIV of making START work as a long-term observational cohort could be immense.

Nathan Geffen is a member of the Community Advisory Board for the START Study.

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Why dolutegravir might get us closer to ending AIDS: next step, further research

This blog discusses the implications for HIV positive people about several studies at the 15th EACS conference in October 2015.

Simon Collins, HIV i-Base

Introduction

Several research groups - from Argentina, France, Spain and the Netherlands - presented results at the 15th European AIDS Conference (EACS) in Barcelona from small independent pilot studies that have the potential to dramatically change HIV globally.

If the early results are supported by larger studies, the implications include the potential:

- To improve quality of life by using fewer drugs associated with fewer side effects. Perhaps only one drug might be needed which already has one of the lowest reports of side effects.
- To reduce costs of antiretroviral treatment (ART) at a time when health budgets are being cut in many high-income countries, including the UK, and when funding programmes for low- and middle-income countries have a new challenge to double the number of people accessing ART.
- To improve the choices of treatment worldwide. This is not just related to cost but to speeding up access to better second-line and first-line drugs.
- To speed up the option to treat HIV with a long-lasting injection instead of daily pills. It might be possible to use one injection every three months. Until now, the concern to avoid drug resistance to cabotegravir (very similar to dolutegravir) has meant that researchers have been preoccupied with developing two injectable drugs to use in combination.

- To play a new and unexpected role in research into either a cure or long term HIV remission. This is really jumping ahead but might be an outcome if the mechanism to explain the early results is that dolutegravir disables HIV in a way that makes it unable to replicate.

But these remarkably grand hopes need to be tempered with serious caution and patience. The current results are tentative, short-term and in small numbers of people. The results are exciting because our understanding of the dynamics of HIV mean that they shouldn't have happened, but they did - and coming as a surprise means that even experts are unsure of their significance.

Further research will be essential before trying this at home or even trying this with your doctor's advice. This is because these risks are serious too: dolutegravir might for example cause HIV to mutate in a way that makes the virus more difficult to treat, even with drugs that were working beforehand.

Larger studies are already planned or ongoing. Perhaps within a year the long-term outlook for treatment might be different for a significant percentage of HIV positive people.

What were these studies at EACS?

The studies all looked at whether ART could be simplified from standard 3- 4 drug combinations to using fewer drugs. The studies all used dolutegravir - the most recently approved HIV drug - either with one of the earlier HIV drugs called lamivudine (3TC), or on its own. Three of the studies were in the same session at the conference and these talks will hopefully soon be available as a webcast. [1]

Dolutegravir belongs to a class of drugs called integrase inhibitors and it is probably one of the most effective drugs to reduce viral load and also has a low risk of side effects. 3TC is still widely used, and it is also very well tolerated with very few or no side effects. Because 3TC came off patent several years ago, generic versions are available very cheaply in all countries.

Treatment with only one or two HIV drugs is not a new idea - but until now results have never been able to match results using three active drugs. So the current studies were carefully designed to include very close and frequent monitoring, especially for viral load. The people taking part often had complications with the HIV drugs that they were already taking due to difficult side effects, lack of available treatment or complicated drug interactions with other important medicines. So there were clinical reasons to consider this experimental approach based on individualised care.

Three studies at EACS 2015 used dolutegravir (50 mg) in a two-drug combination with 3TC (300 mg). Both drugs were taken together, once daily, with or without food. One of these studies was in people starting treatment for the first time and two were in people switching treatment, who had already been undetectable for some time. Four other studies used dolutegravir as a single drug - ie with no other HIV meds.

What were the early results?

The first results – in small numbers of people for short periods of time – showed that viral load generally stayed undetectable for 24 weeks. However, viral load did not stay undetectable for everyone. Some people were unlucky. And when viral load did rebound, some of these people developed drug resistance.

Although the possibility of using fewer drugs might sound tempting, the risks are also real.

What happened in the dolutegravir and 3TC dual therapy studies?

Two studies reported on two-drug (dual) therapy using dolutegravir with 3TC.

The first was an oral presentation from Argentina called the PADDLE study. [2]

This study involved 20 people (average age 34) who had never used HIV drugs and who started their first treatment using dolutegravir plus 3TC. Viral load was measured eight times over the first month and then weekly. This involved close monitoring and a lot of clinic visits. As an additional caution, the researchers only expanded the study to 20 people after the first 10 people had shown good responses over the first 8 weeks.

Also importantly, nearly everyone started ART with a low viral load – and the average was 20,000 copies/mL. However, although this was not intended when planning the study, four people started with a viral load greater than 100,000 copies/mL. These high results were because of viral load increases between the screening visit and the start of the study.

After starting treatment, viral load dropped very quickly. Within three weeks, everyone saw their viral load fall to less than 400 copies/mL, with ten people getting to undetectable (less than 50 copies/mL) within 2 weeks. By 8 weeks, all 20 participants had a viral load that was less than 50 copies/mL - with the people starting at highest viral load taking longest to reach undetectable. Although many people might find this viral load response surprising, this was expected. Other studies have reported how quickly integrase inhibitors reduce viral load within the first month of treatment.

What was more remarkable was that all 20 people stayed undetectable through to week 12 and then to week 24.

Average CD4 counts increased by about 200 cells/mm³ – as would be expected with triple combinations. Very few side effects were reported and nearly all were mild. The most serious side effect was a moderate headache (but with minimal need for medication) and there were no serious abnormalities from blood monitoring tests (ie not needing an additional intervention). The PADDLE study will continue to follow participants for two years and larger studies are already planned.

The second dual therapy study was presented as a poster in the exhibition hall and had a different design and studied people with a different HIV history. [3]

In this case, 27 French participants who were already on treatment and who had an undetectable viral load that was less than 50 copies/mL for at least a year changed ART to dolutegravir plus 3TC. Everyone in the study was doing well before switching. This was defined as having undetectable viral load on treatment for at least the previous year. People were not only older than those in the PADDLE study (average age was 59) but they had a long HIV treatment history, having been on ART for an average of almost 18 years. What is unusual - and a significant caution - is that seven people had already used another integrase inhibitor (raltegravir) and eight had history of drug resistance to 3TC.

Over 24 weeks, viral load remained less than 20 copies/mL in all participants, with one blip at 52 copies/mL. Tolerability was also good, although two people changed back to their pre-switch combination because of fatigue with dolutegravir and 3TC.

A third study - also from a French group - reported on 31 people who were using dolutegravir as part of dual therapy with a range of other drugs but only three people used 3TC. As this third study also included 21 people using dolutegravir monotherapy, these results are described below with the single drug studies. [4]

What were the results from the dolutegravir monotherapy studies?

Although the results of dual therapy studies were very positive, several studies went a step further. Three studies at EACS showed results from using dolutegravir as a single HIV drug, with a fourth study presented at a meeting linked to the main conference.

The first of these was an oral presentation of a Spanish study in 33 people who were on stable treatment, having had an undetectable viral load on ART for an average of eight years. These were people with a long and complex history of treatment, but with who had no evidence of integrase inhibitor resistance. All participants switched to dolutegravir monotherapy.

Over 24 weeks, all participants except one person maintained an undetectable viral load (this time defined as being less than 37 copies/mL). One person had viral load rebound to low levels at week 4 (155 copies/mL) and despite modifying treatment (changing to a higher twice-daily dolutegravir dose) viral load remained detectable at week 24. This case was complicated by poor adherence. In the study overall, tolerability was good and results of laboratory monitoring tests for cholesterol and kidney function both improved.

A second monotherapy study, also an oral presentation was a French study in 28 people who were treatment-experienced. [6]

This group were stable on current treatment but had long and complex HIV treatment histories having used ART for an average of 17 years. Although 25 of the 28 people had undetectable viral load for 24 weeks, three people had their viral load rebound, one to over 2,000 copies/mL.

In these three cases, adherence was confirmed with good drug levels, but drug resistance still developed against dolutegravir. This might have been linked to previous use of integrase inhibitor treatment, even though integrase resistance was not detected when this was checked at the start of the study.

These three cases temper the hope that dolutegravir monotherapy is without risk and they were the focus of many of the questions after the presentation.

The third study reporting dolutegravir monotherapy, was a poster in which 21 treatment-experienced French people switched from currently stable treatment to dolutegravir monotherapy. [4] This was the study that also reported on 31 people using dolutegravir dual therapy with a range of different drugs, but only three cases where this was 3TC.

Over 24 weeks of follow-up, all participants on dolutegravir monotherapy had undetectable viral load below 50 copies/mL, with 96% of test results being less than 20 copies/mL. The study included some people who had previously used other integrase inhibitors, although all the details for these people were not shown.

One person with previous drug resistance to raltegravir and who used dual therapy with dolutegravir plus maraviroc, experienced viral load rebound and developed new resistance to dolutegravir.

Finally, a small study from the Netherlands, reported results about five treatment-experienced people who switched to dolutegravir monotherapy due serious complications with alternative drugs. Fewer details are available for this study, but although viral load remained undetectable in four people, it rebounded to clinically significant levels in a fifth. [7]

Is this the first time using fewer drugs has been studied?

No, the interest in reducing the drugs to treat HIV has been around for a long time. Almost as soon as the first studies in 1996/7 showed that combination therapy worked, there were studies looking at whether people could start treatment with one combination and then cut back later to a reduced maintenance combination later. But these studies - including the ACTG 343 in the US, the Trilege study in France and the Adam study in the Netherlands failed very quickly. Viral load quickly rebounded when 3 drugs were reduced to one or two drugs and most people developed drug resistance. [8]

About a decade later – through the noughties – monotherapy was studied again using boosted protease inhibitors, especially lopinavir/ritonavir (Kaletra) and then more recently the PIVOT study used darunavir/ritonavir monotherapy. Although these later results were much better than the first maintenance studies, dropping the use of other drugs – especially NRTIs (nukes) – generally led to higher rates of viral rebound and certainly were never as good as combinations with three active drugs. [9, 10]

Why are the new results so surprising and exciting?

The results with dolutegravir are surprising because they would not have been possible with any other single drug.

For the last 30 years, the vulnerability of HIV drugs to develop resistance has been a serious limitation of every HIV drug. This was why early studies using single and dual therapy only produced very short-term benefits. HIV is a rapidly evolving virus and unless viral load is reduced on ART to less than 50 copies/mL and kept this low, the development of drug resistance is nearly always inevitable. With some drugs and combinations, drug resistance takes time to accumulate slowly. But with others, resistance can occur within a few weeks. These results with dolutegravir could change everything, and some prominent researchers, including Professor Mark Weinberg, who has reported on this aspect of dolutegravir over several years, thinking this might play an additional role in strategies for a cure. [11]

In theory, because the results shouldn't have happened the researchers face new challenges in trying to explain them.

Looking further forward, a follow-on drug to dolutegravir with a similar structure (called cabotegravir) is in development with the same manufacturer as a long-acting injection. Until now, cabotegravir was believed to need support from other long-acting injectable HIV drugs. The new results with dolutegravir could mean that cabotegravir monotherapy injections might be effective on their own.

What are the cautions?

Although resistance didn't develop to dolutegravir in the large phase 3 registrational treatment-naive studies this was thought to be because dolutegravir was used in combination with NRTIs. A poster at EACS summarises these data. [12]

Also, although dolutegravir – if used early enough – can sometimes overcome drug resistance to other integrase inhibitors (notably to raltegravir and elvitegravir), this is not always the case, even using a higher double dose (50 mg twice-daily rather than once-daily).

Whether the mono and dual therapy results are sustained will depend on why dolutegravir is special and the mechanism for this protection is not yet understood. Drug resistance might be developing, but just at a very slow rate. Or dolutegravir might be causing a type of resistance that changes the structure of HIV in a way that makes it difficult to replicate - and this is why viral load stay so low.

If dolutegravir causes HIV to mutate in a way that makes other current drugs less effective, this might actually be a serious problem. Careful research is essential to look at this possibility as HIV has a long history of escaping from effective treatment and mutating so that it ultimately becomes more difficult to treat.

Another concern is that many people in the dolutegravir mono and dual therapy studies were on stable treatment. Unpredictable viral load rebound in a few cases – whether in the first weeks or after several years – might come with a risk of seroconversion symptoms and of becoming infectious again to sexual partners. This risk is at a time when the impact of treatment as prevention is only just getting established as a real and reliable strategy to prevent HIV transmission.

We need to understand the few cases where people had viral rebound, together with the relationship this has to previous use of integrase inhibitor treatment.

Why it is essential to wait for further research

For all the potential benefits, the following bulleted list shows why further research is needed before these mono and dual strategies can be tried outside a study setting.

- With longer follow-up, dolutegravir monotherapy might not be enough.
- With longer follow-up, dual therapy with dolutegravir and 3TC might not be enough.
- The short-term results may not last. Maybe not until a year, maybe not until a few years. Resistance might be developing, but just very slowly in a few people – or in everyone.

- Using only one or two drugs might cause HIV to change into a virus that is more difficult to treat, even for people without resistance to current drugs.
- A few cases have already been reported where monotherapy has not worked. Some of these people were stable on their previous combination but now have cross-resistance to all integrase inhibitors and cannot use them in the future.
- Current cases where monotherapy failed have involved earlier use of integrase inhibitors but this could also relate to transmitted drug resistance and natural mutations.
- Current resistance testing only has a limited sensitivity. Usually at least 20% of your virus needs to be resistant, or at least 1% in more specialised research tests.
- The unpredictability of viral rebound could be associated with serious symptoms similar to seroconversion.
- The unpredictability of viral rebound would reduce the impact of treatment as prevention and in the risk of transmission to sexual partners if condoms were not routinely used.
- Very few people have a clinical urgency to reduce treatment. Within a year or two, much more data will be available. Historically, maintenance therapy doesn't have a great history of successful results.
- Although the implications of less expensive treatment are important, the first focus should be on whether this strategy is both safe and effective for treatment. ART is already one of the most cost effective medical interventions, in all countries and at current prices.

Given these cautions, for people wanting to join a research study, the early data is encouraging, especially if there are clinical reasons for needing to use fewer drugs. If this is the case for someone, then the most cautious approach would be to include 3TC with dolutegravir as dual therapy, and have very close monitoring.

C O M M E N T

Although these studies generated interest at EACS, many people were cautious about the results.

The studies were all single-arm pilot trials in small groups of people with short periods of follow-up.

They all concluded that results need to be confirmed in larger studies with close follow up and where results are compared to using standard three-drug ART. The new studies will need to look into how effectively mono and dual therapy works in different body compartments - not just in results from blood tests.

Nevertheless, for people struggling on current ART, the results offer great hope if the early promise is sustained.

Even if turns out that dolutegravir monotherapy can only be relied on safely for 24 weeks with frequent monitoring, a fixed-time maintenance period might have extensive potential. This might be able to cover short periods where drug interactions, for example with chemotherapy, include an increased risk of side effects relating to NRTIs.

For many people, six months on dolutegravir monotherapy might get very close to the long outdated concept (and horrible term) of a drug holiday.

For global access, manufacturers ViiV Healthcare have already agreed to dolutegravir being included in the Patent Pool for generic companies to be able to produce. [13]

Several possible explanations have been suggested for why dolutegravir has not lead to resistance. One hypothesis is that the active drug attaches to the binding site on the virus for longer than other integrase inhibitors. Another is that resistance might be occurring, but the resulting virus is so dramatically changed that it is too unfit to replicate. [14]

More likely, is that the dolutegravir targets a section of the HIV genome that is both highly conserved and essential for replication. Again, if a change is taking place, the reduced fitness mean that it appears as if no ongoing replication is occurring. [15, 16]

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FUTURE MEETINGS

Conference listing 2015/16

The following listing covers some of the most important upcoming HIV-related meetings and workshops. Registration details, including for community and community press are included on the relevant websites.

7th International Workshop on HIV Persistence During Therapy

8 – 11 December 2015, Miami

<http://www.hiv-persistence.com>

European HIV Hepatitis Coinfection (EHHIC) Conference

10 – 11 December 2015, London

<http://www.bhiva.org>

International HIV Drug Resistance Workshop

20 – 21 February 2016, Boston

<https://www.informedhorizons.com/resistance2016>

6th HIV & Women Workshop

20 – 21 February 2016, Boston

<http://www.virology-education.com>

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

22 – 25 February 2016, Boston

<http://www.croiconference.org>

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

19–22 April 2016

<http://www.bhiva.org>

21st International AIDS Conference (IAS 2016)

17-22 July 2016, Durban

<http://www.aids2016.org>

Congress on HIV Therapy (Glasgow 2016)

23-26 October 2016

<http://hivglasgow.org>

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<http://www.i-Base.info>

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

- Introduction to ART (September 2015)
- 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).

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