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EDITORIAL

In this last issue of HTB for 2014, we lead with reports of UK stock-outs that resulted in people having to interupt treatment. This is unacceptable on every level.

Several themes then connect different meetings and reports throughout the rest of this issue.

The first of these might be a comment on the number of medical conferences and meetings that have taken place since the last issue of HTB. So while we include reports from the Glasgow Congress, the BHIVA Autumn meeting and the Southern African Clinicians Society conferences in our main reports, in On The Web we also link to the inaugural HIV Research for Prevention (HIVR4P) and the 5th HIV and Ageing Workshop. Most of these meetings include free to access webcasts, abstracts and presentations.

A second theme is whether some ARVs are currently being used at higher doses than necessary. This refers to efavirenz and tenofovir (TDF) – in reports from Glasgow – and darunavir (based on a review of recent publications and presentations). Dose optimisation of ARVs might reduce the cost of treatment, a theme expanded in detail in a review of Andrew Hill's presentation in Glasgow on potential dramatic savings to the NHS from future use of generic ARVs.

Many people believe that the potential for use of PrEP in Western countries will change in 2017 when TDF comes off patent. Generic TDF, with or without 3TC, could be commercially viable and individually affordable in the UK. Even with a 5-fold mark-up on current generic prices in low income countries, daily generic PrEP could cost less than £4 a week.

We report on two randomised European PrEP studies - PROUD and IPERGAY have both terminated the control arms based on DSMB-noted efficacy in the active arms. Although both studies are in gay men and transgender women, they show that PrEP can be highly effective in European countries.

These early results argue for prompt UK access to PrEP for people who otherwise are at high risk of becoming HIV positive next year. This same call is even made in the 2014 report on HIV in the UK from Public Health England, which we also review in this issue. HIV incidence in gay men reached a new high at 3250 diagnoses in 2013, many of which were likely to be recent infections, and 16% were in men younger than 24 years.

For HIV in the UK to benefit from both the impact of treatment as a prevention and PrEP, requires significantly reducing the percentage of people who are not yet diagnosed.

As the European testing *week* comes to a close as this issue goes to press, together with seasonal greetings for the upcoming holiday we need the New Year to make 2015 "the *year* of HIV testing".

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TREATMENT ALERT

ARV supply issues cause treatment interruptions in a UK clinic

Simon Collins, HIV i-Base

An email question to the i-Base treatment information service in September reported ARV stock-outs in the UK that resulted in patients having to interrupt HIV medication due to problems in drug supply. [1]

This case related to drug delivery services contracted to Healthcare at Home to be delivered to the HIV clinic in Taunton. Supply problems had been ongoing for several months.

Any UK clinic should be able to contact the closest hospital pharmacy where ARVs are routinely stocked. Between-clinic support should have been arranged in time to ensure continuous supply, even if this required a courier service that was later invoiced to the contractor.

It is difficult to understand why a UK clinic would allow problems to develop to the point that this happened not just once, but several times.

BHIVA guidelines are clear about risks from treatment interruptions. The first instance should have been a red flag for arranging an emergency interim solution that worked. Instead, the lack of supply seems to have been minimised as a problem, with one email referring to a "temporary disruption" in "a small number of patients".

Taunton stopped stocking ARVs after contracting all medicines to Healthcare at Home, including being delivered back to the clinic for patients to collect. These problems occurred even when prescriptions were ordered several weeks in advance.

No senior manager at the Taunton clinic elevated this to either a regional or national commissioning level. At the very least, an emergency plan should have been rapidly established at the hospital after the first case of non-delivery.

An additional two further cases of treatment interruptions occurred after patients attended the clinic to collect pre-ordered medications and were sent home with nothing.

Responses from within the hospital have been limited, with no hospital manager willing to respond formally.

A lack of response from Jo Cubbon, the Chief Executive, and Selina Riggs, the lead commissioner for HIV for the South West Specialist Commissioning Group, led to this issue being raised directly by community representatives on the Clinical Reference Group (CRG) and to commissioners at NHS England.

It is difficult to decide whether it was more disconcerting to hear that some commissioners were aware of an ongoing problem and yet had not resolved it or that some were unaware of such serious faults in the services that they are ultimately responsible for commissioning.

Importantly, within weeks of the alert, Taunton reversed its earlier policy and now stocks some ARVs at the hospital. We have heard from patients that this has improved the service. It is still unclear why this was not done months ago.

C O M M E N T

It is essential to raise this supply issue as a treatment alert because of a concern that this might happen in other clinics, especially given pressure within the NHS to privatise services.

Partly due to the intervention by i-Base, these incidents have now been formally classified as serious events. An internal investigation is now expected to take several months. Until this is resolved, these patients should be formally contacted to explain the process. This should include an applogy.

While services at Taunton have now been changed, the situation should never have arisen in the first place.

It highlights the need for continuous ARV supply to be clarified as a key commissioning standard that should be audited.

Anyone in a similar situation, should either raise it at the highest level in their hospital, or contact i-Base if you would like us to do so on your behalf.

This incident itself would also have been appropriate for an MP to raise as a question in parliament.

References

i-Base online Q&A service. Stock-out and non-delivery of ARVs in Taunton in the UK (and subsequent comments). 19th September 2014.

http://i-base.info/qa/10220

CONFERENCE REPORTS

12th Glasgow Congress on HIV Therapy

2-6 November 2014, Glasgow

Introduction

This two-yearly meeting always provides a good setting for important European research and has the advantage of having a single-track programme with no overlapping sessions.

Abstract are available on the conference website.

http://hivglasgow.org/abstracts

Many of the oral presentations are also available as webcasts:

http://hivglasgow.org/scientificprogramme

Reports in this issue of HTB are:

- Savings to the NHS predicted from switching to generic antiretrovirals
- Lower than standard doses of efavirenz effective in two studies
- Should tenofovir be dosed at 200–250 mg/day with protease inhibitors?
- 3TC inferior to FTC in Dutch cohort but interchangeable in other studies
- Suicide not associated with efavirenz use in D:A:D cohort

- Gender differences in use of cardiovascular disease-related interventions: D:A:D study
- Efavirenz decreases exposure to hormonal contraceptive implant
- Increased risk of ART-related hepatotoxicity in HIV positive pregnant women
- Darunavir pharmacokinetics in pregnancy and postpartum

Savings to the NHS predicted from switching to generic antiretrovirals

Polly Clayden, HIV i-Base

If everyone on HIV treatment in the UK switched from patented originator antiretrovirals to generics, there is the potential to save 1.25 billion in NHS drug costs over the next five years (2015-2019), according to modelling data presented at the 2014 HIV Drug Therapy Glasgow Congress.

The switch to generic antiretrovirals would involve HIV positive people increasing their pill count from and average of 2.3 to 3.5 pills a day.

Andrew Hill presented these findings on behalf of colleagues from St Stephens AIDS Trust, Chelsea and Westminster Hospital, and the Research Department of Infection and Population Health, University College, London.

Dr Hill explained that every year the number of people on antiretroviral treatment (ART) in the UK increases by 7-10%. The total number on ART could rise to over 100,000 by 2019, particularly with successful strategies to find the 20-25% of people with HIV who are currently undiagnosed.

Current antiretroviral drug costs to the UK compared to those for low-income countries are shown in Table 1. Prices can be discounted below these listed UK prices – typically by 30%.

Table 1: Current antiretroviral prices UK vs low-income countries *(per person per year £ sterling)*

Drug	NHS list price	Low-income countries
tenofovir	2880	34
emtricitabine (FTC)	1956	22
abacavir	2136	140
lamivudine (3TC)	1608	18
efavirenz	2400	30
nevirapine	2040	23
rilpivirine	2400	30
darunavir/r	3600	450
atazanavir/r	3636	150
raltegravir	5652	422

Sources: BNF 2014, CHAI 2013, MSF 2014.

Basic patents on individual drugs last for 20 years. After patents expire, drugs can be sold by generic companies at prices that can be 80-90% lower than the discounted originator prices. Table 2 shows how much generic drugs could cost in the UK.

Table 2: Potential prices for generic HIV drugs in UK? *(per person per year £ sterling)*

Drug	NHS list price	-30% (discount)	-80% (generic)	Date
tenofovir	2880	2016	403	2017
emtricitabine (FTC)	1956	1369	274	now (3TC)
abacavir	2136	1495	300	2016
3TC	1608	1126	225	now
efavirenz	2400	1680	336	now
nevirapine	2040	1428	285	now
rilpivirine	2400	1680	-	2023
darunavir/r	3600	2520	504	2017
atazanavir/r	3636	2545	509	2017
raltegravir	5652	3956	-	2025

Sources: BNF 2014, CHAI 2013, MSF 2014

There are also evergreen patents – by which originator manufacturers retain royalties on products with patents that would otherwise expire – on co-formulations of drugs. These evergreen patents can last over 10 years after the patents on the individual drugs expire.

Patents on AZT, 3TC, nevirapine, efavirenz and ritonavir have either already expired or are due to expire this year. Abacavir and lopinavir/ritonavir are due to expire in 2016, tenofovir, atazanavir and darunavir in 2017 and raltegravir in 2025. Co-formulated abacavir/3TC expires in 2019 and tenofovir/FTC in 2024. Patents for fixed dose combinations (FDCs) tenofovir/3TC/efavirenz and tenofovir/3TC/rilpivirine do not expire until 2026. The abacavir/3TC/dolutegravir patent expires in 2029.

At current prices FDCs in the UK cost upwards of £4500 per patient year: tenofovir/3TC/efavirenz £4500, tenofovir/3TC/rilpivirine £5200, and tenofovir/FTC/cobicistat/elvitegravir £7400. The price of abacavir/3TC/dolutegravir in the UK has yet to be announced. Dr Hill noted that using generic abacavir or tenofovir plus generic 3TC plus generic efavirenz or boosted protease inhibitor as single agents (three pills) the price of an ART regimen could be approximately £1000 per patient year in the UK.

For the generics model, the investigators assumed 72,000 people on ART in 2014 rising by 8% per year, with originator companies selling drugs to the NHS at 28% discount on list price. The other assumptions were that generic drugs are 80% cheaper than NHS prices and immediately after patent expiry people switch from originator to generic antiretrovirals.

UK treatment use was estimated using UKCHIC data from 2013; proportions of people using individual antiretrovirals are shown in Table 3.

Table 3: UK antiretroviral use 2013: UKCHIC cohort

NRTIs	
tenofovir	74%
FTC	68%
3TC	24%
abacavir	19%
AZT	6%

NNRTIs	
efavirenz	40%
nevirapine	16%
rilpivirine	5%
etravirine	4%

Protease inhibitors	
darunavir/r	19%
atazanavir/r	16%
lopinavir/r	8%
Integrase inhibitor	
raltegravir	4%

Two scenarios were used for the generic model:

Option 1 – Use only patented, co-formulated drugs (no generics, originator prices remain stable, dolutegravir introduced at a similar price to originator efavirenz).

Option 2 – 100% switch to generic drugs in the year of patent expiry (2014: 3TC, EFV, ABC, NVP, AZT; 2016: ABC, LPV/r; and 2017/8: TDF, DRV/r, ATV/r).

With Option 1 the average pill count remains at 2.3 per day, with Option 2 this would increase by 1.2 pills to 3.5 per day.

With efavirenz plus two NRTIs as first line ART, switches during 2015-2019 would be: in 2015 from FTC to generic 3TC, switch from Atripla to tenofovir plus generic 3TC plus generic efavirenz; 2016 switch to generic abacavir; 2017-19 switch to generic tenofovir. Generic atazanavir and darunavir would be introduced in 2017-2019. Originator integrase inhibitors and etravirine or rilpivirine would only be used for toxicity switching.

In order to better understand the implications of switching from FDCs to individual tablets, the investigators performed a meta-analysis of nine randomised head-to-head trials, including 2,568 participants. Endpoints included: virological failure, development of resistance, discontinuation due to adverse events, switch due to failure and adherence >95%. There was no significant benefit of FDCs vs individual tablet with regards to virological failure, resistance or discontinuation for adverse events. But, people receiving single tablets were more likely to switch treatment +2.6% (95% CI -0.4 to +5.2%), p=0.05 and there was more likelihood of full adherence with FDCs, +5% (95% CI 1.4 to +8.7%), p=0.007. All differences were within the 10% non-inferiority margin.

The generic model predicated annual NHS costs of antiretrovirals of £2.41 billion with Option 1 vs £1.16 billion with Option 2; a potential saving of £1.25 billion. Annual savings increased stepwise as more generic antiretrovirals became available. The relative costs of Option 1 vs Option 2 were £411 million vs £351 million in 2015, these costs were £559 million vs £168 in 2019.

C O M M E N T

This presentation caused quite a stir. Remarks from the audience afterwards included the suggestion that a change from FDCs might not be beneficial for patients and health systems in the long run, that people get attached to one pill once a day, and that changes in products cause confusion. Andrew Hill commented that for most people tolerability is usually more important than one versus two or three pills.

Many researchers and doctors have been very supportive of the potential cost savings to the NHS and have mentioned how much good could be done with this money particularly for HIV prevention and HCV treatment.

It is important that patients, payers, and doctors everywhere understand the difference between the cost and price of drugs. Andrew Hill and his group's work on pricing of drugs – notably the new HCV direct acting antivirals (DAAs) globally and antiretrovirals in middle income countries – is laudable, and gives enormous credibility to fair pricing and access campaigns.

Reference

Hill A et al. Predicted savings to the UK National Health Service from switching to generic antiretrovirals, 2014–2018. HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Oral abstract O-216. Journal of the International AIDS Society 2014, 17(Suppl 3):19497.
http://www.jiasociety.org/index.php/jias/article/view/19497

http://aps.mediasite.com/mediasite/Play/82986e5259d94163bd78fb97af5fcdb01d?usehtml5=true

Lower dose efavirenz effective in two studies

Polly Clayden, HIV i-Base

Efavirenz (EFV) dosed at 400 mg daily remained non-inferior to 600 mg at 96 weeks, and 300 mg was effective as maintenance HIV therapy, according to data from EFV two dose reduction studies presented at the 2014 HIV Drug Therapy Glasgow Congress. [1,2]

ENCORE1 was a multinational, double blind, placebo-controlled study that compared the efficacy and safety of 400 mg and 600 mg EFV with tenofovir/emtricitabine as first-line HIV treatment in adults. At 48 weeks, the primary analysis established that 400 mg EFV was non-inferior to 600 mg. [3]

Dianne Carey from the Kirby Institute, New South Wales, Sydney, Australia, presented data showing the durability, safety and efficacy from the extended follow up of the study.

The primary end point was proportions of participants with viral load <200 copies/mL using a 10% non-inferiority margin. There were 630 participants in the intention-to-treat (ITT) analysis: 321 and 309 received 400 mg and 600 mg EFV; the mean age was 36 years; 32% were women; 37%, 33% and 30% were African, Asian and Caucasian, respectively.

A total of 585 participants completed 96 weeks of randomised treatment: 299 and 286 on 400 mg and 600 mg EFV.

At 96 weeks 90.0% of participants in the 400 mg EFV and 90.6% in the 600 mg EFV arms had viral load <200 copies/mL, difference -0.6 (95% CI -5.2 to 4.0), p=0.72.

Non-inferiority was also shown for viral loads <50 copies/mL, difference -0.4 (95% CI -5.8 to 4.9) and was retained regardless of baseline viral load: ≥100,000 copies/mL, difference -1.6 (95% CI -8.9 to 5.6).

There was no difference between arms in time to loss of virological response >200 copies/mL, or change from baseline viral load.

The mean change from baseline CD4 count at 96 weeks was significantly higher in the 400 mg EFV arm: difference 25 cells/mm3 (95% CI 2 to 48), p=0.03. This difference was observed from week 4 of the study – Dr Carey commented that this difference might be an artefact and probably has no clinical significance.

A substantial proportion of participants (89%) reported adverse events (AEs) in the study; 5% were grade 3 or 4. There was no difference in the frequency or severity of AEs between arms: difference 0.09 (95% CI -4.73 to 4.90) p=0.97.

Participants receiving 600 mg EFV were significantly more likely to report an AE definitely or probably attributable to EFV: 47.9% vs 37.7%, difference -10.2% (95% CI -17.9 to -2.51) p=0.01. More participants stopped EFV due to related AEs in the 600 mg arm: 23.0% vs 8.3%, difference -7.3 (95% CI -14.9 to 0.4), p=0.07, but this did not reach significance. The proportions of participants with EFV related serious AEs was small, approximately 1%, with no difference between arms.

In a related presentation, Chien-Ching Hung from the National Taiwan University Hospital showed data from an open-label, single arm, observational therapeutic drug monitoring (TDM) guided switch study to 300 mg EFV maintenance ART among participants who were stable on 600 mg.

Dr Hung explained that a previous study from the same group found a considerable proportion of HIV positive Taiwanese adults receiving EFV at the standard dose had higher than recommended plasma concentrations – strongly correlated with weight and CYP 2B6 G516T SNP (associated with slower metabolism of EFV).

Based on the 48-week results of ENCORE1, the investigators looked at a reduced dose of EFV as maintenance therapy for people with high concentrations at the standard dose.

Participants were enrolled who had received EFV 600 mg containing ART for at least six months, with viral load <200 copies/mL, C12 EFV >2 ng/mL and who were not taking any concomitant medicines known to affect EFV concentrations.

The investigators designed a pill cutter to divide the 600 mg tablets in two. EFV C12 were determined 4 to 12 weeks after switch using high-performance liquid chromatography. CYP2B6 G516T polymorphisms were determined using polymerase-chain-reaction.

The primary endpoint was viral load <50 copies/mL in ITT analysis at 24 and 48 weeks.

A total of 157 participants were included: 94.3% men; mean age 39 years, weight 64 kg (32.4% <60 kg) and BMI 22; 25.8% HBsAg-positive and 6.0% anti-HCV-positive; and 42.3% had CYP2B6 G516T or TT genotypes.

The mean baseline EFV C12 plasma concentration before switch (n=150) was 3.43 mg/L (IQR 2.48 – 3.99), which decreased to 1.74 mg/L (1.34 – 2.09), giving a mean reduction of 47.0% (IQR, 38.3 – 55.1%) four weeks after switching. The extent of the reduction was similar across the whole population of polymorphisms.

The proportions of participants with viral load <50 copies/mL were 98.7% (n=157), 97.1% (n=138) and 98.6% (n=69) at baseline, two and three months respectively.

Almost 80% of participants reported EFV related adverse events at baseline and about 80% of these reported improvement after switching to the lower dose.

C O M M E N T

Results from ENCORE1 were first announced in July 2013. Subsequent discussions since have identified the need to confirm that the 400 mg dose will be robust in the presence of TB treatment and in the third trimester of pregnancy. Pharmacokinetic studies to look at these two questions are designed and ready to go. These need to be funded and completed.

References
1. Carey D. Efavirenz 400 mg daily remains non-inferior to 600 mg: 96 week data from the double-blind, placebo-controlled ENCORE1 study. HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Oral abstract 0421. Journal of the International AIDS Society 2014, 17(Suppl 3):19523
http://www.jiasociety.org/index.php/jias/article/view/19523
http://aps.mediasite.com/mediasite/Play/8387d9c242e0475f9061f79ca65e65e41d?usehtml5=true
2. Yang S-P et al. Effectiveness of a reduced dose of efavirenz plus 2 NRTIs as maintenance antiretroviral therapy with the guidance of therapeutic drug monitoring. HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Oral abstract 0422. Journal of the International AIDS Society 2014, 17(Suppl 3):19524
http://www.jiasociety.org/index.php/jias/article/view/19524/html
http://aps.mediasite.com/mediasite/Play/7734fa38a31343a782af56e52278bc7f1d?usehtml5=true
3. ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. The Lancet, 26 April 2014;383 (9927):1474 – 1482.
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)62187-X/abstract?rss%3Dyes

Should tenofovir dose be 200 – 250 mg when used with protease inhibitors?

Polly Clayden, HIV i-Base

In drug-drug interaction studies with boosted protease inhibitors and elvitegravir significantly increased concentrations of tenofovir disoproxil fumarate (TDF). A study presented at the 2014 HIV Drug Therapy Glasgow Congress suggested that this interaction might be cancelled out with a lower dose of TDF.

The efficacy of TDF 300 mg once daily was established in trials with efavirenz (EFV), which does not increase TDF drug levels. Lopinavir/ritonavir (LPV/r), darunavir/ritonavir (DRV/r), atazanavir/ritonavir (ATV/r) and elvitegravir/cobicistat (EVG/c) all increase TDF levels. TDF is associated with renal toxicity, particularly in combination with protease inhibitors.

Andrew Hill and colleagues from Liverpool University and St Stephens AIDS Trust, Chelsea and Westminster Hospital, London performed a literature search to determine the effects of these boosted antiretrovirals on TDF plasma concentrations.

The search revealed increases in TDF AUC of +32%, +37%, +22% and +23% with LPV/r, ATV/r, DRV/r and EVG/c, respectively.

Assuming linear dose-proportional pharmacokinetics – seen in TDF dose-ranging studies – the investigators predicted plasma concentrations using paediatric tablets, available at 200 mg and 250 mg strengths would be bioequivalent to TDF 300 mg given with EFV: GMR 1.26 (95% CI 1.14 to1.38).

Using the 250 mg tablet was predicted to achieve:

	TDF AUC (95% CI)	TDF Cmin (95% CI)
LPV/r	+10% (+4 to +15)	+26% (+14 to +38)
ATV/r	+14% (+8 to +21)	+7% (+1 to +13)
DRV/r	+2% (–9 to +12)	+14% (–1 to +31)
EVG/c	+2% (–3 to +16)	+4% (–3 to +13)

Using the 200 mg tablet these predicted values were:

	TDF AUC (95% CI)	TDF Cmin (95% CI)
LPV/r	+12% (–16 to –7)	+2% (–8 to +11)
ATV/r	–8% (–13 to –3)	–14% (–18 to –9)
DRV/r	–18% (–26 to –10)	–8% (–20 to +5)
EVG/c	–18% (–22 to –7)	–16% (–22 to –9)

All were in the bioequivalent range respective to 300 mg TDF given with EFV.

The investigators commented that available lower doses of TDF could compensate for the drug-drug interaction with boosted protease inhibitors and elvitegravir, while maintaining efficacy. They noted that TDF toxicity might be over estimated in clinical trails were it is only combined with these boosted antiretrovirals.

Reference

Hill A et al. Should the dose of tenofovir be reduced to 200–250 mg/day, when combined with protease inhibitors? HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Poster abstract P-51. Journal of the International AIDS Society 2014, 17(Suppl 3):19583

http://www.jiasociety.org/index.php/jias/article/view/19583

3TC inferior to FTC in Dutch cohort but interchangeable in other studies

Polly Clayden, HIV i-Base

The Dutch national observational cohort found emtricitabine (FTC) was associated with better virological response than lamivudine (3TC) in a study presented at HIV Drug Therapy Glasgow Congress 2014. [1]

The study was also published simultaneously in Clinical Infectious Diseases on 3 November 2014, and an accompanying commentary to the journal article compared this finding with data from randomised trials and cohorts with contradictory results. [2, 3]

The AIDS Therapy Evaluation in the Netherlands (ATHENA) study has collected data on people in HIV care since January 1996. By December 2012, the cohort included 21,012 HIV positive people registered in the Netherlands; 20,676 (98.4%) had consented to be included.

Casper Rokx and colleagues from ATHENA performed the comparison of virological responses to 3TC and FTC. The investigators used multivariate and Cox proportional hazard models; sensitivity analyses included propensity score adjusted models.

Between 2002 and 2012, there were 4740 treatment naive participants who started 3TC- or FTC-containing first-line antiretroviral treatment (ART). Participants received 3TC or FTC in the following regimens: 3TC/efavirenz (EFV)/tenofovir (TDF) (n=535), FTC/EFV/TDF (n=3343), 3TC/nevirapine(NVP)/TDF (n=193) and FTC/NVP/TDF (n=669).

At baseline the participants' mean age was 40 years. A greater proportion of men received FTC (88.0% vs 76.4%): MSM (69.2% vs 47.0%) and originally from Western countries (70% vs 53.7%). The median year of starting ART was 2004 for 3TC vs 2009 for FTC. Participants receiving FTC had higher median CD4 count (260 vs 184 cells/mm3) and lower median viral load (82,173 vs 100,000 copies/mL). About 25% of participants receiving 3TC started treatment with CD4 count <100 cells/mm3 vs 12% receiving FTC.

The investigators presented an on-treatment analysis of 3440 participants at 48 weeks. Of the remainder 100/4740 (2.1%) were lost to follow up and 831 (17.5%) had discontinued treatment (largely because of toxicity). A further 369 (7.8%) had no viral load data close to the 48-week analysis – the investigators noted that these participants were evenly distributed among the four regimen groups.

At the time of analysis 38/352 (10.8%) participants receiving 3TC/EFV/TDF had virological failure (defined as $\leq$ 400 copies/mL at 48 weeks $\pm$ 10 weeks) vs 88/437 (3.6%) receiving FTC/EFV/TDF: odds ratio (OR) 3.23 (95% CI 2.17-4.81). For NVP-based regimens, 43/159 (27.0%) participants receiving 3TC/TDF/NVP vs 54/492 (11.0%) receiving FTC/TDF/NVP had virological failure: OR 3.00 (95% CI 1.92-4.72). Both comparisons p<0.001.

The adjusted OR for virological failure were: 1.78 (95% CI 1.11–2.84), p=0.016, with 3TC/TDF/EFV vs FTC/TDF/EFV, and 2.09 (95% CI 1.25–3.52), p=0.005, with 3TC/TDF/NVP vs FTC/TDF/NVP. Analyses by intention to treat and propensity score adjusted models gave similar results.

The time to virological suppression was not significantly different between 3TC and FTC-based ART by 48 weeks. There was no difference in virological failure within 240 weeks among participants receiving 3TC and FTC-based ART who achieved viral suppression <400 copies/mL on their initial regimen.

In 267/4740 participants – 234 who failed within 240 weeks and 33 by week 48 – those receiving 3TC-based regimens had a higher median viral load at failure than those on FTC: respectively 49,231 copies/mL vs 4230 copies mL, p<0.001.

There was no difference in acquired NRTI or NNRTI resistance in 88 participants (44 from the 3TC and 44 from the FTC groups) with $\geq$1000 copies/mL at virological failure and no recorded baseline resistance. The prevalence of primary mutations M184V/I and K65R was also no different between the two groups.

The investigators concluded that their findings suggest that 3TC is not interchangeable with FTC for first line ART.

In the accompanying editorial, Ford et al note that three randomised clinical trials – including 1242 participants – have directly compared 3TC and FTC. The pooled results from the trials found no difference in virological suppression, relative risk (RR) 1.03 (95% CI 0.96-1.10) or virological failure, RR 0.93 (95% CI 0.74-1.18). But the risk of virological failure was three times higher for participants receiving 3TC vs FTC the ATHENA cohort, RR 2.99 (95% CI 2.08-4.30).

"How should clinical guidelines respond to this seemingly contradictory evidence from three randomised trials vs a nonrandomised cohort study?" the authors ask. They note that according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) randomised trials are generally rated as high quality and cohort studies as low quality. Although data from cohort studies can often be very useful in HIV, randomised trials are the best way to make comparisons between drugs. It is not possible to ensure that observed differences between treatments are not due to differences between populations.

They comment that the comparison groups in the ATHENA cohort study by Rokx at al were unbalanced both with respect to region of origin, between Western and sub-Saharan settings, and temporally with median year of ART start 2004 for 3TC and 2009 for FTC. Participants receiving 3TC also had a higher viral load and lower CD4 count at baseline, were more likely to be injection drug users, coinfected with hepatitis B and managed in a large treatment programme. These differences are impossible to fully correct for through methods like propensity scores.

Ford et al point out that the important differences between the two groups in the ATHENA cohort mean the discrepancy between this study and the results from randomised controlled trials could be explained by study design rather than actual differences between the two antiretrovirals.

Rokx et al suggest that additional randomised trials are needed to evaluate 3TC vs FTC, Ford et al agree that such evidence would be valuable and, alongside the evidence to date, might have implications for future guidelines. "In the meantime, on the basis of the currently available randomised evidence, we conclude that lamivudine and emtricitabine can be considered to be interchangeable", they write.

C O M M E N T

It is unclear why this study was published (and presented) for the reasons Ford et al describe. 3TC and FTC should continue to be considered interchangeable.

Reference

1. Rokx C et al. More virological failure with lamivudine than emtricitabine in efavirenz and nevirapine regimens in the Dutch nationwide HIV Cohort. HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Oral abstract O154. Journal of the International AIDS Society 2014, 17(Suppl 3):19491
   http://www.jiasociety.org/index.php/jias/article/view/19491
2. Rokx C et al. Increased virological failure in naive HIV-1-infected patients taking lamivudine compared with emtricitabine in combination with tenofovir and efavirenz or nevirapine in the Dutch nationwide ATHENA cohort. Clin Infect Dis. Advance access 3 November, 2014.
   http://cid.oxfordjournals.org/content/early/2014/11/03/cid.ciu767.full.pdf+html
3. Ford N et al. Comparative efficacy of lamivudine and emtricitabine: comparing the results of randomised trials and cohorts. Clin Infect Dis. Advance access 3 November, 2014.
   http://cid.oxfordjournals.org/content/early/2014/11/03/cid.ciu767.full.pdf (PDF)
4. Puls R et al. A daily dose of 400mg efavirenz (EFV) is non-inferior to the standard 600mg dose: week 48 data from the ENCORE1 study, a randomised, double-blind, placebo controlled, non-inferiority trial. 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 30 June – 3 July 2013, Kuala Lumpur. Oral late breaker abstract WELBB01. http://pag.ias2013.org/Abstracts.aspx?SID=74&AID=3137

Suicide not associated with efavirenz use in the D:A:D cohort study

Simon Collins, HIV i-Base

An analysis from the D:A:D cohort study, presented as an oral abstract by Colette Smith at the 2014 HIV Drug Therapy Glasgow Congress, was notable for reporting no association between suicide in HIV positive people taking efavirenz in European cohorts. [1]

This is important because last year a combined analysis of four studies from the US ACTG network reported a three-fold higher suicide rate in people randomised to efavirenz (n = 3241) compared to non-efavirenz (n = 2091) combinations, even though a relatively low number of actual or attempted suicides were reported (n=22). Suicidality incidence in the ACTG study was 8.08 vs 3.66 per 1000 person-years (47 vs 15 events), in the efavirenz vs efavirenz-free group respectively (hazard ratio, 2.28 [95% CI, 1.27 to 4.10]; p=0.006). [2]

The side effects profile for efavirenz is complex in that efavirenz can affect mood changes, and both suicidal ideation and suicide have been reported. A history of depression and anxiety is a contraindication that makes efavirenz unsuitable for approximately 10% of HIV positive people. A further 10-20% who start with efavirenz, additionally switch to an alternative within the first year.

The potential for underestimating the impact of severe mood changes in clinical management prompted the D:A:D cohort to see whether similar findings to the ACTG study were recorded in this large European cohort collaboration. The analysis included data from almost 49,717 patients followed prospectively, using CoDe methodology that allows for multiple causes of death to be recorded, including one underlying cause, one immediate cause, and up to four contributory causes. The primary outcome in this analysis, included suicide or psychiatric illness listed as any cause, analysed by current ARV use.

All cause mortality included 4420 deaths from 371,333 person years of follow-up (rate 11.9 per 1000 PY). Suicide and psychiatric illness was the underlying cause in 133 cases (0.52 per 1000 PY) and underlying, immediate or contributory cause in 482 cases (1.30 per 1000 PY).

In analysis adjusted for age, gender, nadir and current CD4 count, time since diagnosis, cohort and HIV acquisition risk, neither use of efavirenz or other ARVs or being on ART were associated with suicide.

However, the association between HIV treatment and the risk of suicide being an underlying cause of death was significantly higher in treatment-experienced patients who had discontinued ARVs compared to treatment naive patients: adjusted IRR 3.24; 95%CI 1.95, 5.38. Comparable results were reported for suicide to be any contributory factor: adjusted IRR 2.29; 95%CI 1.63, 3.21.

Death from suicide/psychiatric disease was more common for lower current CD4 count, men, older age and if IDU was the HIV transmission risk.

C O M M E N T

An important part of the conclusion to this talk was a statement that the results do not support a lack of association between efavirenz and suicide. Instead, the analysis provides reassurance that the way efavirenz is being used in these European cohorts is not leading to increased suicide rates.

References

1. Smith C et al. Lack of association between use of efavirenz and death from suicide: the D:A:D Study. HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Oral abstract O315. Journal of the International AIDS Society 2014, 17(Suppl 3):19512.
   http://www.jiasociety.org/index.php/jias/article/view/19512
   http://www.cphiv.dk/Portals/0/DAD%20O315.pdf (PDF)
2. Mollan et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Ann Intern Med 2014.161(1):1-10. doi:10.7326/M14-0293.
   http://annals.org/article.aspx?articleid=1884528

Gender differences in use of cardiovascular disease-related interventions: D:A:D study

Polly Clayden, HIV i-Base

Use of most cardiovascular disease (CVD) interventions was lower among women than men in the D:A:D study, according to data presented at the 2014 HIV Drug Therapy Glasgow Congress.

There is limited data on potential gender differences in the use of interventions to prevent and treat CVD in HIV positive people. D:A:D is an observational study of more than 49,000 people with HIV from 11 cohorts in Europe, Australia and the USA, set up to investigate associations between antiretroviral use and CVD. Data are collected prospectively.

D:A:D investigators evaluated whether gender differences exist among the study participants. Camilla Ingrid Hatleberg presented findings on behalf of the D:A:D group.

The investigators looked at the use of: lipid lowering drugs (LLDs), angiotensin converting enzyme inhibitors (ACEIs), anti-hypertensives and invasive cardiovascular procedures (ICPs).

Follow-up in the gender study was from 1 February 1999 until 1 February 2013. People with myocardial infarction (MI) or stroke at baseline (gender study entry) were excluded.

The investigators calculated the rates of initiation of CVD interventions for the whole period of follow-up and for circumstances when people are known to be at higher CVD risk according to subgroups: 1) total cholesterol >6.2 mmol/L, 2) triglyceride >2.3 mmol/L, 3) hypertension, 4) previous MI, 5) diabetes, 6) age >50 years, 7) predicted 10-year Framington CVD risk score >10%. Poisson regression was used to assess whether initiation rates were higher in men than women, after adjusting for potential confounding.

The number of women in D:A:D was considerably lower than the number of men, 13,039 vs 36,664; and they were younger, median 34 vs 39 years, and less likely to smoke, 29 vs 39%, than men; all comparisons p=0.0001.

The total follow up time spent in one of the seven high risk subgroups was longer for men than women: 269,705 vs 97, 065 person years spent (PYS). Men spent a greater proportion of time with high triglycerides, 30.1 vs 15.3%; being over 50 years, 28.9 vs 15.3%; and with high CVD risk score, 25.6 vs 4.1%.

Women spent the largest proportions of time at risk with high trigycerides, hypertension and being over 50 years, all approx 15%.

Overall, women received ICPs at a rate of 0.07/100 person-years (PYRS) compared to 0.29/100 PYRS in men. The rates of initiation of LLDs (1.28 vs 2.46), anti-hypertensives (1.11 vs 1.38) and ACEIs (0.82 vs 1.37) were all significantly lower in women than men, p=0.001. But in the group of women with established high CVD risk scores, initiation of all LLDs was slightly higher in women than men. Rates of initiation of anti-hypertensives and ACEIs were slightly higher in women than men for women with previous MI; and rates of initiation of anti-hypertensives were slightly higher in women with hypertension.

Unadjusted relative rate (RR) of receipt of the four types of interventions between women and men: LLDs 0.52 (95% CI 0.49 – 0.56); ACEIs 0.60 (95% CI 0.56 – 0.65); anti-hypertensives 0.83 (95% CI 0.78 – 0.89); and ICPS 0.25 (95% CI 0.20 – 0.32) (all comparisons p=0.0001).

Once adjusted for potential confounders (age, calendar year, BMI, total cholesterol, triglycerides, hypertension, previous MI, diabetes, and moderate/high predicted 10 year CVD risk score) RR for receipt of all interventions except anti-hypertensives were attenuated but remained significantly lower in women than men. Adjusted RR: LLDs 0.80 (95% CI 0.75 – 0.86); ACEIs 0.80 (95% CI 0.74 – 0.87); and ICPS 0.49 (95% CI 0.38 – 0.63), all comparisons p=0.0001.

After adjustment the RR for anti-hypertensives shifted from a lower to higher rate in women: 1.21 (95% CI 1.13 – 1.30), p=0.0001. Dr Hatleberg remarked that this phenomenon was driven mainly by hypertension itself and CVD risk score >10%.

These RR remained after sensitivity analyses adjusting for ethnicity, smoking, AIDS, CVD family history and stroke, and with total cholesterol, triglycerides and blood pressure as continuous covariates.

Dr Hatleberg concluded that action should be taken to ensure HIV positive women and men are properly monitored for CVD and receive appropriate interventions. She suggested that women might be monitored less frequently as guidelines focus on moderate/high risk and they are more likely to be low CVD risk.

Reference

Hatleberg CI et al. Gender differences in HIV-positive persons in use of cardiovascular disease-related interventions: D:A:D study. HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Oral abstract O324. Journal of the International AIDS Society 2014, 17(Suppl 3):19516

http://www.jiasociety.org/index.php/jias/article/view/19516

Webcast: Wednesday 5 November, Co-morbidities and Complications Part II.
http://hivglasgow.org/scientificprogramme#wednesday

Efavirenz decreases exposure to hormonal contraceptive implant

Polly Clayden, HIV i-Base

Efavirenz (EFV) significantly decreases exposure to levonorgestrol – the active progesterone component of one commonly used contraceptive implant – according to findings from a study conducted in Uganda, presented at the HIV Drug Therapy Glasgow Congress 2014.

The study showed levonorgestral concentrations in women receiving EFV-based antiretroviral treatment (ART) that were approximately half of those in women not receiving ART, despite the EFV group having significantly lower body weight. But concentrations of levonorgestral in women receiving nevirapine (NVP)-based ART were approximately one third higher than the control group.

Kimberly Scarsi presented these findings on behalf of investigators from University of Nebraska Medical Center, Makerere University, Uganda, and Liverpool University.

Both EFV and NVP induce cytochrome P450 3A, giving the potential for drug-drug interactions with concomitant medications.

The aim of the study is to characterise the pharmacokinetics (PK) of levonorgestrol released from a sub-dermal implant over six months in HIV positive Ugandan women receiving EFV- or NVP-based ART. Interim 24-week data were presented at the conference.

The study is a non-randomised, parallel group study that compares levonorgestrol PK in Ugandan women not yet eligible for ART (control group, n=17) and on stable EFV- (n=20) or NVP- (n=20) based ART.

The women had a two-rod (75 mg/rod) levonorgestrol sub-dermal implant inserted at enrolment. Sampling for PK was performed before the implant and at weeks 1, 4, 12 and 24 after insertion. The investigators used a validated LC-MS/MS method, with an assay calibration range of 50–1500 pg/mL to analyse levonorgestrol concentrations.

At baseline, participants were a mean age of 31 years; CD4 counts were similar between the control, EFV and NVP groups. All women receiving ART were virologically suppressed. Women in the control group had a higher baseline body weight (73 kg) compared to those in the EFV group (59 kg), $p<0.01$, or NVP (63 kg), $p=0.03$, groups.

At week 24 the EFV:control and NVP:control AUC 0-24 ng*wk/mL geometric mean ratios were respectively: 0.56 (90% CI 0.55 – 0.58) and 1.23 (90% CI 1.18-1.31), both $p<0.01$.

Adjusted for weight these values were: 0.47 (90% CI 0.45 – 0.50) and 1.09 (90% CI 1.02 -1.20).

Dr Scarsi noted that in the EFV group, three participants had levonorgestrol concentrations below the proposed level for contraceptive efficacy at two time points. All participants receiving NVP had concentrations above the proposed level for efficacy and no adverse events were observed in this group.

She concluded that levonorgestrol concentrations were reduced by 40-54% over 24 weeks in women receiving EFV-based ART. Conversely women receiving NVP-based ART had consistently higher concentrations by 32-39%, although the increase was less pronounced after controlling for body weight, which gave a 16-21% increase.

“Identifying an effective strategy to provide hormonal contraception options for women receiving EFV-based ART remains a critical public health priority”, she said.

Reference

Scarsi K et al. Efavirenz- but not nevirapine-based antiretroviral therapy decreases exposure to the levonorgestrel released from a sub-dermal contraceptive implant. HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Oral abstract 0131. Journal of the International AIDS Society 2014, 17(Suppl 3):19484.

http://www.jiasociety.org/index.php/jias/article/view/19484

Increased risk of ART-related hepatotoxicity in HIV positive pregnant women

Polly Clayden, HIV i-Base

Evidence from the UK and Ireland that pregnancy increases the risk of liver enzyme elevation (LEE) among pregnant women on antiretroviral treatment (ART) was shown at the 2014 HIV Drug Therapy Glasgow Congress.

Susie Huntington – who presented data, on behalf of colleagues from the UK Collaborative HIV Cohort (UK CHIC) study and the UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC) –noted that previous studies comparing the rate of LEE in pregnant and non-pregnant women on ART have produced conflicting results.

The analysis included combined data from UK CHIC – an observational cohort study of HIV positive women at 19 collaborating centres – and NSHPC – an observational surveillance study of HIV positive women accessing antenatal care in the UK and Ireland.

Pregnant and non-pregnant women aged 16 – 49 years, starting ART 2000 – 2012, with at least one alanine aminotransferase (ALT) measurement on ART were included. Ten women with severe baseline LEE were excluded.

ALT data was assessed according to the Division of AIDS toxicity guidelines to identify factors associated with LEE (grade 1 - 4). LEE was defined as $\geq$ 1.25 times the upper limit of normal (ULN) women with baseline ALT$\leq$ULN (n=3511) and ALT $\geq$ 1.25 times the baseline ALT women with baseline ALT>ULN (n=304).

The investigators used Cox proportional hazards to assess the associations between fixed covariates –ethnicity, exposure group, HBV/HCV co-infection, prior ART use, and age, year, pregnancy status, viral load and CD4 count at ART start –and time-dependent covariates –pregnancy status, age, year, CD4 count, viral load, duration on ART, antiretroviral drugs in regimen – and the risk of LEE.

Among 3815 women, the rate of LEE was 14.5/100 person years (95% CI 11.4 – 17.5) in pregnancy and 6.0/100 person years (95% CI 5.6 – 6.4) outside pregnancy. ART was started in pregnancy in 541 and 735 conceived on ART, the respective LEE rates were for these women were: 36.3/100 person years (95% CI 27.3 – 45.2) and 5.8/100 person years (95% CI 3.5 – 8.0).

LEE occurred at a median of 30 weeks (IQR 25 – 33) gestation and 8 weeks (IQR 4 – 12) after ART was started in women who began treatment in pregnancy. For those who conceived on ART LEE occurred at median 16 weeks (IQR 9 - 28) gestation.

The risk of LEE was increased during pregnancy, adjusted hazard ratio (aHR) 1.66 (95%CI: 1.3 – 2.1), p<0.001.

Other factors associated with LEE were: lower CD4 count (<250 vs 251–350 cells/mm^3) aHR 1.25 (1.02–1.54), p=0.05; HBV/HCV co-infection, aHR 1.85 (1.5 – 2.3), p<0.001; HIV acquired through injecting drug use, aHR 1.55 (1.1 –2.2), p=0.02 vs heterosexually; and calendar year, aHR 1.05 (1.0 –1.1), p<0.001 per one year increase.

Two antiretrovirals were associated with increased risk of LEE: efavirenz aHR 1.26 (1.1 –1.5), p=0.005; and nevirapine aHR 1.54 (1.3 –1.9), p <0.001.

AZT was associated with decreased risk of LEE, aHR 0.73 (0.6 –0.9), p<0.001; as was increasing time on an NNRTI-based regimen, aHR 0.9 (0.9 – 1.0), p<0.001 per additional year.

Pregnancy status, CD4 count or previous ART use, when starting ART, ethnicity or age, were not associated with increased risk of LEE.

Reference

Huntington S et al. Does pregnancy increase the risk of ART-induced hepatotoxicity among HIV-positive women? HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Oral abstract O133. Journal of the International AIDS Society 2014, 17(Suppl 3):19486

http://www.jiasociety.org/index.php/jias/article/view/19486

Darunavir pharmacokinetics in pregnancy and postpartum

Polly Clayden, HIV i-Base

Data presented at the 2014 HIV Drug Therapy Glasgow Congress found once-daily darunavir/ritonavir (DRV/r) 800/100 mg achieved adequate therapeutic drug levels during pregnancy in most cases.

John Lambert showed findings on behalf of colleagues from Mater and Rotunda Hospitals, University College Dublin, and Department of Pharmacology and Therapeutics, University of Liverpool from a prospective, open-label study of pregnant, HIV positive women receiving DRV/r as part of their routine care.

The investigators looked at pharmacokinetics (PK) of DRV/r 800/100 mg once daily during pregnancy and postpartum.

DRV plasma trough concentrations were determined in the first and/or second and/or third trimester and postpartum using validated HPLC-MS/MS (lower limit of quantification of 78 ng/mL). Where possible paired maternal and cord blood samples were taken at delivery.

Twenty-three women (14 black African, 9 white) were enrolled in the study. At baseline their median CD4 count was 354 cells/mm3 and viral load was 555 copies/mL. All but two women were <50 copies/mL (114 and 176 copies/mL) at delivery. About half the women started ART in pregnancy at a median gestational age of 19 weeks; the majority (78%) received tenofovir/emtricitibine backbone ART.

There were 23 live births and no cases of vertical transmission.

The investigators found the DRV plasma concentrations were 47% and 52% lower in the second and third trimesters compared with postpartum, p<0.02. All accept one woman achieved minimum DRV trough concentrations for wild type (55 ng/mL) throughout pregnancy. All except for four women in the third trimester achieved minimum trough concentrations for protease inhibitor resistant virus (550 ng/mL).

Geometric mean DRV plasma concentration was: 3790 ng/mL (n=1), 1323 ng/mL (95% CI 864 - 1782), 1195 ng/mL (95% CI 914 - 1475) and 2511 ng/mL (95% CI 1705 - 3317) in the first, second and third trimesters and postpartum respectively. Second trimester vs post partum, p=0.02, and third trimester vs post partum, p=0.003.

Maternal and cord DRV concentrations were available for 10 mother/baby pairs. Mean maternal DRV concentration at the time of delivery was 1668 ng/mL (range 607 - 5528), and mean cord DRV was 254 ng/mL (<LLQ - 745). The median cord to maternal blood ratio was 0.11 (0.06 – 0.49). Dr Lambert concluded that in most cases examined, DRV/r 800/100 mg once daily achieved adequate therapeutic drug levels during pregnancy. Reduced DRV concentrations in the second and third trimesters suggest TDM should be used in this population. He commented that the case for switching to twice daily dosing – as recommended by BHIVA and other guidelines – might not outweigh the advantages of continued once daily dosing. Although twice daily might be necessary for women with resistant virus or who start treatment in late pregnancy.

C O M M E N T

Although total DRV exposure decreases during pregnancy, studies have shown no significant changes in unbound DRV concentration compared with postpartum – there are limited data to characterise this for the currently available PIs and a protein binding effect has only been studied in lopinavir. Lambert et al plan to examine the effect of pregnancy and protein binding with DRV in their cohort.

For dosing DRV/r, BHIVA pregnancy guidelines currently recommend: "Consider twice-daily darunavir if initiating darunavir- based ART or if known resistance." (Grading2C) The guidelines also note that the clinical relevance of pharmacokinetic studies such as the one above has yet to be determined. When a woman conceives on DRV/r-based ART and has a fully suppressed viral load on a once-daily regimen, the guidelines suggest this is continued. A more cautious approach using twice-daily DRV/r can be considered if starting ART in pregnancy with DRV/r or when there is known protease inhibitor resistance.

The guideline writing group note that although the pharmacokinetic data are consistent across studies, the virological impact during pregnancy and post partum are unknown. Such outcome data are needed.

Reference

Lambert J et al. Darunavir pharmacokinetics throughout pregnancy and postpartum. HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Oral abstract O132. Journal of the International AIDS Society 2014, 17(Suppl 3):19485

http://www.jiasociety.org/index.php/jias/article/view/19485

http://aps.mediasite.com/mediasite/Play/181c76b8039e4498937eeb886f3a7c4f1d?usehtml5=true

CONFERENCE REPORTS

BHIVA Autumn Conference 2014

9-10 October 2014, London

Introduction and webcast highlights

The BHIVA Autumn conference was held this year on 9-10 October 2014.

Presentations and webcasts online are posted promptly after the meeting as a free online access.

The report in this issue of HTB is:

- Good management of HIV positive pregnant women in UK – with some room for improvement

Good management of HIV positive pregnant women in UK – with some room for improvement

Polly Clayden, HIV i-Base

Management of HIV positive pregnant women is broadly in line with the British HIV Association (BHIVA) guidelines, according to results of a national survey presented at the 2014 BHIVA Autumn Conference.

Yvonne Gilleece from the Royal Sussex County Hospital showed findings from this audit in which lead clinicians at UK HIV services were invited to participate. The respondents were asked to consult maternity and paediatric colleagues for relevant data. Responses were from 112 HIV services with 124 associated maternity services.

Dr Gilleece compared guideline recommendations to survey responses for the following categories:

Working in multidisciplinary teams

The guidelines recommend multidisciplinary working, in teams including a dedicated specialist midwife and/or a women's HIV clinical nurse specialist.

The survey revealed that 111 of the 112 services have multidisciplinary teams, and only one does not. All of the 110 services with a description of the team included an HIV physician, one had no obstetrician, two no paediatrician and eight had no midwife.

Twenty-nine (26%) of the services had neither an HIV midwife nor a women's clinical nurse specialist, but 31 (28%) had both, 29 (26%) and 21 (19%) had an HIV midwife and a women's clinical nurse specialist respectively. Two services (0.02%) did not respond.

Time to be seen in HIV clinic

Following diagnosis via routine antenatal screening, the guidelines recommend women needing antiretroviral treatment (ART) for their own health start within two weeks.

Forty (35.7%) HIV services reported that women were seen in an HIV clinic on the same or the next working day as their diagnosis, 23 (20.5%) reported within two to three days, 29 (25.9%) within a week and 19 (17.0%) in one to two weeks. One service (0.9%) did not answer this question.

Sexual health screening

Screening for sexually transmitted infections (STIs) near the start of pregnancy is recommended for newly diagnosed pregnant women and suggested for all HIV positive pregnant women. The guidelines also state that a repeat screening at 28 weeks might be considered.

The survey found that 84 (75.0%) services screen all women with HIV for STIs at the start of pregnancy, 24 (21.4%) screen women who are diagnosed in pregnancy and three (2.7%) only screen women who are considered to be at risk. There was no answer from one service (0.9%).

Repeat screening for all women with HIV was undertaken in 55 (49.1%) services, five (4.5%) screened women who planned a vaginal delivery, 50 (44.6%) those that were considered to be at risk and/or had an STI earlier in pregnancy, and two (1.9) for other unspecified reasons.

ART in pregnancy

The majority of HIV services (109, 97.4%) have a policy for ART in pregnancy, two do not and one gave no answer.

Antiretroviral regimen preferences were largely as recommended in the guidelines, but 35 (31.3%) services included boosted darunavir among preferred drugs and seven (6.3%) included nevirapine for women with viral load <10,000 and CD4 >350 cells/mm3.

Raltegravir was quite widely used for women presenting late (>28 weeks) with viral load >100,000 copies/mL: 56 (50%) services did so routinely, 43 (38.4%) might use raltegravir, but 11 (9.8%) had no policy, as the situation had not arisen. Only one (0.9%) service would not use raltegravir and one (0.9%) was not sure.

Resistance testing after short-term ART

The guidelines recommend a resistance test after stopping a short course of ART in pregnancy to ensure mutations are not missed due to reversion to wild type virus while a woman is off treatment.

About half (55, 49.1%) of the services do routine resistance tests in this situation. The procedure is not routine for 49 (43.8%) and eight (7.1%) services were not sure.

Of those testing routinely, 77.4% do so within six weeks but 7.5% defer until re-starting ART.

Urgent HIV testing

For women presenting in labour, with ruptured membranes, and those needing to deliver with no HIV result the guidelines recommend and urgent HIV test.

The need for urgent testing had not arisen for 55 (49.1%) HIV services; testing was provided without problems by 40 (35.7%), but 10 (8.9%) services had experienced problems. The tests took over two hours to provide during working hours at 21(18.8%) services and outside working hours at 56 (50.0%).

Mode of delivery

The majority (107, 95.5%) of services have a delivery policy for HIV positive women, but two (1.8%) had no policy and three (2.7%) were not sure.

For women on ART with viral load <50 copies/mL at 36 weeks, the guidelines recommend planned vaginal delivery and this is the policy for 95 (84.8%) services. Maternal choice is policy at nine (8.0%) and a pre-labour Caesaren section at three (2.75%) services; five responded "other" or did not answer.

When pre-labour Caesaren section was performed for prevention of vertical transmission, about 70% of services did so at the recommended 38-39 weeks.

Pre-labour rupture of membranes

When pre-labour rupture of membranes occurs at term the guidelines recommend expedited delivery. If a woman's viral load is <50 copies/mL, labour should be induced.

Most (92, 83.6%) services induce labour in this situation. Eight (7.3%) services would perform an immediate Caesarean, six (5.5%) responded "other" and four (3.6%) were not sure or did not answer.

Amniocentesis and obstetric procedures

The guidelines recommend deferring amniocentesis until a woman's viral load is suppressed. Seventy (63.6%) services would delay amniocentesis if possible until <50 copies/mL, nine (8.2%) offer it as for HIV negative women, three (2.7%) always avoid it, 24 (21.8%) do an unspecified "other" and four 3.6%) were not sure or did not answer.

Although the guidelines state that there is no evidence for avoiding episiotomy, amniotomy and foetal blood sampling/scalp monitor in women with viral load <50 copies/mL, about 35%, 45% and 75% of services respectively avoid or would not offer these procedures. About 7% would avoid or not offer external cephalic version.

For instrumental delivery with viral load <50 copies/mL the guidelines recommend to avoid vacuum and use forceps. For this situation: 35% of services would avoid instrumental delivery if possible, 4% avoid forceps and use vacuum, 22% avoid vacuum and use forceps and 35% would use either.

Cabergoline to suppress lactation

There is no recommendation for cabergoline use in the guidelines, but 62 (56.4%) services offer this routinely, 21 (19.1%) do not use, 18 (16.4%) offer it in some circumstances, and nine (8.2%) were not sure or did not answer.

Infant ART prophylaxis and co-trimoxazole

The guidelines recommend commencing ART prophylaxis very soon after birth and "certainly within four hours". Ninety-nine (89.2%) services give the first dose within four hours to all HIV exposed infants, four (3.6%) services reported one case each of delay 2013-2014 and eight (7.2%) were not sure or did not answer.

Co-trimoxazole is recommended for infected/HIV RNA/DNA positive infants or infants born to mothers with viral load >1000 copies/mL, where infection is not excluded. In these situations: 32 (28.8%) services would give co-trimoxazole to infants only if they were infected/HIV RNA/DNA positive, 41 (36.9%) also if maternal viral load was >1000 copies/mL, and 15 (13.5%) also if infection was not included. A further 21 (18.9%) answered "other" and two (1.8%) gave no answer.

Testing of infants/children

According to the guidelines, all potentially exposed infants/children should be tested. All but one service (that did not answer) – 110 (99.1%) – have arrangements to test exposed infants. These testing arrangements are mostly highly effective and all infants are followed up.

Fewer services have arrangements in place for existing children of women diagnosed in pregnancy, 103 (92.8%) with eight (7.2%) not sure or did not answer. These arrangements are effective at some sites but not all.

Conclusions

Dr Gilleece concluded that overall management of HIV positive women and their infants appears broadly in line with the BHIVA guidelines. But, she noted several areas of concern:

- Urgent HIV testing takes more than two hours at 50% of services outside working hours and 19% within in working hours.
- Seventeen percent of services take over a week to see women diagnosed during antenatal screening.
- Only 49% of services test for resistance routinely after stopping short-term ART. Some services delay tests until mutations could have reverted.
- Planned Caesarean sections are being offered unnecessarily.
- Some obstetric procedures might be being avoided unnecessarily.
- Cabergoline is not routinely offered at all services.
- Testing existing children of newly diagnosed women remains a challenge.

Dr Gilleece recommended that services review their management to ensure the guidelines are followed – particularly for urgent HIV testing – Caesarean and obstetric procedures also need to be reviewed, and use of cabergoline should be addressed in future guidelines.

C O M M E N T

Results of the audit using data routinely reported to the National Study of HIV in Pregnancy and Childhood will be presented in the next BHIVA conference spring 2015.

Outcomes including adherence to guidelines on timing of ART initiation, regimen choice, planned mode of delivery and sexual health screening will be reported.

Reference

Gilleece G. National survey of management of pregnancy in women living with HIV. BHIVA Autumn Conference. 9-10 October 2014. London.

http://www.bhiva.org/documents/Conferences/Autumn2014/Presentations/141009/YvonneGilleece.pdf (PDF)

CONFERENCE REPORTS

Southern African Clinicians Society Conference

24-27 September 2014, Cape Town, South Africa

Introduction

Articles in this issue of HTB from this important South African conference include:

- Efavirenz-associated gynaecomastia reported to the national HIV and TB healthcare workers hotline in South Africa
- Infants start ART too late but improvement over time in Southern Africa
- Treatment outcomes in HIV positive and negative people with drug resistant TB in Khayelitsha, Cape Town
- Pregnancy a risk factor for poor antiretroviral treatment outcomes in South African adolescents

Efavirenz-associated gynaecomastia reported to the national HIV and TB healthcare workers hotline in South Africa

Polly Clayden, HIV i-Base

Efavirenz-associated gynaecomastia (benign proliferation of glanular breast tissue in males) has been frequently reported to the South African national HIV and TB healthcare workers hotline. Results from a study conducted to look at this phenomenon were presented at the 2014 Southern African Clinicians Society Conference.

Christine Njuguna from the Division of Clinical Pharmacology, University of Cape Town showed data from the study, which included likely gynaecomastia cases reported to the hotline between 1 June 2013 and 31 July 2014.

Fifty-one cases were reported, which made up 11% of 469 adverse event queries during the study period. The mean age of the men and boys was 34 years (SD +/- 12); 86% were adults >18 years and the remaining 14% were adolescents aged 10-17 years. Overall, the mean baseline CD4 count was 188 cells/mm3 (SD +/-94) and 51% of the cohort was virally suppressed <50 copies/mL. Onset of gynaecomastia occurred and a median of 15 months (IQR 6-41) after ART initiation.

All cases were receiving efavirenz-based regimens. Additional other drugs were suspected in 31% of cases: isoniazid (n=12), d4T (n=5) and amlodipine (n=1).

Out of 51 cases, 35 (16%) were followed up for a median of 4 months (IQR 1-6). Testosterone was measured at follow up in 25/35 (71%) of which 19 (76%) had normal and 2 (8%) had low levels. Efavirenz was switched in 29 (82%) cases, of which 16 had normal testosterone levels. The majority (n=27) switched to nevirapine and two cases switched to lopinavir/ritonavir.

Overall outcomes in 35 men and boys with follow up were: 7 (20%) resolved, 14 (40%) improved, 3 (8%) were unchanged and 11 (31%) unknown. The median time to improvement was 3 months (IQR 2-4, range 1-8).

In conclusion Dr Njuguna noted that efavirenz-associated gynaecomastia was frequently reported to the hotline. Most cases had prolonged efavirenz exposure and normal testosterone. Seven cases were in adolescents for which data are sparse.

She suggested that prospective studies are needed to look at: incidence and risk factors, the proportion associated with hypogonadism, optimal management (continue or stop efavirenz), including in puberty.

Reference

Njuguna C et al. A case series of ART-associated gynaecomastia reported to the national HIV and TB healthcare workers (HCW) hotline. 2014 Southern African Clinicians Society Conference, 24-27 September 2014, Cape Town, South Africa.

http://sahivsoc2014.co.za/wp-content/uploads/2014/10/Thurs_Christine_Njuguna-obwolo%20A%20case%20series%20of%20antiretroviral%20therapy.pdf (PDF)

Infants start ART too late but improvement over time in Southern Africa

Polly Clayden, HIV i-Base

Infants start antiretroviral treatment (ART) too late – with advanced HIV and at older ages than recommended – according to data from the International epidemiologic Databases to Evaluate AIDS (IeDEA) presented at the Southern African Clinicians Society Conference 2014. But, there has been improvement since the 2010 World Health Organisation (WHO) guidelines recommended universal treatment for this age group.

Mireille Porter from the University of Cape Town presented findings from an examination of baseline characteristics of infants starting first line ART in routine care sites within Southern Africa. The study was conducted across 11 IeDEA sites in South Africa, Malawi, Zambia and Zimbabwe.

In IeDEA, routine data is collected prospectively. Sites with infant ART initiation before and after 1 January 2010 (2004-2012) were included. Infant inclusion criteria for the study were: HIV infected (with PCR diagnosis), ART naive (except for PMTCT exposure), first-line ART and recorded date before 1st birthday.

The investigators evaluated mortality, loss to follow up (no visit for >9 months), transfer out and virological suppression in the participants.

Overall the median age of 4945 infants starting ART during the study period was 5.9 months (3.7-8.7), 76.5% were WHO stage 3 or 4, their median CD4 percentage was 18.5% and 87.2% had severe immunosuppression.

There was a modest improvement in baseline characteristics over time. Infant age, proportion WHO 3 or 4, CD4 percentage and proportion with severe immune suppression during 2004-2009 vs 2010-2012 were respectively: 6.1 vs 5.4 months, 81.2% vs 63.4%, 18% vs 20,7% and 89.2 vs 81.3%.

The majority (69.7%) of infants started with d4T-contaning regimens, 15.2% started with AZT and 14.9% abacavir. Most (68.1%) received a protease inhibitor and just over half (57.9%) were exposed to antiretrovirals through PMTCT.

At three years, 39.4% of children were alive and in care. Three-year mortality probability was 13.1%; loss to follow up was 23.2% and transfer out 24.5%. In multivariate analysis, severe immune suppression, HR 2.19 (95% CI1.44-3.33), p<0.001; WHO stage 3 or 4, HR 1.36 (95% CI 1.04-1.78), p=0.023; and lower weight for age z-score less than -3, HR 2.23 (95% CI 1.78-2.8), p<0.001, were associated with higher mortality. Starting treatment from 2010 was associated with lower mortality, HR 0.75 (95% CI 0.59-0.94), p=0.015.

In a subset of 1364 infants with baseline and one other viral load result the probability of viral suppression was 21% at 6 months and 41% at 12 months. Starting treatment from 2010 was the only predictor of viral suppression.

Dr Porter noted a "very different picture to the CHER trial". Infants continue to start treatment late and at older ages with high mortality and suboptimal outcomes.

But there was an improvement from the start of 2010, which suggests that WHO 2010 guidelines did lead to earlier initiation of ART with better outcomes.

C O M M E N T

Hopefully the improvement is continuing.

Reference

Porter M et al. Outcomes of infants starting antiretroviral therapy in Southern Africa, 2004-2012. 2014 Southern African Clinicians Society Conference, 24-27 September 2014, Cape Town, South Africa.

http://sahivsoc2014.co.za/wp-content/uploads/2014/10/Thurs_Mireille_Porter%20Outcomes%20of%20infants%20starting%20antiretrovira.pdf (PDF)

Treatment outcomes in HIV positive and negative people with drug resistant TB in Khayelitsha, Cape Town

Polly Clayden, HIV i-Base

An analysis of treatment outcomes in HIV positive and negative people with drug resistant (DR) tuberculosis (TB) in Khayelitsha showed similar treatment success and long-term mortality in the presence of ART.

This study – presented at the 2014 Southern African Clinicians Society Conference – showed greater mortality in HIV positive participants before and during DR-TB treatment. But, loss to follow up was greater in HIV negative participants, leading to higher mortality after this occurred.

Khayelitsha is a township in Cape Town with a population of about 500,000. About half the population live in informal dwellings. In 2012 antenatal prevalence of HIV was 34% and the vertical transmission rate 1.7%.

Three quarters of about 6,000 TB cases that are registered in Khayelitsha each year are in HIV positive people. Approximately 200 TB cases are DR-TB. The success rate for treating DR-TB is about 46% and the mortality rate about 20%. In March 2014, 11 health facilities in Khayelitsha were providing TB and HIV care and 28, 738 people were receiving ART.

Vivian Cox from Médecins Sans Frontières (MSF) presented a retrospective analysis of treatment outcomes and mortality from routine Khayelitsha DR-TB data.

Of 839 diagnosed DR-TB cases, 607 were in HIV positive and 232 in HIV negative people. Respectively 1% and 11% were presumed to have MDR-TB, 21% and 12% were rifampicin mono-resistant, 61% and 62% had MDR-TB and 16% and 15% MDR-TB plus resistance to 2nd line TB drugs.

Of those diagnosed 736 started DR-TB treatment. Of the 116 (100 HIV positive) who did not start treatment, 62 died before treatment started, 55 (89%) HIV positive and 7 (11%) negative, p<0.001. A total of 470/507 HIV positive people who started DR-TB treatment were on ART and 440/470 had final treatment outcomes available. Of 216 HIV negative people starting DR-TB treatment, 189 had final treatment outcomes available.

Similar proportions, 48% vs 47%, of the HIV positive and negative groups respectively achieved treatment success (defined as cure and treatment completion). Loss to follow up occurred in 27% vs 37%, p=0.01. There was no difference in the proportion of the two groups with treatment failure: 6% vs 7%. But a greater proportion of HIV positive people died: 18% vs 9%, p=0.004.

Similar proportions died after loss to follow up: 26% vs 21% at a median of 6.7 (IQR 2.5-16.1) vs 5.5 (IQR 3.5-13.3) months. A greater proportion of the HIV positive group died after treatment failure: 77% vs 50% at a median of 0 (0-0.2) vs 5.7 (1.5-17.5) months.

Overall mortality was 132 in the HIV positive group, IR/100py 19 (95% CI 16-22) vs 39 in the HIV negative group, IR/100py 17 (95% CI 12-22); IRR 1.14 (95% CI 0.80-1.67).

Dr Cox noted that loss to follow up masks mortality in HIV positive and negative people. Overall treatment success and mortality in HIV positive people on ART is similar to that in HIV negative people.

Reference

Cox V et al. Treatment outcomes in HIV infected and uninfected drug resistant tuberculosis patients in Khayelitsha, Cape Town. Southern African Clinicians Society Conference, 24-27 September 2014, Cape Town, South Africa.
http://sahivsoc2014.co.za/wp-content/uploads/2014/10/Thurs_Vivian_Cox%20Outcomes%20in%20HIV.pdf (PDF)

Pregnancy a risk factor for poor antiretroviral treatment outcomes in South African adolescents

Polly Clayden, HIV i-Base

Adolescent girls starting antiretroviral treatment (ART) have high incidence of pregnancy and higher probability of poor outcomes in South Africa, according to data presented at the 2014 Southern African Clinicians Society Conference.

On the whole, adolescents started ART with advanced HIV but pregnant adolescent girls started earlier – likely due to testing at maternal facilities. Pregnant adolescents were more likely to be lost to follow-up, have poor viral suppression and viral failure after starting ART.

Geoffrey Fatti from Kheth'Implio – an organisation that supports the South African Department of Health in HIV service delivery – showed findings from an evaluation of gender differences in baseline characteristics of adolescents (aged 9-19 years) starting ART at routine facilities.

The investigators used data from 82 public facilities in four provinces supported by the organisation. ART-naive adolescents starting ART between 2004-2011 were included in the analysis. Of 3175 adolescents, 67% (n=2127) were girls with a pregnancy rate of 10.7% (n=227).

Multivariate analysis revealed that the age of ART initiation was younger among boys in the cohort, and non-pregnant girls started earlier than those who were pregnant, respectively: 11.6, 15.5 and 18.9 years, p=0.0001. Pregnancy incidence increased over the study period to 25.3% in 2011.

The median baseline CD4 count at initiation was significantly higher among pregnant girls: 147, 143 and 205 cells/mm3 for boys, non-pregnant and pregnant girls respectively, p=0.0001.

At 36 months from starting ART, cumulative incidence of mortality was similar among the different groups, pregnant girls aSHR 1.03 (95% CI 0.23-4.51), p=0.96. But loss to follow up was significantly higher in pregnant girls compared to boys, aSHR 1.94 (95% CI 1.03-3.65), p=0.04 (non-pregnant girls aSHR 1.29[95% CI 0.91-1.86], p=0.2).

At 24 months a smaller proportion of pregnant girls achieved viral suppression aSHR 0.58 (95% CI 0.39-0.86), p=0.006 (non-pregnant girls aSHR 0.92 [95% CI 0.57-1.48], p=0.73). By 36 months the cumulative probability of viral failure was greater among pregnant girls, aSHR 4.85 (95% CI 1.78-13.1), p=0.002 (non-pregnant girls aSHR 1.12 [95% CI 0.67-1.88], p=0.65).

Dr Fatti stressed that programmes targeted at reducing adolescent pregnancy and increased adherence support for pregnant adolescents are essential. Both to improve outcomes of adolescents on ART, as well as potentially reduce vertical transmission of HIV.

Reference

Fatti G et al. Gender differences in antiretroviral outcomes amongst adolescents: a multicentre cohort from South Africa. 2014 Southern African Clinicians Society Conference, 24-27 September 2014, Cape Town, South Africa.

http://sahivsoc2014.co.za/wp-content/uploads/2014/10/Thurs_Geoffrey_Fatti%20Gender%20differences%20in%20antiretroviral%20treatment%20outcomes.pdf (PDF)

ANTIRETROVIRALS

Equivalent efficacy with lower dose darunavir

Polly Clayden, HIV i-Base

A reduced dose of darunavir boosted with ritonavir was effective in two reports from Italy and Spain. [1, 2]

Dose optimisation strategies aim to reduce the cost and possibly the toxicity of antiretroviral treatment (ART) while maintaining its efficacy. [3]

In a letter to the Journal of Antimicrobial Chemotherapy – published as an advance access article on 8 October 2014 – Massimiliano Lanzafame and colleagues described the efficacy of 600 mg darunavir boosted with 100 mg ritonavir (DRV/r 600/100 mg) once daily in a cohort of 26 HIV positive adults.

Twelve of the cohort were women and the remaining 14 men; their age ranged from 21 to 53 years. Twelve participants were treatment-naive (Group 1) and received DRV/r 600/100 mg once daily in regimens with tenofovir/FTC (n=9) or abacavir/3TC (n=3). Seven had been virologically suppressed on a previous regimen but due to reasons other than virological failure had switched to DRV/r 600/100 mg once daily (Group 2) plus tenofovir/FTC (n = 2), abacavir/3TC (n=2), nevirapine (n=1) or AZT/3TC (n=1), and one participant received DRV/r 600/100 mg monotherapy once daily. Seven were treatment experienced (Group 3) with a detectable viral load, that had switched to DRV/r 600/100 mg once daily plus tenofovir/FTC (n=5), abacavir/3TC (n=1) or raltegravir (n=1).

Group 1 had a mean baseline viral load of 134,024 copies/mL (range 4526-397,932); after a mean follow-up of 27.4 months (range 12–33), 11/12 had undetectable viral load (<20 copies/mL). The mean pharmacokinetic (PK) DRV trough level in this group was 2920 ng/mL (range 1268-4562).

PK samples were collected 24 hours after the last dose of DRV/r. The researchers noted that one participant had virological failure after 14 months (39,300 copies/mL) but no DRV-associated resistance was detected. His viral load was suppressed again following a dose adjustment to DRV/r 600/100mg twice daily.

Group 2 participants were virologically suppressed for a mean of 32.8 months (range 21-54). A PK trough level was only available for one participant (3442 ng/mL).

Group 3 participants had mean baseline viral load of 24,167 copies/mL (range 112-111,426), five were suppressed for a mean of 46.2 months (range 31-67), one participant interrupted ART for 3 months, then restarted and achieved viral load 628 copies/mL after 5 weeks of treatment. The researchers noted that this participant had the I47V mutation. Another participant from Group 3 failed after 42 months (3930 copies/mL) and re-suppressed after the dose was adjusted to DRV/r 600/100 mg twice-daily.

PK trough levels were available for three participants from Group 3 and these were a mean of 2502 ng/mL (range 844-4518).

The researchers wrote: "In our clinical experience of 26 patients, the use of darunavir/ritonavir at a dose of 600/100 mg once-daily led to sustained HIV RNA suppression in 23 patients with acceptable pharmacokinetic exposures to darunavir".

Results from the related DRV600 study were presented at the 15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy in May 2014.

This study, authored by José Moltó and colleagues, compared the efficacy and safety of a reduced dose with the standard dose of DRV in 100 virologically suppressed (<50 copies/mL) participants. It was a multicentre, randomised, open-label clinical trial.

Study participants were on stable DRV/r 800/100mg once-daily plus two NRTIs. DRV resistance, or prior virologic failure while receiving protease inhibitor-based ART, were exclusion criteria.

The participants were randomised to continue on the standard DRV/r 800/100mg once-daily dose or to switch to 600/100 mg once-daily. Two consecutive viral load tests >50 copies/mL or discontinuation of treatment by week 48 was defined as failure.

Across both study arms, 81% of participants were men, they were approximately 45 years of age, and 20% were co-infected with HCV. Their mean CD4 count at baseline was 562 cells/mm3 (SD 303). Approximately 65% received DRV/r plus tenofovir/FTC and 35% abacavir/3TC.

Two participants in the DRV/r 800/100mg arm and three from the DRV/r 600/100mg arm developed virologic failure by week 48. One participant from each arm was lost to follow-up and one from the DRV/r 600/100mg arm died of septic shock.

In intent-to-treat analysis, the proportion of patients with viral load<50 copies/mL at week 48 in was 90% in the DRV/r 600/10 mg and 94% in the DRV/r 800/100mg arm, difference -4% (90% CI -12.9 to 4.9), p=0.46). This met protocol defined non-inferiority: 95% CI for delta less than -15% (80% power).

CD4 cell counts remained stable during follow-up in both arms and were similar, p=0.415. DRV trough levels were comparable between the two arms, p=0.776.

Adverse events occurred in 12 participants receiving DRV/r 800/100 mg and 7 receiving 600/100 mg. These were gastrointestinal, dyslipidaemia and other (<5%), occurring in 6 and 4, 5 and none, and 1 and 3 participants, in the DRV/r 800/100 mg and 600/100 mg arms respectively. There was a modest difference in total cholesterol and triglycerides (both slightly lower in the 600/100 mg arm) but neither was significant: respectively p=0.284 and p=0.157.

The study investigators calculated that lower dose of DRV could represent an approximate saving of 1000 Euros per patient per year according to Spanish antiretroviral prices. They noted that four patients on DRV/r 600/100 once daily = one free compared to dosing 800/100 mg once daily.

C O M M E N T

In two pivotal trials of DRV/r (ODIN and TITAN), there was evidence of negative PK/PD, that is, people with higher concentrations of DRV have significantly lower overall efficacy. [4, 5] These correlations have been seen for the 800/100 once-daily and 600/100 mg twice-daily doses.

Although the numbers in the second study were small and did not reach statistical significance, it is possible that there might be an improvement in tolerability with the lower dose with a larger sample size. DRV/r has shown worse overall safety than dolutegravir in the head-to-head Flamingo study, suggesting that there is the potential to improve its safety profile. [6]

The two reports described above (as well as suggestions from the early DRV/r trials) add weight to the argument that optimised DRV/r dosing needs to be thoroughly investigated, particularly for low-income countries, where cost savings could be considerable.

Various plans are being discussed to look at DRV/r 400/100 mg once daily, with the aim to develop a simplified one pill, once-daily second-line treatment (co-formulated with dolutegravir) for people failing the current recommended first-line regimen.

Donors need to ensure that the research to generate the data to inform this development programme is done sooner rather than later.

References

1. Lanzafame M et al. Efficacy of a reduced dose of darunavir/ritonavir in a cohort of antiretroviral naive and experienced HIV-infected patients: a medium-term follow-up. J. Antimicrob. Chemother. 8 October 2014. doi: 10.1093/jac/dku390.
   http://jac.oxfordjournals.org/content/early/2014/10/07/jac.dku390.extract
2. Moltó J et al. Reduced darunavir dose is as effective in maintaining HIV suppression as the standard dose in virologically suppressed HIV-infected patients. 15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy. 19-21 May 2014. Washington DC. Oral abstract_02.
   http://regist2.virology-education.com/2014/15HIVHEP_PK/3_Molto.pdf (PDF)
   http://regist2.virology-education.com/abstractbook/2014_4.pdf (PDF)
3. Clayden P. Fit for purpose: treatment optimisation. i-Base/TAG Pipeline Report. 19 July 2014.
   http://i-base.info/htb/26960
4. Cahn P et al. Week 48 analysis of once-daily vs. twice-daily darunavir/ritonavir in treatment-experienced HIV-1-infected patients. AIDS. 24 April 2011;25(7):929-39.
5. Bánhegyi et al. Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN. Curr HIV Res. March 2012;10(2):171-81.
6. Clotet B et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. The Lancet. 28 June 2014; 383(9936): 2222 – 2231.
7. Clayden P. Pill A, Pill B: simplified second-line treatment for low-income countries. HTB. 1 August 2014.
   http://i-base.info/htb/27169

SIDE EFFECTS & COMPLICATIONS

Poppers-related maculopathy linked to permanent and serious vision loss

Simon Collins, HIV i-Base

Serious vision loss linked to recreational use of poppers that has not resolved after six months was reported as a case study in the 1st November issue of the Lancet.

Anna M Gruener and colleagues from Guy's and St Thomas' NHS Foundation Trust and Queen Mary's Hospital, Sidcup published a case of maculopathy associated with use of poppers in the 1st November 2014 edition of the Lancet.

This case involved a 30-year old man with no ocular history who presented with bilateral central vision loss following inhalation of poppers. Visual acuity was 6/12 in the right eye and 6/18 in the left eye.

Further examinations showed subtle macular changes in the form of yellow foveal spots by slit lamp biomicroscopy, and clear disruption of the foveal cone inner segment/outer segment layer by spectral domain optical coherence tomography.

Neither visual acuity nor examination findings have resolved despite the man having no further use of poppers for six months.

The case study report notes that other cases of poppers maculopathy have been described since legislation in 2006 led to isopropyl nitrite being changed to isobutyl nitrite. The mechanism for poppers to damage central photoreceptors is unknown, although there is a clear cause-effect relationship. The case study report also highlights that reports of similar cases are increasing.

The authors comment that the risk of damage is potentially serious and irreversible.

Poppers is the common name for a stimulant commonly branded as a room odouriser, when it is inhaled as a recreational drug to enhance dancing, sex, or both.

C O M M E N T

Details on the estimated exposure to poppers that prompted these symptoms or previous history of poppers use were not included in the report.

One of the purposes of a case study is to highlight previous unknown or underestimated serious events. This should prompt further research that might be able to evaluate how common this might be.

People using poppers, even with no previous history of eye problems should be aware that this is a potential risk. The case also raises concerns for sub-clinical damage that may not be reported but might have longer term consequences.

Reference

Gruener AM et al. Poppers maculopathy. The Lancet, Volume 384, Issue 9954, Page 1606, 1 November 2014. doi:10.1016/S0140-6736(14)60887-4.

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)60887-4/fulltext

HEPATITIS C

US activists called on Gilead to set a per-treatment price for sofosbuvir/ledipasvir

In a press release on 13th October 2014, the Fair Pricing Coalition, a US treatment activist organisation, called for Gilead to set a single uniform per-cure price for the coformulation of sofosbuvir and ledipasvir (brand name Harvoni) irrespective or whether 8, 12, or 24 weeks of treatment is required.

"The FPC, a coalition of HIV and viral hepatitis treatment activists, recognises the significant advance in treatment success and convenience of Harvoni, but is disappointed at the Wholesale Acquisition Cost (WAC) of $1,125 per once-daily tablet, or $63,000, $94,500, and $189,000 for an 8-, 12-, and 24-week course of treatment, respectively."

"The FPC maintains that these costs, particularly for the 12- and 24- week courses of treatment, are exorbitant. Since they are now published, however, FPC concludes that the WAC of $63,000 for eight weeks of Harvoni, which is projected to be the most common duration of treatment as more people living with genotype 1 hepatitis C learn of their infection and seek care, should be made the uniform cost per cure, regardless of the length of therapy."

Reference:

Fair Pricing Coalition. Fair Pricing Coalition welcomes approval of Gilead Sciences' combination tablet for hepatitis C, urges a uniform price for curative treatment. (13 October 2014).

http://fairpricingcoalition.org

PREVENTION

UK PROUD study to provide PrEP to all participants earlier than expected: planned follow-up to continue to two years

Simon Collins, HIV i-Base

On 16th October, UK researchers announced an important change in the PROUD study. Because of an early result about the effectiveness of PrEP when used by gay men in the UK at high risk of HIV, all participants will be offered immediate treatment. [1]

PrEP was approved in the US in July 2012 and involves taking a daily pill (Truvada) to reduce the risk of catching HIV. Approval was based on results from two large international studies: the iPrEX study in about 2,499 gay men and the PARTNERS PrEP Study in more than 4758 heterosexuals. [2] For PrEP to become available in the UK, the NHS wanted additional data on cost-effectiveness in a UK population.

The PROUD study randomised 545 gay men (in a 1:1 ratio) to either immediate access to PrEP for two years or to waiting for 12 months before getting PrEP. All participants received advice, information and condoms to reduce the risk of HIV throughout the study. [3] This design avoided using a placebo pill and ensured all participants would receive the active drug for at least 12 months.

For the study to change in this way due to early efficacy results is especially impressive. It is also surprising because PROUD was a pilot study that was too small to show efficacy differences. The main aims were to firstly see whether people were interested enough in PrEP to take a daily pill, and secondly, whether this would change their level of risk.

The change in the study is based on a recommendation from an independent data monitoring committee (IDMC). When it became clear to this expert panel that the difference in infection rates was significant, they recommended amending the study design.

The effectiveness result may be because men in the study were at higher risk of HIV than was initially expected when the study was planned. A recent presentation of these risk factors for people entering the study was recently presented at the International AIDS Conference in July 2014. [4]

Although it may take several weeks for these changes to be put n place, all participants will now have the chance to use PrEP. Details about the different rates of HIV incidence in each group have not been included in the statement, but a full analysis of these data are due to be released early in 2015.

The PROUD study will continue to follow-up all participants for the full two years, to collect information about behaviour and risk, in order to look at longer-term issues relating to PrEP.

C O M M E N T

This decision by the PROUD study increases the urgency for the NHS to produce recommendations for PrEP access in the UK. Earlier this month, the latest figures from Public Health England reported that incidence rates in gay men are still increasing. Current health programmes to reduce new infections are not effectively reaching the people at highest risk.

The latest figures report that 3250 gay men were diagnosed HIV positive last year, including more than 450 men aged 15-24 and more than 1100 aged between 25-34. [5]

Based on results from the iPrEX study, including later follow-up, occasionally missing PrEP is still likely to provide good protection (estimated at more than 90% protection with 4 or more doses a week). Daily PrEP provides protection that approaches 100%. [6]

Following this announcement from the PROUD study, the DSMB for the French/Canadian IPERGAY study rapidy assessed their results. This revealed a similar early efficacy finding and similar desicion to terminate the conrol arm, offering all participants immediate PrEP (see artcila below).

IPERGAY uses an alternative schedule to daily PrEP that includes taking a double dose of PrEP at least two hours before sex (preferably the day before) and then at least two subsequent single doses every 24 hours afterwards. IPERGAY used a placebo study design that resulted in slow enrolment. [7]

References
1. PROUD statement, (16 October 2014).
2. FDA press release. Truvada approved to reduce the risk of sexually transmitted HIV in people who are not infected with the virus. (16 July 2012). http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm312264.htm
3. Examining the impact on gay men of using Pre-Exposure Prophylaxis (PrEP) - the PROUD Study. http://www.proud.mrc.ac.uk
4. Antonucci S et al. The UK PROUD PrEP Pilot Study: a baseline analysis. Poster abstract THPE197. http://pag.aids2014.org/abstracts.aspx?aid=7659
5. Public Health England. National HIV surveillance data tables, Table 7, (October 2014). https://www.gov.uk/government/statistics/hiv-data-tables
6. Grant RM et al. Results of the iPrEx open-label extension (iPrEx OLE) in men and transgender women who have sex with men: PrEP uptake, sexual practices, and HIV incidence. Oral late breaker abstract TUAC0105LB. http://pag.aids2014.org/abstracts.aspx?aid=11143
7. On demand antiretroviral pre-exposure prophylaxis for HIV infection in men who have sex with men (IPERGAY) http://clinicaltrials.gov/show/NCT01473472

IPERGAY PrEP study shows early efficacy in protecting gay men from HIV: all participants to switch to active drug

Simon Collins, HIV i-Base

On 29 October 2014, French and Canadian researchers announced early efficacy of a PrEP study to protect gay men from catching HIV. This has led to a change in the study design. [1]

If taken daily, Truvada provides close to 100% protection against HIV.

The IPERGAY study is being run at six hospitals in France and one site in Canada. Participants in the placebo arm of the study will now be offered active PrEP.

This decision was based on a safety assessment mid-way through the study, prompted by news that a UK PrEP study called PROUD had made similar changes a few weeks earlier, also based on unexpected early efficacy. [2]

The early results in IPERGAY and PROUD are likely to be related to a combination of the participants being at high risk of HIV and having good adherence to treatment.

However, both studies have only released the top-line decision to make PrEP available to all participants. This limits further discussion about either the detailed results or why PrEP was so effective. Full analyses are being prioritised but are still likely to take several months.

The full analysis is especially important for IPERGAY as it uses an experimental dosing. The study press statement does not include details of whether infections still occurred using this dosing or how effective it is compared to daily dosing.

Although a daily pill was approved in the US in July 2012 to reduce the risk of catching HIV, earlier PrEP studies found conflicting results. These larger PrEP studies faced two main challenges. The first was to enrol people who were at genuinely high risk of catching HIV and who continued to be at high risk during the study. In the absence of risk, even the most effective intervention will be unable to prove a benefit. The second challenge, also considerable, was dependent on people at risk actually taking the prescribed pill (or placebo).

Some studies, despite finding PrEP effective, involved following thousands of participants for several years, to only avert relatively few infections.

Other studies, also large and carefully designed, reported no benefit largely due to low adherence.

Differences between IPERGAY and PROUD

IPERGAY and PROUD have very different study designs.

Although the IPERGAY dosing schedule is referred to as “on demand” it includes the need to take the first PrEP dose 2-24 hours before sex. This requires a degree of planning or forethought (but there is no safety concern if the pre-dose was optimistic and sex does not occur).

Dosing continues as long as the person is sexually active, although not taking more than one dose every 24 hours. This is completed with a pill after sex and the final tablet 24 hours after this.

IPERGAY also uses a placebo design. This meant that half the participants used the real drug and half used an inactive dummy tablet. Participants, doctors and researchers did not know who was getting the real drug.

PROUD uses a daily dosing schedule. Participants were asked to take a single pill every day, whether or not they were sexually active. This study did not use a placebo but compared immediate PrEP to deferred PrEP. Half the participants in this study used PrEP from the beginning of the study and half were due to start after 12 months. All participants received health advice and condoms and kept a diary of sexual activity in order to look at whether PrEP affects behaviour risk.

The PROUD study announced on 16 October 2014 that all participants were going to be offered immediate PrEP because of significant and unexpected differences in HIV rates in the two groups. [3]

For further information there is a non-technical leaflet about PrEP and the PROUD study, produced by i-Base. [4]

C O M M E N T

Although both IPERGAY and PROUD have amended their initial study designs, both continue as active studies. This continued follow up is essential.

Although the IPERGAY researchers state that they have found efficacy to be much higher than the iPrEX study, this needs to be interpreted cautiously until the full analysis is available. The statement was apparently made in reference to the 42% effect in iPrEX overall rather than the 99% risk reduction in people taking daily PrEP. It is also important not to interpret the IPERGAY statement as implying that the IPERGAY dosing schedule is more effective than that used in iPrEX.

Background rates of HIV and adherence might make the relative results between the two groups in the IPERGAY study higher than relative rates between groups in iPrEX study, but this doesn't make it more effective.

The early announcement about the IPERGAY study also risks an interpretation that the IPERGAY dosing schedule is more effective than daily dosing in iPrEX. The reduced dosing schedule used in IPERGAY is still being investigated and until these data are available, daily dosing remains the optimal way to use PrEP.

Reference
1. IPERGAY press statement. Un grand success dans la lutte contra le VIH./SIDA. Un médicament pris au moment des rapports sexuels réduit efficacement le risque d'infection. (29 October 2014).
   http://www.ipergay.fr Press release (English version) IPERGAY october 2014 (Word.doc)
2. PROUD press statement. PROUD study interim analysis finds pre-exposue prophylaxis (PrEP) is highly protective against HIV for gay men and other men who have sex with men in the UK. (16 October 2014).
   http://www.proud.mrc.ac.uk/PDF/PROUD%20Statement%20161014.pdf (PDF)
   http://www.proud.mrc.ac.uk
3. Collins S. UK PROUD study to provide PrEP earlier than expected: planned follow-up in this HIV prevention study to continue for two years. (16 October 2014).
   http://i-base.info/uk-proud-study-to-provide-prep-earlier-than-expected
4. Q&A on PrEP in the UK and changes to the HIV PROUD study.
   http://i-base.info/qa-on-prep-in-the-uk-and-changes-to-the-hiv-proud-study

BASIC SCIENCE & CURE RESEARCH

Three papers on macrophages and HIV infection

Richard Jefferys, TAG

The question of whether HIV infection of macrophages plays an important role in pathogenesis remains controversial and unresolved.

For cure researchers, the related question of whether macrophages contribute to viral persistence during antiretroviral therapy is crucial, but also unanswered. Three recent papers describe results from studies designed to shed light on this subject.

In the journal *Immunity*, Jason Brenchley's research group presents results from experiments in the SIV/macaque model using viruses that do and do not express the Vpx protein, which has previously been reported to be important for infection of myeloid cells (including macrophages). [1]

To their surprise, the researchers found that Vpx did not significantly influence the extent to which SIV was detectable in myeloid cells. Mucosal tissues showed little evidence of myeloid cell infection despite depletion of CD4 T cell targets, but in 40% of animals SIV DNA was detectable in myeloid cells in the mesenteric lymph nodes and spleen. However, further analyses revealed the presence of T cell receptor DNA in addition to the SIV DNA, suggesting that these cells were macrophages that had phagocytosed SIV-infected CD4 T cells. The researchers state: "we believe our data clearly suggest that viral RNA and DNA within myeloid cells can be attributed to clearance of virally infected cells and immune complexes and not bone fide SIV infection of myeloid cells in vivo."

An open access paper in *Cell Host & Microbe* offers a possible twist to this tale, reporting that phagocytosis of HIV-infected CD4 T cells by macrophages can lead to them becoming productively infected. [2]

The findings are derived from in vitro laboratory experiments. The data indicate that macrophages selectively target HIV-infected CD4 T cells for phagocytosis, although the researchers have yet to identify the exact mechanism for this selectivity. The online version of the paper is accompanied by three quicktime videos of macrophages phagocytosing multiple HIV-infected CD4 T cells. [3]

Lastly, in *PLoS Pathogens* Luca Micci and colleagues show that artificial depletion of CD4 T cells in SIV-macaques (using a CD4-targeting monoclonal antibody) produces evidence of extensive infection of macrophages, as well as microglial cells in the brain. [4]

In lymphoid tissues of non-depleted animals, T cells made up more than 80% of the cells containing SIV RNA, whereas in the setting of CD4 T cell depletion more than 80% of the cells containing SIV RNA displayed macrophage markers. The macrophages showed evidence of high levels of activation and were shorter-lived than was expected based on previous studies. Since CD4 T cells were not completely depleted in the animals, it seems possible that phagocytosis of SIV-infected CD4 T cells might have contributed to the presence of SIV RNA in macrophages in this study, but the researchers do not specifically assess the possibility.

Unfortunately, it appears that the publication of these papers within a short time period precluded the authors from being able to comment on each other's work, which would have been helpful in understanding how the data fit together. Because it involves in vivo results from macaques without any manipulations, the *Immunity* paper may arguably represent the most reliable gauge of the contribution of macrophages in SIV infection.

The results imply that previously reported studies documenting the presence of HIV DNA in macrophages are explained, at least in part, by phagocytosis of infected CD4 T cells. However, the study published in *Cell Host & Microbe* suggests that additional work might be needed to fully distinguish between macrophages containing viral DNA solely due to phagocytosis and those that are also productively infected.

None of the papers offer a definitive answer to the question of whether infected macrophages make up part of the long-lived HIV reservoir that persists despite antiretroviral therapy. Brenchley and colleagues argue that, based on their findings, therapeutic interventions aiming to target latent HIV should continue to focus on CD4 T cells.

Source
TAG basic science blog. (25 Nov 2014).
http://tagbasicscienceproject.typepad.com

References

1. Calantone N et al. Tissue myeloid cells in SIV-infected primates acquire viral DNA through phagocytosis of infected T cells. Immunity. 2014 Sep 18;41(3):493-502. doi: 10.1016/j.immuni.2014.08.014.
http://www.cell.com/immunity/abstract/S1074-7613(14)00308-2
2. Baxter AE et al. Macrophage Infection via Selective Capture of HIV-1-Infected CD4+ T Cells. Cell Host & Microbe, Published Online: November 20, 2014. Open access.
http://www.sciencedirect.com/science/article/pii/S1931312814003886
3. Ibid, Baxter et al. (Click the video tab under the Images/Data menu).
http://www.cell.com/action/showImagesData?pii=S1931-3128%2814%2900388-6
4. Micci L et al. CD4 depletion in SIV-infected macaques results in macrophage and microglia infection with rapid turnover of infected cells. PLoS Pathog. 2014 Oct 30;10(10):e1004467. doi: 10.1371/journal.ppat.1004467. eCollection 2014. Open access.
http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1004467

OTHER NEWS

HIV in the UK 2014: Public Health England report on incidence and care

Simon Collins, HIV i-Base

The latest Public Health England (PHE) report on HIV in the UK was published on 17th November 2014, based on data collected to the end of 2013. [1]

The 50-page report has 15 appendices of summary data tables showing HIV incidence, patterns of infection and HIV management outcomes, including breakdowns by age, gender, risk group and geographic location. The report also includes data on other STIs and tuberculosis.

The following key findings are highlighted from data related to UK figures for 2013.

Selected overall results

- 107,800 people are now estimated to be living with HIV in the UK (95% credible interval 101,600-115,800).
- Overall adult prevalence (aged 15-59 years) is now 2.8 per 1,000 population (1.9 per 1,000 women and 3.7 per 1,000 men).
- A quarter (24%, 26,100) of people living with HIV are not yet diagnosed. They risk HIV progression and ongoing transmission if they are not consistently using condoms.
- 6,000 people were diagnosed in 2013, and 98% were linked to care within three months.

- Of the 530 HIV positive people who died, 210 were younger than 60 years old. Late diagnosis is associated with a ten fold increase mortality risk in the first year after diagnosis, compared with diagnosis at a CD4 count >350, but this difference is driven almost completely by those diagnosed very late (CD4 <100).
- 42% (2,500/5,960) of people were diagnosed late, defined by having a CD4 count less than 350 within three months of their diagnosis. 62% of heterosexuals and 31% MSM were diagnosed late. The CD4 count was lower than 200, categorised as extremely immunocompromised, for 24% diagnosis (1,430).
- The report notes that people living with HIV can expect a near-normal life span if they are diagnosed while their CD4 count is still above 350. People diagnosed later have a ten-fold increased risk of death in the year following diagnosis compared to those diagnosed earlier.
- 81,500 people received HIV care in 2013 (55,200 men and 26,300 women). This is a 5% increase on the previous year (77,590) and almost double the number a decade ago (41,160).
- One in four people living with diagnosed HIV is now older than 50 years. This is mainly related to the impact of effective treatment that means we live longer. This shows the importance of developing services that are appropriate to an ageing population.
- Data on recent infections highlights that ongoing transmission is a risk at all ages.

Gay, bisexual and other MSM

- HIV still disproportionally affects gay, bisexual and other men who have sex with men. The number of MSM diagnoses was a record high (3250/6000). This approximates to an adult prevalence of 59 per 1,000. In London, an estimated 1 in 8 MSM are HIV positive compared to 1 in 26 outside London.
- By age, 16% of new diagnoses were in men younger than 24 and 10% were in men older than 50.
- Based on RITA data from 1080 MSM, approximately 30% indicated recent infection.
- Approximately 16% of MSM are undiagnosed (~7,200). This percentage has been consistent for the last ten years. Most of these people are likely to have been recently infected (in the last 1-2 years).
- 25% of newly diagnosed MSM had concurrent acute STIs (chlamydia, gonorrhoea and/or syphilis). This compared to 5.9% and 2.8% among newly diagnosed heterosexual men and women respectively.
- Using a back calculation analysis based on CD4 count at diagnosis, the report estimated that 2800 MSM were infected in 2013 - a number that has been broadly consistent annually for the last ten years.

Transgender people

- No data is presented for transgender people, despite disproportionally high rates reported in other countries. However, trangender data will now be collected through HARS, the new HIV surveillance system.

Heterosexual transmission

- Approximately 59,500 people in the UK are living with HIV due to heterosexual transmission.
- Based on RITA data from 657 samples, approximately 13% indicated recent infection.
- A steady decline in new heterosexual infections is related to fewer diagnoses in people born in sub-Sahara Africa. However, approximately 60% of infections occurred in the UK (1500/2490).
- HIV disproportionally affects black Africans (~65% of heterosexual infections).
- Adult HIV prevalence among black-African heterosexuals is 56 per 1,000 (71 per 1,000 women and 41 per 1,000 men). This compares to prevalence of 0.6 per 1,000 for non black-African heterosexual men and women.
- Approximately 31% of heterosexuals are undiagnosed (~18,500). This includes 13,000 black-Africans (almost two in five men and one in three women).

People who inject drugs (PWID)

- Infection through drug use remained low with 130 cases, similar to the previous two years.

Mother to child transmission

- 90 new diagnosis were related to mother to child transmission, with the vast majority of cases occurring outside the UK.

Treatment cascade

- 76% of people living with HIV are diagnosed.
- >98% of people diagnosed were seen in care (CD4 count within 3 months).
- >95% of people in care retained in care.
- 90% of adults seen for HIV care in 2013 were prescribed ART.
- 90% of all adults receiving ART were virally suppressed <200 copies/mL.

C O M M E N T

These figures clearly show that HIV is far from ended in the UK, with more than 500 people diagnosed each month.

Current prevention programmes are particularly failing young gay men with 16% of MSM diagnoses last year (460 people) in men aged less than 24 years. This highlights the urgency of an early access programme for the option to use PrEP for those at highest risk.

It is unclear why uptake of RITA testing is still so under-used, given that this is paid for centrally, but expanding this to clinics that currently do not use the service would improve our understanding of recent infections.

Although there are currently still no data on HIV rates in transgender communities, recent discussions between tansgender activists and PHE indicates that sexual health clinics will now be expected to collect gender data in non- binary categories. Hopefully, the long-standing lack of data for how HIV affects trangender people, might allow first data to be included in the 2015 report.

The PHE report also includes the importance of new approaches to HIV prevention, including calling for a more rapid access to PrEP. Bringing HIV testing to those people currently unaware of their HIV status and routine testing for those at highest risk are clearly critical stages in the UK cascade. Without this, benefits from both TasP and PrEP are unlikely to dent the ongoing incidence.

2015 needs to be branded as "HIV testing year". Opt-out HIV testing in sexual health clinics is one key recommendation in the report that could help. Having had a recent HIV test needs to become a social norm, especially across all the highest incidence communities.

The UK is fortunate to still have one of the most comprehensive and careful surveillance programmes: this report is essential for the breadth of data and analysis that it contains. However, a few relatively small points from this otherwise excellent service might be useful feedback for 2015.

Firstly, although the report includes page of "PHE messages" apparently aimed at a general reader, this is the least useful section. It is good to include a non-technical summary but this needs to be more appropriately considered. Advice to "avoid overlapping relationships" is unlikely to lead to significant behavioural change.

Secondly, the use of the term "unprotected sex" is outdated and needs to be replaced by language specifying when this means not using a condom, given the prevention benefits of TasP and PreP.

Thirdly, most pages on the PHE website look and feel more like the prison service or tax office. Even if the HPA has gone, a little colour, warmth and a few graphics would help - given that these cost nothing.

References
1. Public Health England. HIV in the United Kingdom: 2014 report. 18 November 2014. https://www.gov.uk/government/statistics/hiv-in-the-united-kingdom
2. HIV data tables are available at: https://www.gov.uk/government/statistics/hiv-data-tables.
3. The 2014 HIV Surveillance Overview will include estimates of undiagnosed HIV infection, HIV incidence trends, the impact of treatment as prevention and the monitoring of HIV care quality. http://www.phoutcomes.info/public-health-outcomes-framework#gid/1000043/pat/6/ati/102/page/0/par/E12000004/are/E06000015.

ON THE WEB

Conferences

Several recent conferences that we have not reported on in HTB haveaccess to some presntations online.

HIV Research For Prevention (HIVR4P)

28-31 October 2014 in Cape Town, South Africa.

This is a new meeting focussed on HIV prevention research.

http://hivr4p.org

The meeting included 722 abstract presentations (177 oral, 545 posters, with 29 poster discussions and 65 late-breakers. The abstract book is available online.

http://hivr4p.org/abstracts-and-conference-materials

Webcasts from many of the oral presentations are also available.

http://webcasts.hivr4p.org

5th International Workshop on HIV & Ageing

20 - 21 October 2014, Baltimore, MD, USA.

The abstract book from this meeting focussed on HIV and ageing is available online, as are PDF slides from the majority of the presentations.

Unfortunately, the abstract book file is locked which prevents printing, so this can only be read electronically.

http://www.infectiousdiseasesonline.com/abstract-book

http://www.infectiousdiseasesonline.com/5th-hivaging_-presentations

Direct link for abstract book:

http://regist2.virology-education.com/abstractbook/2014_7.pdf (PDF)

Online articles

Mortality in patients with HIV-1 infection starting antiretroviral therapy in South Africa, Europe, or North America: A collaborative analysis of prospective studies

Andrew Boulle et al.

http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001718

Cumulative mortality rates after four years ART in a cohort analysis was similar in South Africa compared to North America (16% vs 15%) - and sometimes lower in adjusted analysis - despite early differences related to high rates of late diagnosis. The rate in Europe was around 5%.

FUTURE MEETINGS

Conference listing 2014/2015

The following listing covers some of the most important upcoming HIV-related meetings and workshops.

Registration details, including for community and community press are included on the relevant websites.

Five Nations Conference on HIV and Hepatitis

8-9 December 2014, London

http://www.bhiva.org

7th International Workshop on HIV Persistence during Therapy

8-11 December 2015, Miami

http://www.hiv-persistence.com

XXIV International HIV Drug Resistance Workshop

21-22 February 2015, Seattle, Washington USA

http://www.informedhorizons.com/resistance2015

5th International Workshop on HIV & Women, from Adolescence through Menopause

21-22 February 2015, Seattle

http://www.virology-education.com

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

23-26 February 2015, Seattle

http://www.croi2014.org

21st BHIVA Spring Conference

21 - 24 April 2015, Brighton, UK

http://www.bhiva.org/AnnualConference2015.aspx

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

19-22 July 2015, Vancouver, Canada

http://www.ias2015.org

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

Date and venue TBC, but linked to EACS, Barcelona

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

15th European AIDS Conference (EACS)

21–24 October 2015, Barcelona

http://www.eacs-conference2015.com

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website: updates for PDA access

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

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

Publications and regular subscriptions can be ordered online.

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

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

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

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

Non-technical treatment guides

i-Base treatment guides

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

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

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

Publications and reports

HIV Treatment Bulletin (HTB)

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

HTB South

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

HTB Turkey

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

HTB West Balkans

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

Why we must provide HIV treatment information

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

Translations of i-Base publications

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

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

Advocacy resources

UK CAB: reports and presentations

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

http://www.ukcab.net

Phoneline and information services

Online Q&A service

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

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

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http://i-base.info/order

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- **Guide to Changing Treatment and Drug Resistance** *(February 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **HIV and your Quality of Life: Side Effects and other Complications** *(July 2012)*
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- **Guide To HIV and hepatitis C coinfection** *(November 2013)*
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- **Clinical Trials: a community guide to HIV research** *(March 2009)*
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