ISSN 1472-4863

hiv treatment bulletin (e)

htb(e): volume 17 number 1/2

january-february 2016

CONTENTS

Published by HIV i-Base

EDITORIAL

With barely a nod since the New Year, this issue of HTB is especially sparky with international and UK news that affects important aspects of both current and future HIV care.

Reports from the 44th World Lung Conference include a promising nine-month regimen for MDR-TB and PK data for children.

And reports from BHIVA include the political issue of the gap between best clinical evidence (in NICE accredited BHIVA guidelines) and current commissioning guidelines (based on recommendations from 2012). This threatens to make early access to care in England the worst in the world, with little indication there is any urgency for change before 2018.

Luckily the disparity can be easily covered by wider use of Treatment as Prevention (TasP) for people with CD4 counts above the current threshold of 350 cells/mm3 being used by NHS England.

TasP has been commissioned in England since July 2015 and as ART at any CD4 count is already included for clinical reasons in UK, US, European and WHO guidelines, we hope TasP prescribing will enable everyone in the UK to access ART.

Global ART is highlighted relating to WHO guidelines and new generic drugs - most importantly the prospect that dolutegravir could cost as little as US$ 44 a year.

Other reports on reduced ART – either dolutegravir monotherapy or dolutegravir plus 3TC – are covered in additional articles from the perspective of global access. Studies to evaluate these strategies are an urgent priority.

And prevention news includes that tenofovir/FTC has at last been filed in the EU for a PrEP indication. We also report a caution that dual therapy is likely to be essential for optimal protection, rather than simply tenofovir alone (although this still recommended for programmatic reasons in WHO guidelines).

With UK access to PrEP largely dependent on people importing generic medicines for personal use – nicely summarised in one of the talks at BHIVA - it is right that NHS clinics provide the minimal additional monitoring ("it costs pence") in order to ensure these medicines are used safely. VAT however may be payable.

Plus other news on NICE approval of new HCV drugs, promising strategies for a cure, and a warning from Public Health England about microbial-resistant Shigella.

Happy reading for the start of 2016... Our next issue will bring reports from the Conference on Retroviruses and OIs (CROI) being held this year in Boston in a few weeks time.

CONFERENCE REPORTS

44th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease

2 – 6 December 2015, Cape Town.

Introduction

The annual World Conference on Lung Health in 2015 was held from 2-6 December in Cape Town.

Although this meeting has limited access to online content, weblinks are included for the abstracts reported below.

Reports from this meeting in this issue of HTB are:

- Promising first results with a 9-month regimen for multidrug resistant tuberculosis in francophone Africa
- Pharmacokinetics of old and new TB drugs for children
- The REALITY trial: cotrimoxazole/isoniazid/pyridoxine tablets are bioequivalent to individual products and are acceptable to participants

Promising first results with a 9-month regimen for multidrug resistant tuberculosis in French-speaking African countries

Polly Clayden, HIV i-Base

Good preliminary results from an observational trial of a 9-month regimen for multidrug resistant (MDR) TB conducted in francophone Africa were presented at the 46th World Health Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union).

In 2010 a study conducted in Bangladesh in 206 participants reported 88% cure rates without relapse with a 9-month MDR-TB treatment regimen.

Following these results, a group of francophone countries launched an observational study using a similar 9-month regimen. The study was coordinated by The Union and from January 2013 to March 2015 recruited participants in: Benin, Burkina Faso, Burundi, Cameroon, Ivory Coast, Niger, Central African Republic, Democratic Republic of Congo and Rwanda. All participants had confirmed rifampicin resistance. Pregnant women, children less than 18 years of age and people who had previously received second-line TB treatment were excluded.

The regimen was: four months of kanamycin, moxifloxacin, prothionamide, isoniazid, clofazamine, ethambutol, and pyrazinamide (4 Km Mfx Pto H Cfz E Z), and then five months of moxifloxacin, clofazamine, ethambutol and pyrazinamide (5 Mfx Cfz E Z). Treatment was directly observed throughout the study.

Participants had clinical, biological and bacteriological (smear and culture) examinations monthly during treatment and six-monthly after finishing treatment. Drug susceptibility testing was performed on initial strains and on those isolated at six months of treatment or later. Further analyses were done at Supranational Laboratories (Anvers, Milan).

The study recruited 1029 participants over 27 months. Christopher Kuaban presented preliminary results on 408 participants who started treatment before 1 July 2014.

The study population overall was a median age of 33.5 years, 37% women and 22.4% HIV positive. Over half the participants had severe lung disease, 28% had failed first-line TB treatment and 26% category II, 27% had relapsed,14% were new MDR-TB cases and 5% other.

After three months of treatment, 89% of participants were culture negative and 77% smear negative. Treatment outcomes for 408 participants were: 80.4% cured, 1.7% completed treatment, 2.9% failed, 7.8% died, 6.6% lost to follow up and 0.5% not evaluated.

High-level resistance to isoniazid was common and associated with moderately reduced cure rate compared to low and unknown level resistance: 76.1% vs 87.8%, p >0.05. High-level resistance to a fluoroquinalone, although rare, reduced the likelihood of cure considerably compared to low-level or susceptible: 37.5% vs 83.7% vs 83.3%, p <0.001.

A greater proportion of HIV positive (n=91) than HIV negative (n=319) participants included in the analysis died (18% vs 5%). But among those who survived cure rates were similar: 89% in HIV positive and 89.3% in HIV negative participants.

Hearing loss was the most frequent severe adverse event: 4% Grade 3 and 4% Grade 4. Other adverse events (gastrointestinal, hepatic and renal) were common but Grade 3 and 4 events were very rare. Hearing loss occurred more frequently in HIV positive participants (17% vs 7%, p<0.01) and people with hearing loss at baseline (23% vs 4%, p<0.01).

Dr Kuaban said he has "High hopes for the nine-month MDR treatment regimen."

Reference

Kuaban C et al. First results with a 9-month regimen for multidrug-resistant tuberculosis (MDRTB) in francophone Africa. 46th World Health Conference on Lung Health of the International Union Against Tuberculosis and lung Disease. 2 – 6 December 2015, Cape Town. LB CDC.
http://tinyurl.com/hjwp2j3

http://html5.slideonline.eu/event/15UNION/presentation/56a880a2a2195c4c12ffab5d/480/4:3/first-results-with-a-9-month-regimen-for-multidrug-resistant-tuberculosis-mdr-tb-in-francophone-africa-english

Pharmacokinetics of old and new TB drugs for children

Polly Clayden, HIV i-Base

Several presentations at the 44th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease showed pharmacokinetic (PK) data for anti-tuberculosis (TB) drugs in children.

These included new data on first-line drugs in infancy – a time of rapid growth and developmental changes that

potentially influences drug disposition – at World Health Organisation (WHO) recommended higher dosing (since the revision in 2009).

Emerging data on drugs to treat children with multidrug resistant (MDR) TB – from an excellent ongoing programme in Cape Town – as well as the first on delamanid in older children was also shown.

First-line drugs in infants

Infants starting routine first-line TB treatment in Cape Town with WHO-recommended dosing had very low rifampicin (RMP) exposure. Pyrazinamide (PZA) and isoniazid (INH) concentrations met adult target concentrations. Ethambutol (EMB) exposure was similar to that reported from other paediatric studies but lower than adult targets. [1, 2]

This evaluation was conducted between March 2014 and March 2015, to determine the PK of RMP, INH, PZA +/- EMB in infants at respective doses of: 10 (10 to15), 15 (10 to 20), 35 (30 to 40), and 20 (15 to 25) mg/kg/day. Drug concentrations were determined by validated liquid chromatography mass spectrometry and PK parameters calculated using non-compartmental analysis.

The investigators performed intensive PK plasma sampling in infants receiving fixed dose combination (FDC) tablets. They collected samples at: baseline (0 hours), 1, 2, 4, 6 and 8 hours post-dosing. Infants received approved single TB drug formulations on the day of PK sampling, including two different RMP suspensions.

There were 39 infants included in the study: 26 (67%) (74%) male, 29 black, 14 (36%) with culture-confirmed TB, 15 (38%) premature, 22 (56%) HIV-exposed and 5 (13%) were coinfected with HIV. Their mean age was 6.6 months (SD 3.3), and weight 6.45 kg (SD 1.67). All 39 infants received RMP, INH and PZA and 16 (41%) also received EMB.

Plasma Cmax for RMP, INH, PZA and EMB was 2.9, 7.92, 41.9 and 1.26 ug/mL; AUC0-8 was 12.12, 24.68, 239.4 and 5.09 ug.h/mL, respectively.

Adjusted for age and weight, results for the two RMP formulations differed: Cmax GMR 2.55 (95% CI: 1.47 to 4.41), p=0.001; and AUC0-8 GMR 2.52 (95% CI: 1.34 to 4.73), p=0.005.

HIV coinfection was associated with a lower PZA Cmax and AUC0-8: GMR 0.85 (95% CI: 0.75 to 0.96), p=0.013; and GMR 0.79 (95% CI: 0.69 to 0.90), p=0.001, respectively.

The investigators reported no other significant differences associated with age, weight, prematurity, ethnicity or gender. The majority (85%) of infants had favorable TB treatment outcomes.

There were very low RMP exposures in infants, even when dosed at 15mg/kg/day. PZA and INH concentrations compared well to adult targets. EMB exposure was lower than suggested adult target concentrations, but equivalent to other paediatric studies.

The investigators concluded that the low RMP concentrations observed in infants require further investigation, particularly in the context of future treatment shortening trials in children.

First-line drugs in infants and older children

Related data from Ghana showed, despite the use of revised WHO drug doses, low RMP and EMB Cmax were common among Ghanaian children with TB. [3]

Children aged 3 months to 14 years old receiving first-line TB treatment for at least 4 weeks had samples collected pre-dose, and 1, 2, 4, and 8 hours post-dose.

Of 62 children, 32 (51.6%) were male, median age (IQR) was 5.2 (2.8-8.9) years, 29 (46.8%) were less than five years old and 28 (45.2%) were coinfected with HIV.

The median (IQR) Cmax was 4.8 (3.7 to 6.4) ug/mL for INH, 6.3 (3.5 to 8.8) ug/mL for RMP, 28.6 (21.8 to 35.6) ug/mL for PZA and 1.9 (0.9 to 3.1) ug/mL for EMB.

Cmax below the lower limit of the reference range was considered to be low: INH 3 to 6 ug/mL, RMP 8 to 24 ug/mL, PZA 20 to 60 ug/mL, and EMB 2 to 6 ug/mL.

Including only the children who received the revised WHO doses, the proportions with low Cmax were: INH 13.7% (n=51); RIF 58.8% (n=51), PZA 17.9% (n=56) and EMB 51.8% (n=56).

In multivariate analysis, younger age, OR 1.23, p=0.023, and lower RMP dose, OR 1.28, p=0.004, were associated with low Cmax <8 ug/mL. Shorter height, OR 1.05, p=0.011, was associated with low PZA Cmax <20 mg/mL. Shorter height OR 1.04, p=0.009, was associated with low EMB Cmax <2 mg/mL. None of the factors evaluated affected INH concentrations.

The investigators concluded their findings suggest that higher RMP and EMB doses than currently recommended are necessary to achieve target Cmax in children.

Levofloxacin and amikacin for MDR-TB

Early data from suggested that an amikacin dose of 18-20 mg/kg and levofloxacin of 20 mg/kg should probably be given to children. [4]

Levofloxacin is the most frequently used fluoroquinolone for MDR-TB treatment and prevention in young children. It is currently dosed at 10-15mg/kg once daily.

The second-line injectable TB drugs are used routinely in MDR-TB treatment regimens, at a recommended paediatric once daily dose of 15-30 mg/kg. The PK of levofloxacin and the injectables have not been well characterised in children with MDR-TB.

Up to a quarter of children receiving injectables long-term will have permanent hearing loss. This severe adverse event is likely related to the total cumulative drug exposure.

The Department of Paediatrics and Child Health, University of Stellenbosch, Cape Town – that also performed the infant first-line PK study above – has a large ongoing study to characterise PK and toxicity of second-line TB drugs for treatment and prevention of drug resistant TB in HIV positive and negative children, by age and HIV status. [5, 6] The group showed emerging data from this study on the PK of amikacin and levofloxacin (the later using pharmacometric modelling).

The investigators previously reported PK and short-term safety data on amikacin PK in 28 children with MDR-TB at an intramuscular (IM) dose of 20 mg/kg showed a median Cmax of 47.1 ug/mL, which is above the currently proposed target Cmax of 35-45 ug/mL in a large proportion of children evaluated.

Their previous data on levofloxacin dosed at of 15 mg/kg in 22 young children with MDR-TB showed a median Cmax of 6.79 mg/mL and a median AUC0-inf of 32.9 ug.h/mL. These values are below those seen in adults following the currently recommended 750 mg once-daily dose: Cmax 8.6 ug/mL, AUC0-24 90.7 ug.h/mL.

Further evaluation of amikacin dosed at 20 mg/kg and 15 mg/kg in 96 children found age to have a significant influence on IM amikacin by AUC but not by Cmax. There was no effect by HIV-status or nutritional status (WfA).

The investigators suggested that in order to achieve target adult Cmax of at least 35 ug/mL, an IM amikacin dose of 18-20 mg/kg should probably be given.

They noted that as the majority of children achieved a Cmax of >35 ug/mL at 20mg/kg daily, care should be taken not to exceed this dose unless TDM is available, as hearing loss is associated with cumulative amikacin exposure. They have not yet analysed hearing loss in this cohort.

Levofloxacin was dosed at 15 mg/kg and 20 mg/kg in 109 children and using modelling the investigators found the 20 mg/kg dose more closely approximates adult exposures than 15 mg/kg.

Ofloxacin for MDR-TB

Ofloxacin exposures after a 20 mg/kg dose were low compared with adult targets in a further presentation from the Stellenbosch group. [7]

Ofloxacin is another fluoroquinolone used for the treatment of MDR-TB. Although it is gradually being replaced by levofoxacin and moxifloxacin, ofloxacin is still widely available. It is not known whether the current internationally recommended paediatric dose of 15-20mg/kg meets target adult exposures. After a standard 800mg dose in adults, median PK values are: AUC0-24 103 (48 to 755) ug.h/mL, Cmax 10.5 (8.0 to 14.3) ug/mL, and CL/F 0.12 L/h/kg.

In this study the investigators assessed a 20mg/kg dose of ofloxacin. Plasma samples were collected pre-dose and at 1, 2, 4, 8 and either 6 or 11 hours post-dose.

Of 85 children <15 years old with a median age of 3.4 years, 11 (13%) were coinfected with HIV and 14 (18%) underweight.

Mean (range) Cmax and AUC0-8 were 8.97 ug/mL (2.47 to 14.40) and 44.2 ug.h/mL (12.1 to 75.8), respectively; AUC0-24 was 66.7 ug.h/mL (18.8 to120.7) and half-life was 3.47h (1.89 to 6.95), CL/F was 0.33 L/h/kg (0.10 to1.04). The investigators reported more rapid clearance in younger children, p=0.001.

In multivariate analysis each additional kg of body weight increased AUC by 1.46 ug.h/L, p=0.006. Cmax also associated with age (p=0.005) and weight (p=0.029) but the investigators suggested that this should be interpreted cautiously.

The investigators noted that crushing tablets did not affect the overall bioavailability of ofloxacin. HIV and malnutrition had no effect. The investigators are using these data to simulate optimal dosing to achieve adult targets. But, despite low exposures the outcomes (not presented) were good at this dose raising questions about adult targets.

Delamanid for MDR-TB

Exposure to delamanid 100 mg twice daily was safe and well tolerated in adolescents with MDR-TB. Plasma concentrations in this age group were within the range seen in adult studies, suggesting that the current standard adult dose is adequate for this age group. [8]

Data were from a phase 2, open-label, uncontrolled, trial of delamanid in children with MDR-TB aged 12 17 conducted at De La Salle Health Sciences Institute and Lung Center of the Philippines.

Delamanid was given with an optimised background regimen (OBR) for six months followed by OBR alone as recommended by WHO. The investigators performed clinical and safety assessments approximately every 2-4 weeks for up to one year. Sparse PK sampling for concentrations of delamanid and DM-6705 (a key delamanid metabolite) were conducted on days: 1, 14, 56, 98, 154, 182, 189, 196, 203, 210, and 238.

Nine participants were screened and seven enrolled in this study. Six (86%) had confirmed MDR-TB, and one (14%) probable MDR-TB. All seven participants (100%) had pulmonary disease, and six (86%) had previously received treatment for TB. The median age was 15 years (13 to 17); four were male, three female; median weight and BMI were 38.5 (26-45) kg and 15.9 kg/m_2 (15-20), respectively.

No participants discontinued before the end of the study but one had delamanid withdrawn due to non-adherence and subsequent pregnancy. There were no serious adverse events reported. The most common adverse event reported was headache, reported in five participants (71.4%). No one experienced an absolute QTcF greater than 500ms.

During delamanid treatment, the median Cmax ranged from 354 to 657ng/mL. Compared to adults, median delamanid concentrations were higher in this age group but within the adult range. Median DM-6705 levels were lower than in adults.

Delamanid is now being assessed in children younger than 12 years of age.

C O M M E N T S

More data is needed to confirm the delamanid results; n=7 is very small for a drug with relatively high PK variability.

Anneke Hesseling from the Stellenbosch group gave an excellent overview on planned and ongoing paediatric trials for MDR-TB identifying research priorities. [9] These included injectable-sparing, shorter and less toxic regimens and evolving adult targets. The presentation is online.

References

Unless stated otherwise, references are to the programme and abstracts of the 44th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease, 2 – 6 December 2015, Cape Town.

1. Bekker A et al. The pharmacokinetics and treatment of first-line TB drugs for infants. 44th World Lung Conference, Cape Town, 2015. Symposium 8.
   http://tinyurl.com/hmba7c6
   http://html5.slideonline.eu/event/15UNION/presentation/56a880a2a2195c4c12ffaa4c/309/4:3/the-pharmacokinetics-and-treatment-of-first-line-tb-drugs-for-infants
2. Bekker A et al. Pharmacokinetics of rifampicin, isoniazid, pyrazinamide and ethambutol in South African infants at revised WHO recommended dosing guidelines. 44th World Lung Conference, Cape Town, 2015. Poster abstract PC-1081-05.
3. Kwara A et al. Pharmacokinetics of first-line antituberculosis drugs in children with tuberculosis with and without HIV coinfection. 44th World Lung Conference, Cape Town, 2015. Oral abstract OA-424-05.
   http://tinyurl.com/j8co5rm
   http://html5.slideonline.eu/event/15UNION/presentation/56a880a2a2195c4c12ffab33///pharmacokinetics-of-first-line-antituberculosis-drugs-in-children-with-tuberculosis-with-and-without-hiv-coinfection-english
4. Garcia-Prats A. Emerging data on PK and safety of levofloxacin and amikacin informs care and design of new regimens. 44th World Lung Conference, Cape Town, 2015. Symposium 27.
5. Clayden P. Pharmacokinetics and safety of moxifloxacin in children. HTB. 29 January 2015.
   http://i-base.info/htb/27733
6. Clayden P. Preventing and treating TB in children – more baby steps. HTB. 1 December 2013.
   http://i-base.info/htb/24037
7. Garcia-Prats A et al. The pharmacokinetics and safety of ofloxacin for drug-resistant tuberculosis in children. 44th World Lung Conference, Cape Town, 2015. Oral abstract OA-479-06.
   http://tinyurl.com/ja46pxl
   http://html5.slideonline.eu/event/15UNION/presentation/56a880a2a2195c4c12ffac0c///the-pharmacokinetics-and-safety-of-ofloxacin-for-drug-resistant-tuberculosis-in-children
8. Hafkin J et al. Long-term safety, tolerability, and pharmacokinetics of delamanid in children aged 12–17 years. 44th World Lung Conference, Cape Town, 2015. Poster abstract EP-115-04.
9. Hessling AC. Update on MDR-TB treatment in children. 44th World Lung Conference, Cape Town, 2015.
   http://tinyurl.com/z36p98g
   http://html5.slideonline.eu/event/15UNION/presentation/56a880a2a2195c4c12ffaaca/404/4:3/update-on-planned-and-ongoing-trials-on-mdr-tb-prevention-and-treatment-in-children

The REALITY trial: cotrimoxazole/isoniazid/pyridoxine tablets are bioequivalent to individual products and are acceptable to participants

Polly Clayden, HIV i-Base

Cotrimoxazole/isoniazid/pyridoxine (CTX/INH/B6) scored fixed dose combination (FDC) tablets are bioequivalent to individual drugs and are acceptable, reduce pill burden and could improve adherence for adults and children, according to results from the REALITY trial presented at the 46th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union).

FDCs are used widely for treatment of HIV and TB, which help both patients and health systems. HIV positive people, starting ART with low CD4 counts benefit from opportunistic infection (OI) and anti-TB prophylaxis.

But individual drug formulations of isoniazid and cotrimoxazole increase the pill burden of ART and could lead to adherence difficulties early in treatment when mortality risk is high.

Cipla have made a scored generic CTX/INH/B6 (960/300/25 mg) tablet. The new FDC was first used in the REALITY trial. Diana Gibb presented data on bioequivalence and from an acceptability and adherence questionnaire on behalf of the trial group.

The investigators evaluated the FDC tablets for bioequivalence compared with separate tablets of sulfamethoxazole 800 mg/trimethoprim160 mg and isoniazid 300 mg in an open-label, randomised, single-dose, two treatment, two period, 26 sample crossover pharmacokinetic (PK) study.

The evaluation was in 28 fasting healthy participants (18 male and 10 female and found LSGM ratios well within required 80–125% range (and close to 100%) for all parameters. For sulfamethoxazole, trimethoprim and isoniazid respectively these values were: Cmax 103.2% (90% CI: 99.5 to 107.0); 98.2% (90% CI: 93.4 to103.9); and 104.3% (90% CI: 95.1 to 114.4): AUC0-t 99.8% (90% CI: 96.2 to 114.4); 97.2 (90% CI: 93.7 to 100.9); and 103.8 (90% CI: 99.5 to 108.3).

The REALITY trial is looking at reducing early mortality in HIV positive adults and children starting ART. The trial has a 2x2x2 factorial, randomised trial design evaluating 12-week enhanced OI prophylaxis, 4-drug ART and enhanced nutrition in 1800 African adults/children from 5 years of age with CD4 less than 100 cells/mm^3.

The trial is ongoing and being conducted in nine centres in four countries: Kenya, Malawi, Uganda and Zimbabwe. Each intervention is given in addition to and compared with local standard of care for 12 weeks. The trial started in June 2013 and will finish in April 2016. The primary endpoint is mortality at 48 weeks.

Dr Gibb presented acceptability and adherence findings from the enhanced prophylaxis part of the trial. In this factorial, participants are randomised to receive the CTX/INH/B6 FDC and fluconazole, plus five days azithromycin and single dose albendazole vs standard cotrimoxazole prophylaxis and isoniazid added from 12 weeks (except in Malawi, as this is not in guidelines).

An acceptability/adherence questionnaire was administered every 12 weeks. Within-individual data were collected weeks 12-24 on FDC vs cotrimoxazole alone (weeks 0-12) in 319 participants. Between-individual data were collected in weeks 0-12 among those receiving FDC plus fluconazole (n=543) vs cotrimoxazole (n=604).

The questionnaire revealed no within-individual differences in acceptability reported between FDC vs cotrimoxazole: 99.7% vs 99.4% reported none/not much interference with everyday life and 95.6% vs 96.6% reported that the drugs were very easy/easy to take.

The comparison between-individuals gave similar results: 500/543 (92.1%) vs. 565/604 (93.5%), p=0.8 reported taking medication was very easy/easy; 4.0% vs 3.9% reported missing approximately one dose within the last 12 weeks.

Overall the investigators concluded that the new FDCs are acceptable, reduce pill burden and could improve adherence as well as simplifying drug distribution for HIV programmes.

C O M M E N T

The REALITY trial will report in mid-2016 and will provide information on whether or not enhanced, immediate OI prophylaxis reduces mortality, TB and other OI morbidity, and/or increases toxicity in people starting ART with low CD4 counts (approximately 1 in 4 in African countries).

The CTX/INH/B6 FDC was submitted to WHO for prequalification in September 2014. A half-dose scored tablet is needed for less than five year-olds.

References

Gibb DM et al. Sulfamethoxazole/trimethoprim/isoniazid/pyridoxine scored tablets are bioequivalent to individual products and are acceptable to patients with advanced HIV infection in the REALITY trial. 46th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union). HIV-TB LB.

http://tinyurl.com/zquwwvc

http://html5.slideonline.eu/event/15UNION/presentation/56a880a2a2195c4c12ffabdd/576/4:3/sulfamethoxazoletrimethoprimisoniazidpyridoxine-scored-tablets-are-bioequivalent-to-individual-products-and-are-accept-able-to-patients-with-advanced-hiv-infection-in-the-reality-trial-english

CONFERENCE REPORTS

BHIVA Autumn Conference 2015

12 – 13 November 2015, London

Introduction

This year the BHIVA Autumn meeting was notable for highlighting the current differences between clinical guidelines and the current commissioning policy.

Such is the importance of this difference that for the first time BHIVA are now adopting a proactive approach to challenge the commissioners.

It is notable that many doctors were openly saying they will use the option to prescribe treatment as prevention (TasP) in order to overcome the commissioning restriction on prescribing ART at CD4 counts >350 cells/mm^3.

The programme from the meeting is available from the BHIVA website.

http://www.bhiva.org

As with all BHIVA conferences, webcasts of the oral presentations are available as a free educational resource, especially for those who were unable to attend the meeting.

Slides from each talk are also available to download.

http://www.bhiva.org/Autumn2015Presentations.aspx

Selected webcasts from BHIVA Autumn conference 2015

Simon Collins, HIV i-Base

As with previous meetings, the BHIVA Autumn conference included important presentations that are available as webcasts after the meeting.

All the talks at BHIVA are important, but the selections below are perhaps essential for a UK audience. These presentations ranged from around 15 to 30 minutes - easy to watch - of course you can find this time.

- BHIVA treatment guidelines 2016: important changes compared to commissioning guidelines
- Implementing PrEP within a sexual health clinic
- HIV and ageing – a review of the evidence
- The importance of peer support in HIV care
- Smoking cessation - a review for HIV management
- The disclosure of an HIV positive adult to their HIV negative child
- Osteoporosis and HIV
- Hormone Replacement Therapy (HRT): managing HIV through the menopause
- Stigma Index Study: a continued issue in the UK

BHIVA treatment guidelines 2016: important changes that conflict with commissioning guidelines

Dr Duncan Churchill and Dr LaÒura Waters

A clear and unequivocal review of the evidence for universal access to ART at any CD4 count, now supported by the strongest rating. This includes a new recommendation for recent HIV infection (<12 weeks) as an indication for immediate ART, as is Treatment as Prevention.

With >90% of diagnosed people already on treatment, this recommendation directly affect about 7,000 people. Indirectly, the stronger recommendation is hoped to reduce late diagnosis in the UK.

The talk raised the importance of resolving the conflict between the new BHIVA guidelines and current NHS commissioning which is still based on 2012 guidelines. The CRG currently proposes to only undertake a review of TasP in England as a "workplan item for 2016/17" and to only "develop a policy proposition for 2017/18" unless it meets criteria for in-year service development. The recommendation from BHIVA is that clearly this needs to be resolved in year.

Dolutegravir and rilpivirine (within its license for <100,000 viral load) have been added to preferred third-drug options for first-line combinations. Efavirenz has been downgraded from a preferred to alternative option. Tenofovir/FTC is the preferred dual NRTI backbone with abacavir/3TC included as an alternative. Dual darunavir/r plus raltegravir is included as an alternative for people with CD4 counts >200 cells/mm^3 who have no NRTI options.

The impossibility of cost effectiveness analysis was made in the context of a UK pricing structure that is "regionally variable, rapidly changing, and made behind closed doors".

The guidelines are dedicated to Dr Martin Fisher.

http://www.bhiva.org/151112DuncanChurchill-LauraWaters.aspx

http://www.bhiva.org/documents/Conferences/Autumn2015/Presentations/151112/DuncanChurchill-LauraWaters.pdf (PDF)

Implementing PrEP within a sexual health clinic

Dr Mags Portman

This presentation on PrEP highlighted the under-appreciation of individual risk experienced by many HIV negative people, the practical experience of providing PrEP, and the high efficacy reported from programmes where PrEP is now widely available.

The talk showed how most of the services needed to support someone on PrEP are already routinely available free on the NHS. This includes HIV, HBV and other STI testing, discussing and supporting strategies to reduce HIV risk, recreational drug assessment and awareness of seroconversion symptoms and PEP.

The additional services of baseline and routine renal function (3 monthly urinealysis and 6-12 monthly creatinine) are cheap ("it costs pence") plus adherence counselling (including a benefit/risk discussion) that could easily fit within current risk awareness discussions.

The presentation noted that US, European and WHO guidelines already strongly recommend availability of PrEP for people at high risk of HIV infection.

Two quotes: "If PrEP remains unfunded it will remain an unregulated party drug... and drug levels might not be effective in this setting"; and "We ***can*** talk to service users and colleagues about PrEP. We ***can*** inform them where to get PrEP based on community websites. We ***can*** talk about pleasure to reduce stigma. People are making a positive choice to take PrEP, they know they are at risk".

http://www.bhiva.org/151112RobbieCurrie-MagsPortman.aspx

Note: this presentation is the second PrEP talk, starting at 12 minutes in the webcast link.

http://www.bhiva.org/documents/Conferences/Autumn2015/Presentations/151112/MagsPortman.pdf (PDF)

HIV and ageing – a review of the evidence

Professor Brian Gazzard

An overview lecture that broadly set out to allay concerns that growing older is necessarily associated with a range of increased risk of other comorbidities for HIV positive people compared to people who are HIV negative.

This promising outcome is dependent on access to effective ART and adoption of lifestyle changes linked to better health in the general population.

Although these conclusions were reached by a route that included a sometimes less-than-evidence-based criticism of cohort studies, HIV related inflammation, global warming, BHIVA research grants and CHARTER neurological research, this is an easy talk to watch with important references to current research.

http://www.bhiva.org/151112BrianGazzard.aspx

http://www.bhiva.org/documents/Conferences/Autumn2015/Presentations/151112/BrianGazzard.pdf (PDF download)

The importance of peer support in HIV care

Laura K, Marc Thompson, Alex Sparrowhawk and Dr Ian Williams

The four presentations in the community symposium focused on different approaches to peer advocacy including the practical examples from the Mortimer Market which was the first NHS clinic to employ peer advocates as a core part of their HIV services.

These are important talks for any clinic that wants to develop better and cost effective services for their patients.

http://www.bhiva.org/151112CommunitySymposium.aspx (webcasts)

Smoking cessation - a review for HIV management

Dr Louise Restrick

Excellent talk from a respiratory disease doctor talking about COPD, lung cancer and other respiratory diseases based on ten years experience with smoking cessation programmes – now reporting 50% quit rates at 6 months.

Almost 40% of people diagnosed with COPD are still smokers after their diagnosis – a figure unchanged for the last ten years: smoking and nicotine dependence is addictive. As such, it is a chronic condition often started in childhood.

Smoking cessation – with new medication for nicotine replacement (including varenicline) and shared decision making – is, at £2000 per QALY, one of the most cost effective medical interventions.

The talk emphasised the importance of actively asking about and recording smoking status - both cigarettes and cannabis; having a cessation specialist in any team; including a carbon monoxide monitor as a motivational tool; and wide use of nicotine replacement treatment.

More HIV positive life years lost are from smoking compared to HIV (importantly referenced in two key studies: by Helleberg M et al. in CID 2013 and AIDS 2015).

http://www.bhiva.org/151113LouiseRestrick.aspx (webcast)

http://www.bhiva.org/documents/Conferences/Autumn2015/Presentations/151113/LouiseRestrick.pdf

The disclosure of an HIV positive adult to their HIV negative child

Rebecca Brown and Angelina Namiba

As part of the shared programme with CHIVA this talk included two perspectives – one a first-hand account – on the complex issues of telling your child that you are HIV positive: sharing, naming, telling and talking rather than the loaded term “disclosure”.

http://www.bhiva.org/151113RebeccaBrown-AngelinaNamiba.aspx (webcast)

http://www.bhiva.org/documents/Conferences/Autumn2015/Presentations/151113/AngelinaNamiba.pdf

Osteoporosis and HIV

Dr Karen Walker-Bone

Excellent overview about HIV and bone health including screening and management.

http://www.bhiva.org/151113KarenWalkerBone.aspx (webcast)

http://www.bhiva.org/documents/Conferences/Autumn2015/Presentations/151113/KarenWalkerBone.pdf (PDF)

Hormone Replacement Therapy (HRT): managing HIV through the menopause

Dr Shema Tariq

The first time that BHIVA included an overview of the under-researched issues of HIV and menopause. This is an issue that is likely to affect up to 10,000 HIV positive women in the UK over the coming years.

Menopause was discussed as a process taking place over many years (median duration 7 years). Most women (85%) are likely to experience symptoms, with 1 in 4 likely to be sufficiently severe to affect daily life. Menopause has both biological and cultural impact.

This talk includes information about new NICE guidelines on management with HRT and the upcoming UK HIV PRIME study.

http://www.bhiva.org/151113ShemaTariq.aspx (webcast)

http://www.bhiva.org/documents/Conferences/Autumn2015/Presentations/151113/ShemaTariq.pdf (PDF)

Stigma Index Study: a continued issue in the UK

Alastair Hudson, Rebecca Mbewe and Dr Valerie Delpech

Report from the 2015 community initiated stigma index survey of more than 1500 HIV positive people across the UK, a third of whom are from black and minority communities. Preliminary results included that almost half of the participants have had negative self-image relating to HIV over the previous year and that this correlated with avoiding non-HIV healthcare such as GP and dental services.

Fear of disclosure related not just to personal relationships but also to job security. More than half the participants said that disclosure issues had led to avoiding development of specific relationships. Just under one third of the participants had been rejected by a potential partner because of their HIV status, with about 1 in 10 discriminated against at family settings and another 1 in 10 being denied health services.

http://www.bhiva.org/151112ValerieDelpech-AlastairHudson-RebeccaMbew.aspx (webcast)

http://www.bhiva.org/documents/Conferences/Autumn2015/Presentations/151112/ValerieDelpech-AlastairHudson-RebeccaMbew.pdf (PDF)

TREATMENT ACCESS

Treatment as Prevention (TasP) in the UK supports access to ART at any CD4 count

Simon Collins, HIV i-Base

It is a significant advance that since July 2015 the NHS has funded antiretroviral HIV treatment (ART) to reduce the risk of further HIV transmission – commonly referred to as Treatment as Prevention (TasP). [1]

Luckily this policy also enables broad access to ART irrespective of CD4 count, bringing the UK in-line with BHIVA, US, European and WHO treatment guidelines.

Currently, HIV commissioners are attempting to enforce a policy that restricts access to HIV treatment until CD4 cells count dropped to 350 cells/mm^3 even though BHIVA clinical guidelines in 2015 recommend treatment irrespective of CD4 count.

Criteria for commissioning TasP

The Clinical Reference Group (CRG) policy from NHS England lists the following criteria for routinely commissioning of TasP, with expectations that *all* of the criteria below are met.

- Laboratory confirmed diagnosis of HIV infection.
- Sexually active.
- TasP is offered by the doctor.
- Discussion between doctor and patient has identified significant risk of HIV transmission to partners without TasP.
- TasP is prescribed as part of a full assessment of risk factors by the clinical team and is part of a risk reduction plan discussed with the patient.
- Patient has considered the information relating to TasP and understands the risks and benefits of treatment to prevent onward HIV transmission.
- Regimen selected is the lowest cost, clinically appropriate option.

While many of these are not controversial and others seem reasonable, the exact wording is unspecific on some issues, allowing doctors to broadly interpret risk in favour of earlier access to ART.

Interpreting CRG policy

The TasP policy effectively enables all HIV positive people in the UK to access ART, and overcomes an access issue that denies the clinical benefits of ART to people at higher CD4 counts.

Although the policy enables access to ART, the rationale for approval uses language that underestimates the difficulties that most HIV positive people experience.

- Requiring that a person is sexually active ignores the not uncommon decision that many HIV positive people take to abstain from sex, largely on the basis of protecting sexual partners. The requirement for "current" partners in the policy underestimates the continued stigma and prejudice against HIV positive people from HIV negative (or untested) potential partners.

  On both these points the real benefit of TasP should be to support HIV positive people to be able to develop and sustain relationships; but TasP is the essential first step that helps enable this, not the final one. TasP is needed in order to enable people to start to rebuild a health sex life.

- The phrase "identifying significant risk" needs to be broadly interpreted. Significant risk is actually covered by the potential for a condom to break or even the fear that a condom might break. It is very unlikely that the policy requires HIV positive people to say they currently put partners at risk in order to access ART (for either prevention or treatment).

- Current treatment guidelines already cover the cost of treatment in relation to clinical evidence, and the appropriate referral should have been to clinical guidelines, not a reference to cost.

C O M M E N T

The TasP policy from July 2015 is an essential document for people whose CD4 counts are higher than 350 cells/mm^3 and who are otherwise currently excluded from receiving ART based on current commissioning policy. The limited financial impact from the policy is recognised in the document as most HIV positive people who are diagnosed are already on ART.

TasP overcomes a gap between UK clinical guidelines and commissioning policy. BHIVA HIV treatment guidelines, accredited by NICE, recommend that all HIV positive people should start ART for clinical benefits, irrespective of their CD4 count and yet commissioning for earlier ART would not produce changes in policy for at least two years. [2]

NHS commissioners have so far refused to prioritise earlier ART based on results from the START study in July 2015. [3] These results were so significant that the World Health Organisation (WHO) issued a statement within weeks indicating that WHO guidelines would change. [4, 5] Based on results from the START study US guidelines have strengthened the evidence rating for universal ART and European guidelines have removed the CD4 threshold criteria. [6, 7]

Luckily, the NHS allows sufficient flexibility for ART to now be prescribed to all HIV positive people using the TasP policy, irrespective of the current risk of transmission.

Reference

1. Specialised Commissioning Team, NHS England. Treatment as Prevention in HIV infected adults (F03/P/c). July 2015). https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/f03pc-tasp-oct15.pdf (PDF)
2. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy (2015). BHIVA. http://www.bhiva.org/HIV-1-treatment-guidelines.aspx http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf (PDF)
3. Lundgren J et al. Initiation of antiretroviral therapy in early asymptomatic infection. NEJM (20 July 2015). DOI: 10.1056/NEJMoa1506816. http://www.nejm.org/doi/full/10.1056/NEJMoa1506816
4. Clayden P. New directions in the 2015 WHO ART guidelines. HTB August 2015. http://i-base.info/htb/28597
5. WHO. Policy brief. Consolidated guidelines on the use of ARVs for treating and preventing HIV infection: what's new. November 2015. http://www.who.int/hiv/pub/arv/policy-brief-arv-2015/en
6. US DHHS. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. (January 2016). https://aidsinfo.nih.gov/guidelines
7. European AIDS Clinical Society. Guidelines. Version 8.0, October 2015. English edition. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

WHO 2015 guidelines: newly recommended generic ART products on the way for adults

Polly Clayden, HIV i-Base

Generic versions of newly recommended antiretrovirals and fixed dose combination (FDC) regimens will be available for adults this year and next. But for children key formulations to implement 2013 recommendations are still unavailable.

Among the many announcements and outpourings on 1st December 2015, was a stealth policy brief by World Health Organisation (WHO) at ICASA summarising what's new in the upcoming consolidated ART guidelines. [1]

The revised guidelines include 10 new recommendations, most importantly on universal eligibility for ART, so more people

will start ART earlier. Since IAS 2015 WHO has released a couple of sneak previews and we await more details in the full guidelines, expected in the next few months. [2,3]

As well as clinical recommendations (including using antiretrovirals for prevention for all populations at substantial risk of acquiring HIV) the document has guidance on service delivery to support implementation. WHO notes that for the first time recommendations include good practice statements on interventions where the benefit substantially outweighs the potential harm.

The preferred and alternative first-line ART regimens are shown in Table 1. The preferred regimens remain the same as 2013 recommendations. For adults and adolescents the alternatives include the introduction of low dose efavirenz (EFV 400) and dolutegravir (DTG). FDC and once-daily ART regimens are also preferred.

Table 1: WHO 2015 preferred and alternative first-line ART regimens

First line ART	Preferred regimens	Alternative regimens
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG TDF + 3TC (or FTC) + EFV400 TDF + 3TC (or FTC) + NVP
Pregnant / breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG TDF (or ABC) + 3TC (or FTC) + EFV400 TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

Key: ABC, abacavir; AZT, zidovudine; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LVP/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

New recommendations for second line ART are shown in Table 2. Those include ritonavir boosted darunavir (DRV/r) or raltegravir (RAL) as alternatives to boosted lopinavir (LPV/r) for adults and adolescents. For children RAL-based second-line is recommended after LPV/r-based first-line.

Similarly to the 2013 guidelines, third-line includes new drugs (if available) with the least risk of cross resistance to those used already.

Table 2: WHO 2015 preferred and alternative second- and third-line ART regimens

<table>
<tr><th>First line ART</th><th>Preferred regimens</th><th>2nd-line regimens</th><th>3rd-line regimens</th></tr>
<tr><td rowspan="4">Adults</td><td rowspan="2">2 NRTIs + EFV</td><td>2 NRTIs + ATV/r or LPV/r</td><td rowspan="2">DRV/r + DTG (or RAL) ± 1-2 NRTIs</td></tr>
<tr><td>2 NRTIs + DRV/r</td></tr>
<tr><td rowspan="2">2 NRTIs + DTG</td><td>2 NRTIs + ATV/r or LPV/r</td><td>DRV/r + 2 NRTIs ± NNRTI</td></tr>
<tr><td>2 NRTIs + DRV/r</td><td>Optimise regimen using genotype profile</td></tr>
<tr><td rowspan="2">Pregnant / breastfeeding women</td><td rowspan="2">2 NRTIs + EFV</td><td>2 NRTIs + ATV/r or LPV/r</td><td rowspan="2">DRV/r + DTG (or RAL) ± 1-2 NRTIs</td></tr>
<tr><td>2 NRTIs + DRV/r</td></tr>
<tr><td rowspan="3">Children</td><td rowspan="2">2 NRTIs + LPV/r</td><td>Less than 3 years: 2 NRTIs + RAL</td><td rowspan="3">DTG + 2 NRTIs
DRV/r + 2 NRTIs
DRV/r + DTG ± 1-2 NRTIs</td></tr>
<tr><td>Older than 3 years: 2 NRTIs + EFV or RAL</td></tr>
<tr><td>2 NRTIs + EFV</td><td>2 NRTIs +ATV/r or LPV/r</td></tr>
</table>

Key: ATV/r, atazanavir/ritonavir; DTG, dolutegravir; DRV/r, darunavir/ritonavir; EFV, efavirenz; FTC, emtricitabine; LVP/r, lopinavir/ritonavir; NVP, nevirapine; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAL, raltegravir.

For adults and adolescents, three new agreements – announced by the Clinton Health Access Initiative (CHAI), UNAIDS and UNITAID, also on World AIDS Day 2015 – will help to implement the new guidelines. Table 3 shows the generic ART pipeline associated with these agreements. [4]

Under the first, Aurobindo will make generic DTG available for US$44 per patient per year (pppy), once it has been approved. CHAI and colleagues say the leadership of the Government of Kenya partly made this launch price possible. Kenya will include DTG in its national guidelines and start providing it to suitable patients as soon as it is approved.

ViiV licensed Aurobindo for generic DTG and the single formulation is already filed with the US FDA for tentative approval. Aurobindo will also file a DTG-based FDC with the US FDA by the third quarter of 2016.

Secondly, Mylan will file for US FDA tentative approval of an EFV400-based FDC in the first quarter of 2016. Once approved this alternative FDC regimen will be available for $US99. CHAI and colleagues note that this price represents an 8% decrease from current ones, which could mean potential savings of US$80-100 million globally through 2020.

Both DTG and EFV400 are recommended as part of WHO alternative regimens for adults until there are sufficient data for pregnant women and people on TB co-treatment. Studies in these populations are planned or already underway. [5]

The third agreement is a partnership between Janssen (the originator manufacturer of darunavir) and CHAI to develop and deliver a heat-stable version of DRV/r for low- and middle-income countries. This boosted protease inhibitor is finally included in WHO guidelines as part of alternative second- and third-line regimens. One reason for this delay was the lack of a generic heat-stable version of DRV/r. CHAI is partnering with Hetero to develop this co-formulation and the generic manufacturer plans to file for regulatory approval by the third quarter of 2016.

Table 3: New generic antiretrovirals available 2016/2017 for adults

ARV, co-formulation or FDC	Generic manufacturer	FDA filing
DTG	Aurobindo	May 2015
DTG/TDF/3TC	Aurobindo	Q3 2016
EFV400/TDF/3TC	Mylan	Q1 2016
DRV/r	Hetero	Q3 2016

Key: DTG, dolutegravir; DRV/r, darunavir/ritonavir, EFV 400, efavirenz 400 mg; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

Providing all this work goes according to plan, there should be generic FDCs available to implement first-line recommendations and a new generic option for second- or third-line for adults and adolescents by the end of 2017. CHAI and UNITAID are also committed to supporting other generic manufacturers who can develop these products for stringent regulatory approval and/or WHO pre-qualification. They note that the manufacturers included here are closest to such approval.

But, appropriate FDCs for children to implement recommendations still lag behind that of adults. Formulations that were missing and needed to implement the 2013 WHO guidelines – particularly LPV/r-based FDCs for younger children and EFV/ABC/3TC for older ones – are still notable by their absence. [6]

References

1. WHO. Policy brief. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: what's new. November 2015. http://www.who.int/hiv/pub/arv/policy-brief-arv-2015/en
2. Clayden P. New directions in the 2015 WHO ART guidelines. HTB. 1 August 2015. http://i-base.info/htb/28597
3. Collins S. New WHO guidelines for when to start ART and use of PrEP (September 2015). HTB. 30 September 2015. http://i-base.info/new-who-guidelines-for-when-to-start-art-and-use-of-prep-september-2015/
4. UNAIDS. Press release. Three new agreements announced with the potential to expand access to innovative HIV treatment in low- and middle-income countries. 30 November 2015. http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2015/november/20151130_PR_CHAI_UNITAID
5. Clayden P. Fit for Purpose: antiretroviral treatment optimisation. 2015 Pipeline Report. 17 July 2015. http://i-base.info/htb/28509
6. Clayden P. WHO 2013 guidelines: what about the missing formulations? HTB. 25 July 2013. http://i-base.info/htb/21847

Better generic ART for low and middle income countries: dolutegravir at US $44 a year

Simon Collins, HIV i-Base

On 30 November 2015, three new agreements were announced that should increase access to better and more affordable generic HIV drugs, including new fixed dose combinations (FDCs). [1]

The agreements were announced in a joint press statement from the Clinton Health Access Initiative (CHAI), UNAIDS, and UNITAID, and are dependent on regulatory approval and/or World Health Organization (WHO) pre-qualification.

The three compounds are:

1. Dolutegravir as a single drug and in an FDC with tenofovir DF and 3TC. The target price of US$ 44 per year for dolutegravir would be comparable to current generic efavirenz-based ART.
2. An FDC of TDF/lamivudine/efavirenz 400 mg (TLE400). Fixed dose combination using lower dose of efavirenz based on data from ENCORE 1 study.
3. Heat stable darunavir/ritonavir (DRV/r).

WHO now recommends DTG as an alternate first-line therapy in those intolerant of efavirenz. Unlike US, UK and European guidelines, the WHO guidelines do not recommend dolutegravir as preferred first-line treatment due to limited data to for women who are or wish to become pregnant or for people on treatment for tuberculosis.

The press release notes that the launch price agreement for dolutegravir was made possible in part by the leadership of the Government of Kenya, which agreed to incorporate dolutegravir into national treatment guidelines as soon as regulatory approval is received.

Table 1. Plans for new generic formulations announced in November 2015

Compound	Company	Cost per year (US$)	Filing date	Comment
dolutegravir (DTG) and dolutegravir / TDF / 3TC FDC	Aurobindo	$44 Not given	May 2015 Q3 2016	Price is comparable to current first-line efavirenz based combinations and significantly lower than current second-line ART.
TDF/3TC/EFV 400 mg FDC (TLE400)	Mylan	$99	Q1 2016	The cost is 9% lower that FDCs using EFV 600 mg.
Heat staple DRV/r	Janssen/ Hetero	Not stated	Q3 2016	Darunavir is the preferred boosted PI in high-income countries, based on once-daily dosing and reduced risk of side effects.

Reference

UNAIDS, CHAI and UNITAID. Joint press announcement. Three new agreements announced with the potential to expand access to innovative HIV treatment in low- and middle-income countries. (30 November 2015).

http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2015/november/20151130_PR_CHAI_UNITAID

When Global Fund support ends: Sustainability lessons from transitions in Costa Rica, Fiji, Romania, and Bulgaria

Gemma Oberth, Aidspan/Global Fund Observer

In anticipation of The Global Fund's new strategy (2017-2022), many are calling for clarity on how the Fund will ensure the sustainability of its investments. This is particularly relevant as the Fund transitions out of many upper-middle-income countries.

When Aidspan approached the Secretariat with questions concerning the Fund's role in transition planning, the Secretariat responded that it is waiting for directions from the new Strategy currently under development and expected to be approved by the Board at the end of April. Nevertheless, in the absence of a transitions policy, the Secretariat has told several countries that they should not anticipate future funding after the 2014-2016 allocation period, and that they should plan accordingly.

To date, discussions about Global Fund transitions have predominantly centered on HIV grants in Eastern Europe, with a heavy focus on harm reduction. Aidspan has previously reported on this. [1] But HIV grants in the EECA region are not the only ones that are transitioning. Aidspan has previously reported on the transition in China. [2] Open Society Foundations (OSF) has documented transitions in Mexico, Jamaica, and Thailand. [3]

How many others countries are going through this process? How are transitions for TB and malaria grants being managed? With little transparency around which countries are transitioning when, it is difficult to monitor the sustainability of programs and to avoid potential service disruptions.

Through its research on The Global Fund's willingness-to-pay policy (see GFO article) [4], Aidspan became aware that the following countries and disease components are currently going through transitions: Costa Rica (HIV), Fiji (TB), Romania (TB) and Bulgaria (TB). This means that these countries are implementing NFM grants with the knowledge that there will be no future funding from the Global Fund. These are being referred to as "transition grants." Each country is employing different sustainability strategies to help mitigate the anticipated impact once the Global Fund departs.

Costa Rica (HIV)

Costa Rica's NFM HIV grant was the first time the Global Fund had invested in the country since Round 3 (2003). "There was an assumption here that this would be the first and last time Costa Rica would get money," a key informant told Aidspan. This had a significant impact on what the country planned to do with the grant. Key informants suggested that "this is not a standard prevention grant doing outreach. It's a much more catalytic grant trying to figure out how you better link civil society organisations that are working on these issues [HIV prevention] to funding."

To this end, portions of the grant are going towards strengthening the Social Projection Board (JPS), a government funding mechanism which ensures local NGOs are able to access public money to deliver HIV services. The transition grant is also working to ensure that there are specific provisions in the JPS for funding NGOs that do prevention work with transgender women and men who have sex with men. "It's about how you use small and final allocations from the Global Fund in a smart way," said another key informant.

Fiji (TB)

In two years' time, Fiji will no longer have Global Fund resources to support its TB programme. Knowing that it is transitioning, the country is heavily prioritising shifting human resources (HR) within the Ministry of Health that are funded by the Global Fund over to government budget lines. According to key informants at the Global Fund Secretariat, this decision to focus on HR sustainability during the transition emanated from local partners, "but naturally we have been discussing sustainability and saying they should shift the HR costs to the country."

Partners in country note that their transition grant is about strengthening health systems. "We are exploring how best to allocate the government funding after the Global Fund leaves, looking at different models to allocations." Fiji is also exploring innovative ways to leverage additional funding using its transition grant. Country contacts told Aidspan that part of the 2017 budget might be used to leverage additional money from other lenders and sources to sustain the TB programme once the Global Fund leaves.

Romania (TB)

Romania has already been through a transition for its Global Fund HIV programme, with poor results. A specific HIV outbreak among drug users (around 2011) has been directly linked to the significant decline in harm reduction services following the Global Fund transition out of the country. [5]

Now, Romania is managing a transition for the country's TB grant. Key informants said that based on experience from the country's HIV transition, the "guiding principle was really to make sure the gains made from Global Fund investment could be sustained after transition." In order to safeguard sustainability, the National Strategic Plan (NSP) for the Control of Tuberculosis in Romania (2015-2020) has a clear co-financing agreement to guide the transition. "It's all in the strategic plan, which is essentially a transition plan," said one key informant. The Global Fund Secretariat told Aidspan that "we made it a requirement for them to make this transition plan before the grant."

Bulgaria (TB)

Similar to Romania, Bulgaria is making use of its upcoming five-year NSP to integrate a transition plan for its last Global Fund TB grant. "It was common knowledge that it would be the last grant," said one key informant. By 2018, the country must be able to take over elements of the TB response that The Global Fund is currently supporting, including second line drugs, lab reagents for MDR-TB and contact tracing nurses. Along with a transition plan in the NSP, Bulgaria is also reforming its TB care approach to make the entire system more sustainable. The reforms involve a shift in service delivery from facility level to community level to make the TB response more affordable. "They want to move away from the Soviet model towards a cheaper home-based model," said one key informant. "Most of the TB patients are from Roma communities who do not want to be in hospitals anyway."

Conclusion

The sustainability initiatives in these four countries could provide valuable lessons to others countries currently facing, or soon to face, transition. Establishing government funding mechanisms for NGOs (Costa Rica), leveraging investments to secure loans (Fiji), integrating transition planning into NSPs (Romania and Bulgaria), and reforming service delivery models (Bulgaria), are all good ways to ensure greater sustainability following Global Fund transitions.

The interview data in this article was collected in November 2015 as part of Aidspan's research on counterpart financing and willingness-to-pay, funded by the Open Society Foundations (OSF). [6]

Source

Oberth G. Sustainability lessons from transitions in Costa Rica, Fiji, Romania, and Bulgaria. Global Fund Observer (GFO), (25 January 2016).

http://www.aidspan.org/gfo_article/sustainability-lessons-transitions-costa-rica-fiji-romania-and-bulgaria

References

1. GFO. Civil society urges responsible transition towards domestic funding of HIV and TB in EECA. (15 August 2015). http://www.aidspan.org/gfo_article/civil-society-urges-responsible-transition-towards-domestic-funding-hiv-and-tb-eeca
2. GFO. China after the Global Fund. (16 April 2014). http://www.aidspan.org/gfo_article/china-after-global-fund
3. OSF. Ready, Willing, and Able? Challenges Faced by Countries Losing Global Fund Support. Open Society Foundation discussion paper. (30 July 2015). http://globalfund-developedngo.org/wp-content/uploads/2015/09/Ready-Willing-Able_Jul-30.pdf (PDF)
4. GFO. Aidspan releases report on willingness-to-pay commitments in 13 countries. http://www.aidspan.org/gfo_article/aidspan-releases-report-willingness-pay-commitments-13-countries
5. Bridge J et al. The Global Fund to Fight AIDS, Tuberculosis and Malaria's investments in harm reduction through the rounds-based funding model (2002-2014). Int J Drug Policy. 2016 Jan;27:132-7. doi: 10.1016/j.drugpo.2015.08.001. Epub 2015 Aug 13. http://www.ncbi.nlm.nih.gov/pubmed/26342275
6. The "Fair Share" of Shared Responsibility: An Aidspan Report on Willingness to Pay. GFO report (25 January 2016). http://www.aidspan.org/publication/%E2%80%9Cfair-share%E2%80%9D-shared-responsibility-aidspan-report-willingness-pay

ANTIRETROVIRALS

BMS sells pipeline compounds to ViiV Healthcare

Simon Collins, HIV i-Base

On 18 December 2015, Bristol-Myers Squibb (BMS) announced that the company was selling its HIV discovery, preclinical and clinical programmes for its pipeline to ViiV Healthcare. [1]

The clinical pipeline includes an attachment inhibitor (BMS-663068), currently in phase III studies and a maturation inhibitor (BMS-955176), currently in phase IIb development.

Both compounds are especially important for people with drug resistance to existing HIV drugs.

Details of the "active" preclinical and discovery stage programmes were not included in the statement.

ViiV will pay $350 million up front, with potential regulatory and milestone payments of up to $518 million for the clinical assets and up to $587 million for the discovery and pre-clinical programmes. ViiV will also pay sales-based payments for any compounds that become licensed.

If cleared by US anti-trust laws, the divestment should be completed by mid-2016. BMS announced in June 2015 that the company was withdrawing from virology research. [2]

BMS drugs that are already licensed (efavirenz, Atripla, atazanavir and atazanavir/cobicistat) are not affected by the agreement.

References

1. BMS Press Release. Bristol-Myers Squibb to sell its HIV R&D portfolio to ViiV Healthcare, (18 December 2015). http://news.bms.com/press-release/partnering-news/bristol-myers-squibb-sell-its-hiv-rd-portfolio-viiv-healthcare
2. BMS Press Release. Bristol-Myers Squibb Expands R&D Presence Within Hubs of World Class Science and Innovation (25 June 2015). http://news.bms.com/press-release/rd-news/bristol-myers-squibb-expands-rd-presence-within-hubs-world-class-science-and-i

EU provide positive approval for generic lopinavir/ritonavir

EMA newsletter

In November 2015, the European Medicines Agency (EMA) announced that the Committee for Medicinal Products for Human Use (CHMP) had given a positive opinion for a generic coformulation of lopinavir/ritonavir.

The formulation is manufactured by Mylan.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004025/smops/Positive/human_smop_000904.jsp&mid=WC0b01ac058001d127

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004025/smops/Positive/human_smop_000904.jsp

Further results using dolutegravir monotherapy: urgent need for controlled studies

Simon Collins, HIV i-Base

A small case study using dolutegravir monotherapy in treatment naive patients [1] has reported similar results to several other independent studies presented at the 15th EACS conference last year. [2, 3]

Given the significance of these results in showing a lack of viral rebound, this highlights the importance of larger, randomised controlled studies.

The current study was reported in a letter to JAIDS from Massimiliano Lanzafame from University Hospital Verona, and colleagues. [1]

It included retrospective results from nine HIV positive people (2 women, 7 men) who began initial therapy using dolutegravir after having "refused NRTIs". All participants were treatment-naive with baseline viral load <100,000 copies/mL (range 16,000 to 90,000) and no genotypic drug resistance (to NRTIs, NNRTIs, PIs or INSTIs). Mean age was 45 (range 36 to 76 years) and been time since diagnosis was about eight years. [4]

After four weeks, viral load was <50 copies/mL for all participants. This was reported as undetectable in 3 patients, <20 copies/mL in another 3 and at 31, 35 and 45 copies/mL in the remaining three.

Viral load at the last result, after a mean follow-up of 7.3 months (range 6 to 10 months) was <20 copies/mL for all participants. This was reported as undetectable in seven patients, and <20 copies/mL in the remaining two. CD4 counts increased in all participants. The mean increase was 152 cells/mm^3 (range 94 to 284 cells/mm^3).

C O M M E N T

The limited details on the JAIDS study mean that these results are largely case reports.

However, it shows that another research group independently initiated a study of dolutegravir monotherapy almost a year ago in early 2015.

At least half a dozen groups are now running small uncontrolled studies of monotherapy [2] and dual therapy with 3TC [3].

Given the potential savings in drug exposure and financial cost of treatment (if proved successful) it is a considerable missed opportunity for future research not to include a standard of care arm in a randomised design. Should this strategy not prove successful, there is an urgency to establish these concerns quickly, as off-label switching to reduced therapy in the absence of data is otherwise very likely.

For example, the NIH-sponsored ACTG dual therapy study is already enrolling but has no control group. [5]

This means that it might take several years until a sufficiently powered study establishes whether or not a significant risk exists for this strategy.

References

1. Massimiliano L et al. Dolutegravir monotherapy in HIV-infected naive patients with <100,000 copies/mL HIV-RNA viral load. Letter to the editor. JAIDS, 08 January 2016, Publish Ahead of Print. doi: 10.1097/QAI.0000000000000931. http://journals.lww.com/jaids/toc/9000/00000
2. Collins S. Remarkable results with dolutegravir monotherapy. HTB November/December 2015. http://i-base.info/htb/29154
3. Collins S. First-line ART with dolutegravir plus 3TC: 24-week early results. HTB November/December 2015. http://i-base.info/htb/29212

4. clinicaltrials.gov. Dolutegravir plus lamivudine dual therapy in treatment naïve HIV-1 patients. (not yet recruiting). https://clinicaltrials.gov/ct2/show/NCT02582684

Potential economic impact of dolutegravir/3TC dual therapy

Simon Collins, HIV i-Base

With cost driving so much in healthcare, the economic impact of a current experimental strategy might undermine the current dependence on three-drug combination therapy.

A study looking at the economic impact on US health costs if treatment with dolutegravir/3TC proves to be effective modeled five-year savings of $550 to $800 million based on 50% uptake of dual therapy for new patients starting ART. Savings reached more than $3 billion if only 25% of people currently stable on ART switched to dolutegravir/3TC dual-drug maintenance therapy. [1]

The model looked at various options depending on whether the reduced drug combinations are shown to be effective as initial treatment or as a switch strategy after viral suppression.

Early results presented at the 15th EACS conference in October 2015 hinted that reduced combinations using dolutegravir – with or without 3TC – might maintain viral load below detection, with little indication of viral rebound out to 24 weeks. [2, 3]

C O M M E N T

The paper rightly notes the ethics issue from recommending lower cost treatment that might be less effective, even if this is only marginally so. Currently we have insufficient data to know this.

The paper also notes that such a shift in prescribing would not be included in US treatment guidelines without data from a fully powered randomised study. Given current studies are still small underpowered and uncontrolled, this level of evidence is unlikely to become available for many years.

However, although this paper modelled US health costs, the results clearly have a significant impact on a global scale. Although international funding is impressive, it consistently fails to meet levels needed to ensure universal ART based on the current treatment strategies.

In addition to the other potential benefits of lower risk of drug interactions, side effects and drug resistance, generic dolutegravir plus 3TC looks likely to be available at a similar cost to generic first-line efavirenz-based combinations and significantly less expensive than all current second-line combinations. [4]

References

1. Girouard MP et al. The cost-effectiveness and budget impact of two-drug dolutegravir-lamivudine regimens for the treatment of HIV infection in the United States. Clin Infect Dis. (2015). doi: 10.1093/cid/civ981. Published online: 9 December 2015. http://cid.oxfordjournals.org/content/early/2015/12/27/cid.civ981.full
2. Collins S. Remarkable results with dolutegravir monotherapy. HTB November/December 2015. http://i-base.info/htb/29154
3. Collins S. First-line ART with dolutegravir plus 3TC: 24-week early results. HTB November/December 2015. http://i-base.info/htb/29212
4. UNAIDS, CHAI and UNITAID. Joint press announcement. Three new agreements announced with the potential to expand access to innovative HIV treatment in low- and middle-income countries. (30 November 2015). http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2015/november/20151130_PR_CHAI_UNITAID

TREATMENT GUIDELINES

New US guidelines strengthen recommendation for ART irrespective of CD4 count (January 2016)

Simon Collins, HIV i-Base

On 29 January 2016, the leading US HIV treatment guidelines were updated online, strengthening the recommendation for early treatment. [1]

The main change is a stronger rating for using ART irrespective of CD4 count; increased to the highest A1 (strongest recommendation based on highest quality of scientific evidence). This change was based on results from the START and TEMPRANO studies. [2. 3]

The recommendations are similarly strengthened (also to A1) for people diagnosed in early infection, noting "earlier ART initiation may result in less residual immune dysfunction during treatment, which theoretically may result in reduced risk of disease for decades to come".

While recognising some circumstances where treatment might be deferred, the guidelines broadly view access to treatment as an essential right for all HIV positive people, irrespective of mental health, substance use and psychological issues.

The main recommendations are listed below.

- ART is recommended for all HIV positive individuals, regardless of CD4 cell count, to reduce the morbidity and mortality associated with HIV infection (AI).
- ART is also recommended for HIV positive individuals to prevent HIV transmission (AI).
- When initiating ART, it is important to educate patients on the benefits and considerations regarding ART, and to address strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as possible.
- Antiretroviral therapy (ART) is recommended for all individuals with HIV-1 infection (AI) including those with early HIV-1 infection.
- ART is especially important for older patients because they have a greater risk of serious non-AIDS complications and potentially a blunted immunologic response to ART.
- The fixed-dose combination of elvitegravir/cobicistat/tenofovir alafenamide/FTC is included as a new preferred first-line option.

References

1. US Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents. January 2016.
http://aidsinfo.nih.gov/guidelines
https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf (PDF download)
2. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic infection. NEJM (20 July 2015). DOI: 10.1056/NEJMoa1506816.
3. The TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med 2015; 373:808-822. (27 August 2015). DOI: 10.1056/NEJMoa1507198.
http://www.nejm.org/doi/full/10.1056/NEJMoa1506816

SIDE EFFECTS AND COMPLICATIONS

Renal monitoring in HIV positive patients: a new review

Simon Collins, HIV i-Base

A useful and comprehensive review of evidence for frequency of renal monitoring, including which tests to use has been published by Jean Cyr Yombi and colleagues in the September edition of HIV Medicine.

The article reviews renal complications that can be identified from routine monitoring and whether annual monitoring might be appropriate for many patients.

Given that HIV is a risk for both acute (AKD) and chronic kidney disease (CKD) and that early identification reduces the risk of complications, regular (3–6 monthly) screening using eGFR, urine dipstick and the albumin:creatinine ratio (ACR) or protein:creatinine ratio (PCR) is recommended for HIV positive people in several clinical guidelines.

The combination of eGFR (using CKD-EPI and not Cockcroft-Gault) plus albuminuria or proteinuria provides the best markers for those at greatest risk of progression to advanced CKD.

The review recommends annual monitoring in HIV positive patients with preserved kidney function (eGFR >60 mL/min/1.73 m^2 and urine ACR <300 mg/g or PCR <500 mg/g). In those with eGFR <60 mL/min/1.73 m^2 and/or ACR >300 mg/g (or PCR >500 mg/g), renal function should be monitored more closely and renal and cardiovascular risk factors managed more aggressively in line with guidance for the general population.

Annual monitoring of kidney function is recommended for the majority of patients with normal or mildly impaired kidney function (eGFR >70–75 mL/min/1.73 m^2 and ACR <300 mg/g or PCR <500 mg/g).

Patients with stage 3 CKD (eGFR 30–59 mL/min/1.73 m^2) should have renal and cardiovascular risk factors reviewed and managed aggressively, and their ARV regimens and dosing schedule reviewed; drugs such as tenofovir and atazanavir may be best avoided in those with CKD and those at greatest risk of developing CKD.

More frequent monitoring is recommended within the first year of starting or switching ART, especially if the ART contains tenofovir DF and cobicistat and dolutegravir that may affect creatinine secretion.

The article also reviews management of albuminuria, haematuria. proximal renal tubular injury and monitoring. For patients on PrEP, dipstick urinalysis, eGFR and plasma glucose and phosphate measurements are recommended for being widely available and easily applied in clinical practice.

The article concludes: "Harm reduction strategies, including smoking cessation, achievement of a healthy BMI, management of hypertension, diabetes and dyslipidaemia, and avoidance or judicious use of agents with nephrotoxic potential, are paramount in reducing the risk of kidney disease progression, cardiovascular events and death in patients with CKD."

Reference

Yombi JC et al. Monitoring of kidney function in HIV-positive patients. HIV Medicine Sept 2015 16(8) 457-477. DOI: 10.1111/hiv.12249
http://onlinelibrary.wiley.com/doi/10.1111/hiv.12249/abstract

TRANSMISSION & PREVENTION

European application underway for PrEP indication for tenofovir/FTC

Simon Collins, HIV i-Base

On 1 February 2016, Gilead Sciences issued a press release about its application for an extended license in the European Union for tenofovir/FTC to be prescribed as pre-exposure prophylaxis (PrEP).

The application has been reviewed and accepted by the European Medicines Agency (EMA) and is now under evaluation.

Until now, it was unclear whether or not Gilead had submitted a dossier for PrEP and indeed whether the EMA had resolved their criteria - and priorities - in order to make such an evaluation.

Both Gilead and the EMA have been widely criticised, including by community groups, for the slow timeline compared to the US, where the FDA first approved PrEP in July 2012.

The role of the EMA was particularly helpful, overstepping its role to evaluating drug safety and efficacy by suggesting PrEP was a low priority due to concerns over potential behaviour changes that have not been reported in randomised studies.

While the lack of an indication should not be a barrier to current prescribing – ART is widely used as PEP for example without an indication – approval is an essential step to enable broad commissioning and widespread access in many countries.

Tenofovir/FTC was also approved for PrEP in Kenya and South Africa in 2015, with regulatory submissions pending in Australia, Brazil, Canada, Peru and Thailand and access in France following a Temporary Recommendation for Use by the French regulatory agency.

C O M M E N T

If this application is given an accelerated review, a decision might be given with 90-120 days.

The timeline for the EMA decision however has not yet been reported.

Reference

Gilead press statement. European Medicines Agency validates Gilead's type II variation application for Truvada for reducing the risk of sexually acquired HIV. (01 February 2016).

http://www.gilead.com/news/press-releases/2016/2/european-medicines-agency-validates-gileads-type-ii-variation-application-for-truvada-for-reducing-the-risk-of-sexually-acquired-hiv

VAT may be payable when importing generic medicines in to the UK

Simon Collins, HIV i-Base

The i-Base Q&A resources about buying generic medicines online have been modified to include examples of paying VAT and a customs clearance fee.

This is based on reports that some people ordering PrEP online have been asked for an additional payment.

For example, one person ordering three months of PrEP was asked by Parcel Force to pay Import VAT of £21.60 before the parcel could be released. They also had to pay a clearance fee of £13.50.

These additional charges don't seem to affect all orders, but are legal.

It might be just good or bad luck whether this happens, depending on whether the parcel is picked up for this duty.

We have updated the following related question to include this information.

- Where can I buy PrEP or HCV meds online and is it legal in the UK?

http://i-base.info/qa/10734

South African Medicines Control Council approves tenofovir/FTC for PrEP

Simon Collins, HIV i-Base

On 3 December 2015 the South African Medicines Control Council (MCC) approved a fixed dose formulation of tenofovir DF/FTC for HIV preexposure prophylaxis (PrEP).

Although limited details were provided, the MCC also requested a risk management plan, to collect safety data on side effects, and to report these every six months.

The Medicines Control Council (MCC) is responsible for regulating all medicines and medical devices in South Africa.

Reference

MCC press release. Medicines Control Council approves fixed-dose combination of tenofovir disoproxil fumarate and emtricitabine for pre-exposure prophylaxis of HIV. (3 December 2015).

http://www.mccza.com

http://www.mccza.com/documents/2e4b3a5310.11_Media_release_ARV_FDC_PrEP_Nov15_v1.pdf (PDF)

Two cases of HIV transmission on tenofovir DF monotherapy

Simon Collins, HIV i-Base

Case studies were recently published of two men who became HIV positive even though they were using daily tenofovir DF to treat hepatitis B (HBV).

The cases are important because this provides evidence that in the context of good adherence that both tenofovir DF and FTC might be needed to reach close to 100% protection for men.

Both cases were in gay men with good adherence. This was demonstrated by undetectable HBV viral load without blips for >3 years supported by pharmacy records, and by therapeutic drug levels tenofovir at the time of HIV diagnosis.

One case was diagnosed in acute HIV infection following 4 day of flu-like symptoms after an exposure risk - and 10 days after a negative antibody test. Viral load was <50 copies/mL.

The second case was identified after hospitalisation for severe seroconversion illness, diagnosed with a viral load of 160,000 c/mL.

Both men had immediate escalation to full ART – within approximately three weeks after likely date of infection – but this did not prevent infection. Established infection was verified by HIV total DNA and integrated DNA in both cases.

The results are also important because the WHO currently recommend tenofovir DF as a single drug option for PrEP based on non-significant differences compared to tenofovir DF/FTC in the (heterosexual) PARTNERS PrEP study.

C O M M E N T

While these two cases show proof of principle that infection is possible in the presence of likely good adherence to tenofovir, the absence of a denominator makes it impossible to quantify the level of risk.

The cases show the likely importance of dual therapy for PrEP which for many people is important for achieving close-to 100% protection.

The results also support people at risk of HIV infection who are being treated for HBV switch to tenofovir/FTC for their HBV treatment.

These cases were first presented at conferences in Glasgow in 2014 and at BHIVA in 2015. [2, 3]

Reference
1. Fox J et al. Tenofovir Disoproxil Fumarate Fails to Prevent HIV Acquisition or the Establishment of a Viral Reservoir: Two Case Re-ports. Infect Dis Ther .published online: 09 January 2016. DOI 10.1007/s40121-015-0102-x.
2. Davies O et al. Failure of daily tenofovir to prevent HIV transmission or the establishment of a significant viral reservoir despite contin-ued antiretroviral therapy. 14th International Congress on Drug Therapy in HIV Infection, 23-26 October 2014, Glasgow. Poster abstract P199. http://www.jiasociety.org/index.php/jias/article/view/19731
3. Fox J et al. Pre-exposure prophylaxis fails to prevent HIV-1 infection or the establishment of a significant viral reservoir. 21st BHIVA conference, 21-24 April 2015, Brighton. Poster abstract P10. http://www.bhiva.org/documents/Conferences/2015Brighton/AbstractBook2015.pdf (PDF)

HEPATITIS COINFECTION

NICE approves ombitasvir, paritaprevir, ritonavir with or without dasabuvir to treat adult HCV

On 25 November, NICE published guidance for use of ombitasvir, paritaprevir, ritonavir with or without dasabuvir, to treat adults with hepatitis C genotype 1 or 4. [1]

A summary of recommendations is included below in Table 1, but please refer to the full NICE document for details.

This is dependent on the company providing these drugs at the same price or lower than that agreed with the Commercial Medicines Unit.

Ombitasvir/paritaprevir/ritonavir is a single tablet formulation has the brand name Viekirax. Dasabuvir has the brand name Exviera.

All drugs are manufactured by AbbVie.

Table 1. NICE indication for ombitasvir/paritaprevir/ritonavir with or without dasabuvir

HCV genotype, liver disease stage	Treatment	Duration (weeks)	Recommendation according to treatment history	
			Untreated	Treated
1a, without cirrhosis	Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin	12	Recommended	
1a, with compensated cirrhosis	Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin	24	Recommended	
1b, without cirrhosis	Ombitasvir–paritaprevir–ritonavir with dasabuvir	12	Recommended	
1b, with compensated cirrhosis	Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin	12	Recommended	
4, without cirrhosis	Ombitasvir–paritaprevir–ritonavir with ribavirin	12	Recommended	
4, with compensated cirrhosis	Ombitasvir–paritaprevir–ritonavir with ribavirin	24	Recommended	
Abbreviation: HCV, hepatitis C virus. Treated – the person's hepatitis C has not adequately responded to interferon-based treatment.				

C O M M E N T

A price for ombitasvir–paritaprevir–ritonavir is approximately £32,200 for 12 weeks and £64,400 for 24 weeks of treatment, both excluding VAT. The price for dasabuvir is £2800 and £5600 for 12 and 24 week course respectively (excluding VAT).

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

Treatment should be available on the NHS within 3 months of the guidance being issued.

Reference

NICE guidance. Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C. NICE technology appraisal guidance [TA365] Published date: November 2015

http://www.nice.org.uk/guidance/ta365

NICE approves daclatasvir to treat adult HCV

On 25 November, NICE published guidance for the limited use of daclatasvir to treat adult with hepatitis C genotype 1, 3 or 4. [1]

A summary of recommendations is included below in Table 2, but please refer to the full NICE document for details.

This is dependent on the company providing these drugs at the same price or lower than that agreed with the Commercial Medicines Unit.

Daclatasvir has the brand name Daklinza and is manufactured by BMS.

Table 2. NICE guidelines for daclatasvir baased on previous HCV treatment

Type of hepatitis C	Treatment recommended by NICE	Length of treatment
If hepatitis C has not been treated before		
1, without cirrhosis	Daclatasvir plus sofosbuvir only for people with significant fibrosis	12 weeks
4	Daclatasvir plus peginterferon alfa and ribavirin only for people with significant fibrosis or cirrhosis	24 weeks
If hepatitis C has been treated before		
1 or 4 without cirrhosis	Daclatasvir plus sofosbuvir only for people with significant fibrosis	12 weeks
4	Daclatasvir plus peginterferon alfa and ribavirin only for people with significant fibrosis or cirrhosis	24 weeks
If interferon cannot be used		
1, 3 or 4 without cirrhosis	Daclatasvir plus sofosbuvir only for people with significant fibrosis	12 weeks
1 or 4 with cirrhosis	Daclatasvir plus sofosbuvir, with or without ribavirin	24 weeks
3, with cirrhosis	Daclatasvir plus sofosbuvir and ribavirin	24 weeks

C O M M E N T

A price for daclatasvir alone is approximately £24,500 for 12 weeks and £49,000 for 24 weeks of treatment, both excluding VAT.

The average cost of daclatasvir plus sofosbuvir is £59,501 for a 12-week course and £119,002 for a 24-week course; when ribavirin is added these costs increase to £60,304 and £120,608 respectively. The average cost of a course of treatment with daclatasvir in combination with peginterferon alfa and ribavirin ranges from £53,628 to £58,221 (depending on whether peginterferon alfa and ribavirin are taken for 24 or 48 weeks; daclatasvir may only be taken for 24 weeks).

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

Treatment should be available on the NHS within 3 months of the guidance being issued.

Reference

NICE guidance. Daclatasvir for treating chronic hepatitis C (TA364). NICE technology appraisal guidance [TA364] (November 2015).

http://www.nice.org.uk/guidance/ta364

BASIC SCIENCE & CURE RESEARCH

Developing multi-pronged antibodies to target the HIV reservoir

Richard Jefferys, TAG

In an example of publication kismet, three recent open access articles all converge in describing a new strategy for depleting the HIV reservoir.

The research involves engineering antibodies or antibody-like molecules capable of simultaneously binding two targets: the CD3 receptor, a human protein expressed on T cells, and parts of the HIV envelope (Env) protein, which are typically displayed on the outside of infected CD4 T cells when the virus is active. The rationale is that the region of the antibody that targets HIV Env binds to infected cells, while the CD3-targeting region binds to passing T cells and activates them to kill the cell.

The idea for this two-pronged—termed bispecific—antibody attack originated in cancer research, and one candidate that targets CD19 (a protein expressed by B cells) and CD3 is already FDA-approved as a second-line treatment for certain forms of acute lymphoblastic leukemia.

In the Journal of Clinical Investigation, Julia Sung and colleagues report results obtained in vitro with "Dual-Affinity Re-Targeting" (DART) proteins designed to bind CD3 and HIV Env epitopes targeted by the broadly binding (but non-neutralising) monoclonal antibodies A32 or 7B2. These DART proteins were able to significantly reduce HIV levels in cultured, HIV-infected CD4 T cells and also showed activity against latently infected CD4 T cells isolated from individuals on ART and exposed to the latency-reversing agent vorinostat. [1]

In PLoS Pathogens, a research team from Gilead Sciences and MacroGenics, Inc. describe similar studies conducted with a larger array of candidate DART proteins targeting CD3 and one of several different HIV Env epitopes, including those bound by A32, 7B2 and the broadly neutralising antibodies PGT121, PGT145, VRC01 and 10E8. The most active DART proteins were those derived from PGT121, PGT145, A32 and 7B2, confirming and extending the results of Sung et al. Of potential importance for clinical development, modified versions of the DART proteins designed to allow for relatively infrequent dosing in humans maintained activity. [2]

The third study, by Amarendra Pegu and colleagues from the Vaccine Research Center at the National Institutes of Health, employed a bispecific antibody that attaches to CD3 and the HIV Env epitope recognised by the broadly neutralising antibody VRC07. In experiments using latently infected CD4 T cells isolated from individuals on ART, the antibody was found to both activate HIV gene expression and reduce HIV DNA levels in most donor samples. [3]

An important, overarching concern with all these bispecific antibodies is the extent to which the CD3-binding region might cause generalised T cell activation. Many years ago, anti-CD3 antibodies were tested in people with HIV with the aim of broadly activating CD4 T cells as means to reverse latency and deplete the HIV reservoir, but the results were disastrous: the treatment led to a massive depletion of T cells, inflammatory cytokine release (leading to transient renal failure in one case) and no evident HIV reservoir reduction (see Prins et al,1999). [4]

All three research groups conducted laboratory assessments of T cell activation, and found little or no evidence that it occurred in the absence of HIV Env expression; in other words, binding of the bispecific antibodies to both targets appeared necessary for inducing activation. However, Pegu et al also performed a safety assessment in SHIV-infected macaques receiving antiretroviral therapy and this revealed a sharp but short-lived drop in peripheral blood CD3+ T cells and a sizable, albeit transient, increase in levels of several inflammation-related cytokines (TNF-α, MIP-1β and IL-10). These immunological perturbations resolved within 24 hours and there were no increases in SHIV viral load or clinically evident adverse events, leading the researchers to conclude that: "overall, these short-term toxicity studies indicate that the treatment was well tolerated."

Taken together, the three papers suggest that bispecific antibodies may have promise as an anti-reservoir strategy. A particular appeal of the approach is the capacity to recruit T cells to destroy HIV-infected cells without regard to their antigen specificity—this could be important because HIV-specific T cells are typically functionally compromised in HIV-positive people. Tempering enthusiasm somewhat are the macaque data showing transient T cell depletion and inflammation, a phenomenon that will need to be evaluated in further animal studies.

Barring additional safety concerns arising, human trials appear likely given the involvement of Gilead Sciences (a company with a large HIV cure research programme).

Source:

Jefferys R. Developing multi-pronged antibodies to target the HIV reservoir. . TAG basic science blog. (11 November 2015).

http://tagbasicscienceproject.typepad.com

References

1. Sung JA et al. Dual-affinity re-targeting proteins direct T cell-mediated cytolysis of latently HIV-infected cells. J Clin Invest. 2015 Sep 28. pii: 82314. doi: 10.1172/JCI82314. [Epub ahead of print]
   https://www.jci.org/articles/view/82314
2. Sloan DD et al. Targeting HIV Reservoir in Infected CD4 T Cells by Dual-Affinity Re-targeting Molecules (DARTs) that Bind HIV Envelope and Recruit Cytotoxic T Cells. PLoS Pathogens (5 November 2015). DOI: 10.1371/journal.ppat.1005233.
   http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1005233
3. Pegu A et al. Activation and lysis of human CD4 cells latently infected with HIV-1. Nat Commun. 2015 Oct 20;6:8447. doi: 10.1038/ncomms9447.
   http://www.nature.com/ncomms/2015/151020/ncomms9447/full/ncomms9447.html
4. Prins JM et al. Immuno-activation with anti-CD3 and recombinant human IL-2 in HIV-1-infected patients on potent antiretroviral therapy. AIDS; 3 December 1999 - Volume 13 - Issue 17 - pp 2405-2410.
   http://journals.lww.com/aidsonline/toc/1999/12030

OTHER NEWS

Public Health England reports cases of microbial resistant Shigella

PHE press statement

Public Health England (PHE) recently identified five cases of Shigella sonnei phage type 6 which show high levels of antimicrobial resistance – typically only seen before in Shigella infections associated with travel and therefore imported.

The Shigella sonnei isolated in these cases are clustered by whole genome sequencing suggesting they belong to an outbreak.

Four cases are adult men who have sex with men (MSM) from London with sample dates from 21 September to 27 October inclusive. The fifth case, from mid-November, is an adult man from outside London with a likely sexual exposure in London.

The isolates from these cases have genes conferring resistance to amoxicillin, ceftriaxone (first line treatment for HIV positive individuals with invasive shigellosis), trimethoprim, sulphonamides, tetracycline, including the extended-spectrum beta-lactamase (ESBL) resistance gene CTX-M-27 and macrolide resistance genes ermB/mph(A). These resistance genes are plasmid mediated and therefore readily transmissible. The isolates are phenotypically sensitive to quinolones, carbapenems, aminogylcosides and fosfomycin.

Our primary concerns are as follows: a) that this strain might spread rapidly among HIV positive MSM in high-risk sexual networks, including outside of London b) potential spread of resistance to other Shigella and other organisms c) the possibility of treatment failure for severe shigellosis disease in the immunocompromised.

PHE would therefore recommend that all GUM and HIV doctors:

- Provide written advice to all MSM attending their services (especially HIV positive patients) on how to prevent infection with Shigella. Materials are available on the PHE website here:

  https://www.gov.uk/government/publications/shigella-leaflet-and-poster
- Obtain appropriate and timely stool samples for patients presenting with acute diarrhoea, abdominal pain and fever.
- Provide advice to patients with Shigella on how to prevent onward transmission.
- Discuss the need for antibiotic management of severe disease (fever, bloody diarrhoea or signs of sepsis) with their microbiologist.
- Notify cases to their local Health Protection Team.
- Record any Shigella diagnosis in England using the appropriate SHHAPT code (SG1, SG2 or SG3) in the patient's medical record, so that it can be reported in GUMCAD. See SHHAPT code look-up here:

  https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/420625/GUMCADv2_SHHAPT_Code_Look-up.pdf (PDF)

ON THE WEB

Conference materials online

6th International Workshop on HIV and Aging

Webcasts and presentations from this workshop held from 5–6 October 2015 in Washington are now available online.

http://www.infectiousdiseasesonline.com/6th-hivaging_webcast (webcasts)

http://www.infectiousdiseasesonline.com/6th-hiv-aging-workshop-presentations/ (presentations)

15th EACS Conference: webcasts online

Oral presentations from the EACS 2105 conference in Barcelona in October 2015 are now available online and on the TALKS on the GO iPad/iPhone and Android apps.

For people who did not attend the meeting, login details are also available online, although this involves registering for a free and instant login.

http://eacs.multilearning.com/eacs

These details are also needed to access presentations on the iPad/iPhone and Android apps.

The same username and password enables access to the previous EACS webcast library including presentations from the Advanced HIV Courses, the ECReCo (European Clinical Research Course), and past EACS Conferences.

Community reports

RITA: HIV and smoking

The latest issue of RITA includes three main articles.

1. An interview with HIV smoking expert Jonathan Shuter on motivating and helping HIV positive smokers to quit, including discussion of his online quitting programme, "PositivelySmokeFreeMe".
2. A review article analysing smoke-ending strategies in people living with HIV.
3. A review article summarising the impact of smoking on health of HIV positive people and how that impact differs from the effect of smoking in the general population.

The issue also includes two 2-page summaries: "Ten things every HIV positive smoker should know" and "Ten things every HIV clinician should know about smoking."

http://centerforaids.org/pdfs/rita0116.pdf (PDF)

FUTURE MEETINGS

Conference listing 2016

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.

XXV International HIV Drug Resistance Workshop

20 – 21 February 2016, Boston

https://www.informedhorizons.com/resistance2016

6th HIV & Women workshop

20 – 21 February 2016, Boston

http://www.virology-education.com

23rd Conference on Retroviruses and OIs (CROI 2015)

22 – 25 February 2016, Boston

http://www.croiconference.org

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

19–22 April 2016

http://www.bhiva.org

10th Annual Conference of the Children's HIV Association

27 May 2016, Bristol

http://www.bhiva.org

17th HIV & Hepatitis Clinical PK Workshop

8-10 June 2016, Washington DC

http://www.virology-education.com

18th Annual Conference of the National HIV Nurses Association

29 June–1 July 2016, Manchester

http://www.bhiva.org

HIV Paediatrics Workshop 2016

15 Jul 2016 - 16 Jul 2016, Durban

http://www.virology-education.com

3rd International HIV/Viral Hepatitis Co-Infection Meeting

17 July 2016, Durban

http://www.iasociety.org/co-infections/hepatitis

21st International AIDS Conference (IAS 2016)

17-22 July 2016, Durban

http://www.aids2016.org

BHIVA Autumn Conference 2016

6–7 October, London

http://www.bhiva.org

Congress on HIV Therapy (Glasgow 2016)

23-26 October 2016

http://hivglasgow.org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

http://www.i-Base.info

The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

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

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

Three new pocket guides: ART, pregnancy and side effects

A new series of pocket-size concertina folding leaflets that is designed to be a very simple and direct introduction to HIV treatment.

The first three pocket leaflets are:

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

We hope this is especially useful as a low literacy resource.

The leaflet uses simple statements and quotes about ART, with short URL links to web pages that have additional information in a similar easy format.

i-Base treatment guides

i-Base produces six booklets that comprehensively cover 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 ART (September 2015)
- HIV testing and risks of sexual transmission (February 2013)
- HIV and quality of life: side effects & complications (July 2012)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (November 2013).

Order publications and subscribe by post, fax or online

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

http://i-base.info/order

htb(e)

HIV TREATMENT BULLETIN (e)

HTB(e) is the electronic version of HTB, which is published six times a year by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered by fax or post using the form on the back page or directly from the i-Base website:

http://www.i-Base.info

by sending an email to: subscriptions@i-Base.org.uk

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

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

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

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

http://www.i-Base.info

HIV i-Base is a registered charity no 1081905 and company reg no 3962064.

HTB was formerly known as DrFax.

HIV i-Base

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

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

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

Title: _____ First Name _____ Surname _____

Address _____

_____

_____ Postcode _____

Email _____ @ _____

Telephone (s) _____ _____ _____

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

Please debit my account number _____

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

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

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

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

_____

_____

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

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

ONE-OFF DONATION

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

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

GIVE AS YOU EARN

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

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

REFUNDS FROM THE TAX MAN

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

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

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

i-base

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

i-base 0808 800 6013

Fax-back orders and subscriptions

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

Name _____ **Position** _____

Organisation _____

Address _____

_____

Telephone _____ **Fax** _____

e-mail _____

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

- **HIV Treatment Bulletin (HTB) every two months** ☐ **by e-mail (PDF file)** ☐ **by post**

- **NEW - Pocket ART leaflet** *(September 2015) - A7 small concertina-folded leaflets*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____

- **NEW - Introduction to ART guide** *(September 2015) - 48-page A5 booklet*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____

- **HIV Treatment 'Passports' - Booklets for patients to record their own medical history**
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____

- **Guide To HIV Testing and Risks of Sexual Transmission** *(February 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____

- **Guide To HIV, Pregnancy and Women's Health** *(March 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____

- **Guide to Changing Treatment and Drug Resistance** *(February 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____

- **HIV and your Quality of Life: Side Effects and other Complications** *(July 2012)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____

- **Guide To HIV and hepatitis C coinfection** *(November 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____

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

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

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

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

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