

september–october 2012

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EDITORIAL

The September/October issue of HTB leads with HIV-related studies that stood out from the programme of the 52rd ICAAC, including some new HIV and TB pipeline compounds.

We also continue our coverage from the IAS World AIDS Conference, with reports that include the HPTN-52 study, an analysis of hormonal contraception and risk of HIV transmission, and the second part of a cure-based review. We also include a non-technical 8-page supplement on AIDS 2012 that may be useful for use in clinics (see below).

Closer to home - and on a timeline that will be in place before you get to read this - the UK policy to provide free HIV treatment to anyone in the UK, irrespective of residency status, is something that needs to be widely publicised. The political decision to follow the evidence suggesting this will result in better health as a nation for minimal cost, will also improve the lives of a significant minority of people who delay HIV testing or seeking treatment until HIV has already progressed to symptomatic stages.

In the current confusion over restructuring changes to the NHS, it is important to have confirmed that HIV will remain under specialised national commissioning in England, at least in the short-term, and model standards that will hopefully be useful to inform this process have been developed by BHIVA. These are now online for consultation in draft format, prior to a launch planned to commemorate World AIDS Day later in the year.

Also, contentious for healthcare in the UK, is the increasing speculation about treatment options once generic formulations of efavirenz become available from the end of 2013. In reporting the welcome news of FDA approval for a new single-pill integrase-based combination (Quad) for use in selected treatment-naïve patients, our comments question whether company pricing will allow many people in the UK to access this drug.

Finally, we review new TB compounds in late stage development and report price reductions for the GeneXpert cartridges that have the potential to revolutionise diagnosis and management of TB in settings where this technology becomes available.

Happy Autumn reading...

HTB SUPPLEMENT

AIDS 2012: a non-technical review of the 19th IAS Conference

This 8-page review from the recent conference is written in non-technical language as an introduction to the wide range of presentations from this important conference held in Washington in July.

Available in print, online and in PDF format. Please order print copies online, free to all UK clinics, organisations and individuals.

<http://i-base.info/htb/20120>

<http://i-base.info/wp-content/uploads/2012/09/HTB-supplement-Sep2012e-FINAL.pdf>



CONFERENCE REPORTS

52nd International Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

9-12 September 2012, San Francisco

Introduction

The annual ICAAC conferences tend to have such a reduced focus on HIV in recent years that i-Base rarely prioritises attending this meeting.

Also, unlike most HIV meetings, only limited access is provided to abstracts and presentations. This is not a good model for health news. Some reports are restricted to data that was included in the abstract which have very limited peer review.

So the few articles included in this issue are mainly flag potentially interesting studies that will hopefully be presented with greater detail with better access at either the HIV Congress in Glasgow in November, or at CROI in Atlanta in March next year.

For a limited period, abstracts and sessions can be searched and browsed online:

<http://www.abstractsonline.com/Plan/browse.aspx>

Despite their short access period and tediously long URLs, links to abstracts are included in each report.

PowerPoint slides from selected studies are also posted to the free-access NATAP.org which includes approximately 50 reports from ICAAC.

<http://www.natap.org/2012/ICAAC/ICAAC.htm>

Reports in this issue of HTB are:

- Study summaries from ICAAC 2012
 - Dolutegravir superior to efavirenz at week 48 in treatment-naive patients
 - Elvitegravir/cobicistat has no clinically significant interactions with methadone or buprenorphine
 - Albuvirtide: long-acting formulation T-20
 - High rates of adherence and virological suppression with once-daily raltegravir and directly observed therapy (DOT) in IDU patients
 - Role of HIV DNA, recent cellular infection and poor immunological responses despite viral suppression
- Antiviral activity in vitro with S/GSK1265744
- Efavirenz interaction studies with TB compounds bedaquiline and delamanid

Study summaries from ICAAC 2012

Simon Collins, HIV i-Base

The following brief summaries on new drugs and treatment strategies include links to the ICAAC online abstracts and/or links to slidesets or articles posted at natap.org.

Dolutegravir results superior to efavirenz at week 48 in treatment-naive patients

The top-line results from the randomised, double-blinded, placebo-controlled, non-inferiority, Phase 3 SPRING study were first released in July just prior to the IAS conference.

Dolutegravir (50 mg once-daily) was paired with abacavir/3TC and compared to efavirenz/tenofovir/FTC (Atripla) in 674 treatment-naive patients, generally in early stage infection.

At week 48, the dolutegravir arm showed superiority with 88% vs 81% of patients suppressed to <50 copies/mL (difference +7.4%; 95%CI: +2.5, +12.3; p=0.003).

This result was driven by fewer discontinuations due to toxicity in the dolutegravir arm (2% vs 10%). Virological failure occurred in 4% of patients in each group.

Ref: Walmsley S et al. Dolutegravir (DTG; S/GSK1349572) + abacavir/lamivudine once daily statistically superior to tenofovir/emtricitabine/efavirenz: 48-week results - SINGLE (ING114467). 52nd ICAAC, 9-12 September 2012, San Francisco. Abstract H-556b.

<http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=e1c18d5b-830f-4b4e-8671-35bcfb20eed5&cKey=af219b7d-2171-46b2-91ef-b8049552c9e5&mKey=%7b6B114A1D-85A4-4054-A83B-04D8B9B8749F%7d>

http://www.natap.org/2012/ICAAC/ICAAC_06.htm

Elvitegravir/cobicistat has no clinically significant interactions with methadone or buprenorphine

Results from two small PK studies in patients on stable opiate substitution therapy (n=12 methadone; n=18 buprenorphine) reported no indications of an interaction between elvitegravir/cobicistat and methadone and only modestly increased buprenorphine levels that did not require dose modification.

Ref: Bruce RD et al. Pharmacokinetics of cobicistat-boosted elvitegravir administered in combination with methadone or buprenorphine/naloxone. 52nd ICAAC, 9-12 September 2012, San Francisco. Abstract A-1250.

<http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=a96a704b-ee24-44df-8955-f1688ac7663&cKey=7c849c73-6efd-4fce-9e2c-218df03ff40c&mKey=%7b6B114A1D-85A4-4054-A83B-04D8B9B8749F%7d>

http://www.natap.org/2012/ICAAC/ICAAC_40.htm

Albuvirtide: long-acting formulation T-20

The first *in vivo* virological data were presented for a new long-acting formulation of the fusion inhibitor T-20. This compound is in development with the Chinese company Chongqing Biotechnologies.

The limited information from the abstract reported results from a dose-finding study in Chinese HIV positive patients who received single IV injections daily for three days, followed by once-weekly injections for a further two weeks.

Mean maximum declines of 0.68 and 1.05 log copies/mL were reported with 160 mg and 320 mg doses respectively. In a single-dose study, viral reduction was maintained for 6-10 days, with albuvirtide showing a plasma half-life of 10-13 days.

Ref: Wu H et al. Albuvirtide, the first long-acting HIV fusion inhibitor, suppressed viral replication in HIV-infected adults. 52nd ICAAC, 9-12 September 2012, San Francisco. Abstract H554.

<http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=e1c18d5b-830f-4b4e-8671-35bcfb20eed5&cKey=70d14bcc-bad6-4754-b4b1-66b7d2559a23&mKey=%7b6B114A1D-85A4-4054-A83B-04D8B9B8749F%7d>

http://www.natap.org/2012/ICAAC/ICAAC_27.htm

High rates of adherence and virological suppression with once-daily raltegravir and directly observed therapy (DOT) in IDU patients

Although results of once-daily raltegravir studies did not support a label change or further research into this dosing option, a Canadian study reported very high rates of success in a cohort of 121 HIV positive treatment experienced injecting drug users (n=103 male) that also included comprehensive adherence support. DOT was used by 81% of patients.

Over a median follow-up of 12 (6-18) months, 80% of the cohort achieved or maintained virologic suppression to <50 copies/mL (approximately half the group switched with undetectable viral load at baseline).

Importantly, CD4 counts increased by a median 80 cells/mm³ from a median of 425 cells/mm³ (range 20-1600) at baseline. Adherence exceeded 90%. Virologic rebound to >400 copies/mL occurred in 10% of patients but resuppression was achieved in all cases over the subsequent three months. There were no cases of emergent raltegravir resistance.

Ref: Stewart K et al. Safety and efficacy of once daily raltegravir to enhance adherence and efficacy of HAART in vulnerable HIV-infected patients. 52nd ICAAC, 9-12 September 2012, San Francisco. Abstract H-884.

<http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=e47a6478-452a-4c7c-9ebc-86a50a648cc7&cKey=8eb48052-2257-4337-8e1d-51658c50fefe&mKey=%7b6B114A1D-85A4-4054-A83B-04D8B9B8749F%7d>

http://www.natap.org/2012/ICAAC/ICAAC_21.htm

Role of HIV DNA, recent cellular infection and poor immunological responses despite viral suppression

A group of French researchers looking at immunological non-responders despite viral suppression <50 copies/mL reported an association with HIV DNA as a marker of recent cellular infection and ongoing replication and overexpression of the activation marker CD38+, that was higher in patients with reduced CD4 responses on treatment. The natap report linked below report this study in detail.

Ref: Psomas KC et al. Poor CD4+ T-cell restoration linked to residual HIV-1 reverse transcription under antiretroviral therapy. 52nd ICAAC, 9-12 September 2012, San Francisco. Abstract H-1570a.

<http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=0bc31dda-3bfe-443f-8051-1788529cb053&cKey=e7b3f725-db08-4db9-953e-126811e32026&mKey=%7b6B114A1D-85A4-4054-A83B-04D8B9B8749F%7d>

http://www.natap.org/2012/ICAAC/ICAAC_35.htm

Antiviral activity in vitro with S/GSK1265744

Polly Clayden, HIV i-Base

The development of long acting formulations of antiretrovirals arouses great interest – and frequently tops the wish lists of treaters of adolescents.

Cell culture data from S/GSK 1265744, the investigational integrase inhibitor, shown at ICAAC 2012, suggests it has a favourable resistance profile. [1]

S/GSK1265744 is in development both as a long acting parental formulation and the back up oral formulation to dolutegravir. Phase 1 data shown at IAS 2012 using 200 mg/mL nanosuspension administered by intramuscular - dosed at 100 to 800 mg - or subcutaneous abdominal injection – at 100 mg to 400 mg – in HIV negative people produced an apparent plasma half-life of 25-50 days and supports parenteral once monthly dosing. [2]

Results presented at ICAAC were from a study accessing resistance in cell culture, in which HIV-1 IIIB was passaged in MT-2 cells with increasing concentrations of S/GSK1265744 and the integrase gene was sequenced. Fold changes were calculated as a ratio of IC₅₀ against wild type virus.

The investigators reported S/GSK1265744 IC₅₀ of 0.22 nM in human peripheral blood mononuclear cells (PBMC). IC₅₀s for dolutegravir, raltegravir and elvitegravir were respectively 0.51, 2.0 and 2.0 nM. The fold potency shift for 100% human serum was 408 for S/GSK1265744, and 75, 4.7 and 22 for dolutegravir, raltegravir and elvitegravir. The protein adjusted IC₅₀ estimate for S/GSK1265744 was 102 nM compared to 38, 5.6 and 20 nM for dolutegravir, raltegravir and elvitegravir respectively.

Exposure of MT-2 cells infected with HIV-1 IIIB to S/GSK1265744 for up to 112 days did not produce highly resistant mutants. The maximum resistance was 8.4 fold. Raltegravir/elvitegravir resistant signature mutation site-directed molecular clones had less than 2-fold change in susceptibility to S/GSK1265744, except for Q148K/R, which had 5.6/5.1 fold change, respectively. Fold changes of 14 double mutants among 15 site directed molecular clones were less than 12.

C O M M E N T

A poster at ICAAC showed results from a phase I, open-label, two-cohort, single sequence crossover study, looking at the effects of oral co-administration of rilpivirine with S/GSK1265744 (also dolutegravir). [3]

HIV negative subjects received S/GSK1265744 30 mg once daily for 12 days followed by a washout, rilpivirine 25 mg once daily for 12 days, and rilpivirine 25 mg plus S/GSK1265744 30 mg for 12 days, taken following a moderate fat meal. Serial PK sampling was performed on the last day of each dosing period.

This evaluation found similar S/GSK1265744 and rilpivirine PK parameters when administered separately or together. Bioequivalence criteria were met for all parameters except S/GSK1265744 decreased rilpivirine C_{min} by 8%, which is not considered clinically relevant. This lack of interaction is promising for co-administration in long-acting depot injection regimens.

References

1. Yoshinaga T et al. Antiviral characteristics of S/GSK1265744, an HIV integrase inhibitor (INI) dosed by oral or long-acting parenteral Injection. 52nd ICAAC, San Francisco, 9-12 September 2012. Oral abstract H-550.
2. Spreen W et al. Pharmacokinetics, safety and tolerability of the HIV integrase inhibitor S/GSK1265744 long acting parenteral nanosuspension following single dose administration to healthy adults. 19th International AIDS Conference 22-27 July 2012. Washington, DC. Poster abstract TUPE040.
3. Ford SL et al. Lack of pharmacokinetic (PK) interaction between rilpivirine and the integrase inhibitors dolutegravir and S/GSK1265744. 52nd ICAAC, San Francisco, 9-12 September 2012. Poster abstract A-1249.

Efavirenz interaction studies with TB compounds bedaquiline and delamanid

Polly Clayden, HIV i-Base

HIV and TB co-infection is common and treatment is complicated by drug-drug interactions. Two poster presentations at 52nd ICAAC described potential reduced exposure of bedaquiline and lack of interaction with delamanid when co-administered with efavirenz (EFV).

Bedaquiline, is metabolised to an N-monodesmethyl metabolite (M2) by CYP3A4.

For the population pharmacokinetic (PK) study presented, data were obtained from a previously reported drug-drug interaction trial (ACTG A5267) conducted in 33 HIV negative volunteers, who received two doses of 400 mg bedaquiline, the second co-administered with EFV after two weeks of receiving this at 600 mg once daily. Samples were obtained over 14 days after each bedaquiline dose. The investigators used non-linear mixed effects modeling for this analysis.

They reported oral clearance of bedaquiline (CL/F) and M2 (CL/F_{fm}) of 3.1 L/h (relative standard error, RSE, 6.9%) and 13.2 L/h (RSE 7.1%) respectively. The impact of induction was described as an immediate change in CL/F one week after starting EFV. The estimated change in CL/F was the same for bedaquiline and M2, an increase of 104% (RSE 4.3%).

Both bedaquiline and M2 exposure was decreased by 40-50% under a range of plausible assumptions used in this model-based analysis. This is more than previously concluded from the single-dose data.

Delamanid does not inhibit or induce CYP enzymes. EFV is metabolised by CYP2B6.

Data were presented from a phase 1, open-label, randomised, multiple dose trial in 30 (15 per group) healthy volunteers, conducted to investigate the effect on drug exposure and safety of co-administered delamanid 100 mg twice daily and EFV 600 mg once daily.

In this study, EFV was given alone for 10 days (Group 1); delamanid was given alone for seven days and with EFV for a further 10 days (Group 2). Pre-dose and at trough samples were obtained before full PK sampling. For EFV PK, samples were taken on day 10/11 (Group 1) and day 17/18 (Group 2); for delamanid PK on day 7/8 (Group 1) and day 17/18 (Group 2).

The investigators calculated plasma PK parameters including geometric mean ratios for C_{max} and AUC_t with 90% CI. This revealed that exposure to both drugs does not appear to be affected by co-administration. One participant in each group had elevated EFV exposure associated with CYP2B6 polymorphisms.

Adverse events were reported in 93% of participants who received both drugs, 73% EFV alone and 60% delamanid alone. All were mild to moderate. One participant discontinued while on two drugs due to abnormal liver function tests.

The phase 3 trial of delamanid is now enrolling a subgroup of HIV positive people receiving ART.

References

1. Svensson E et al. Population pharmacokinetics (PK) of TMC207 and its M2 metabolite with efavirenz (EFV) demonstrate reduced Exposure. 52nd ICAAC, San Francisco, 9-12 September 2012. Poster abstract A-1256.
2. Petersen C et al. Delamanid, a new drug for multi-drug resistant tuberculosis (MDR-TB), and efavirenz do not show clinically relevant drug interactions in healthy subjects. 52nd ICAAC, San Francisco, 9-12 September 2012. Poster abstract A-1255.

CONFERENCE REPORTS

19th IAS World AIDS Conference

22–25 July 2012, Washington

Simon Collins, HIV i-Base

Introduction

In this issue, includes further coverage from this important meeting.

Abstracts are easily accessed on-line through a searchable 'Programme at a glance' database on the conference website.

Although many presentations are web cast (and pod cast) this does not comprehensively cover all the clinical treatment sessions.

Some PowerPoint slides are also online.

<http://www.aids2012.org>

Reports in this issue include:

- HPTN-052: clinical advantages from earlier treatment
- Hormonal contraception and the risk of HIV acquisition
- Towards an HIV cure: Early developments reported at IAS: pt 2
- Online video interviews between researchers and activists

HPTN-052: clinical advantages from earlier treatment

Simon Collins, HIV i-Base

A late breaker oral presentation from the HPTN-052 study was widely reported from IAS this year, with the simple conclusion that it added to the evidence supporting clinical benefits of earlier treatment. [1]

These findings are reassuring, and certainly take away nothing away from the more important primary prevention endpoint results that treatment dramatically reduces the risk of sexual transmission. [2] However, the primary clinical endpoint of benefits to the HIV positive partners, were driven by a few very specific events.

The study randomised over 1700 HIV positive people with CD4 counts 350-550, who were in serodifferent heterosexual relationships, to either start treatment immediately or wait until their CD4 count dropped to 250 cells/mm³. Patients were recruited at sites in Africa (54%), Asia (34%) and South America (16%).

HPTN-052 presented first results following a DSMB recommendation to discontinue the study four years earlier than expected. This year, data from a final 855 patient years of follow up (total 4038 years) and a broader range of clinical events was presented by Beatriz Grinsztejn for the study team.

Median (IQR) CD4 and viral load at baseline was approximately 430 cells/mm³ (360-520) and 4.4 log copies/mL (3.8-4.9). Median follow-up was 2.1 years (1.6-2.9) across both arms. A total of 213 patients (24%) in the deferred arm started treatment at a median CD4 count and viral load of 230 cells/mm³ (197-249) and 4.4 log copies/mL (3.9 - 4.9). Time to ART was a median 3.8 years (IQR 3.5-4.4) with approximately 1 year on ART compared to 2 years in the immediate treatment group.

134 people experienced at least one primary clinical event (77 vs 57; 9% vs 6%) including 26 deaths (15 vs 11) and 21 non-AIDS events (9 vs 12), all in the delayed versus immediate arms respectively.

Compared to immediate ART, delayed ART was associated with higher rates of AIDS-defining events ($p=0.03$) and tuberculosis ($p=0.02$); and higher incidence (per/100 years) of tuberculosis (1.8, 95% CI=[1.3, 2.6] vs 0.8, [0.5, 1.3], $p=0.009$) and all targeted clinical events (29.0, [26.3, 31.9] vs 24.7, [22.3, 27.3]; $p=0.02$).

However there was only a trend to shorter time to first primary clinical event [HR 1.37 (0.97 - 1.93), $p=0.07$] with no differences seen in the Kaplan-Meier plots over the first year.

The number of secondary endpoints was numerically similar between both groups ($n=317$ vs 298 ; 36% vs 34%), although incidence rates became significant (incidence 494 vs 427/100 PY; $p=0.05$). Herpes and candida were more likely with delayed ART and dyslipidaemia was more likely with early ART.

C O M M E N T

Although the study reported clinical benefits from earlier treatment this was not consistent across all events and all analyses. While earlier treatment may have advantages, this study should not clearly translate to a conclusion for treatment at higher CD4 counts.

Firstly, the significantly higher rate of extrapulmonary tuberculosis in the delayed arm (17 vs 3 cases; $p < 0.002$) was driven by higher reports in two sites in India, rather than reflecting a trend from the study as a whole. [3] Secondly, serious non-AIDS events, rather than being reduced by earlier treatment, occurred more frequently with immediate treatment.

Another detail, from the supplementary information made available with publication in the New England Journal of Medicine last year, is that the three suicides in HPTN-052 were all in the immediate arm in patients taking efavirenz: a caution that should temper any recommendation to widely prescribe treatment at higher CD4 counts.

Even with the best intentions, these individuals may have died many years before they were likely to have a demonstrable clinical benefit from treatment.

References

1. Grinsztejn B et al. Effect of early versus delayed initiation of antiretroviral therapy (ART) on clinical outcomes in the HPTN 052 randomized clinical trial. 19th International AIDS Conference. 22-27 July 2012, Washington. Oral late breaker abstract THLB05.
<http://pag.aids2012.org/abstracts.aspx?aid=21278>
<http://pag.aids2012.org/flash.aspx?pid=3892>
2. Cohen M et al. Antiretroviral treatment to prevent the sexual transmission of HIV-1: results from the HPTN 052 multinational randomized controlled trial. 16th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 17–20 July 2011, Rome Oral abstract MOAX0102.
<http://pag.ias2011.org/Abstracts.aspx?SID=98&AID=4735>
<http://pag.ias2011.org/flash.aspx?pid=680>
3. Cohen MS et al for the HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. Supplementary information. NEJM 2011; 365:493-505. (11 August 2011).
<http://www.nejm.org/doi/full/10.1056/NEJMoa1105243>

Hormonal contraception and the risk of HIV acquisition

Polly Clayden, HIV i-Base

Hormonal contraception is widely used and plays a critical role in women's health, education, employment, economic development and autonomy.

But there is considerable controversy about the role of hormonal contraception in HIV acquisition. There have also been concerns over its potential role in disease progression. A session at IAS 2012 explored the evidence to date. [1]

A prospective cohort study of 3790 couples from East and southern Africa, the Partners in Prevention HSV/HIV Transmission Study recently found that HIV negative women in partnerships with HIV positive men and using injectable contraceptives had a 2-fold increase in HIV acquisition risk (aHR 2.05, 95% CI 1.04 – 4.04, $p=0.04$). [2] These results gained a great deal of international attention. Following an expert consultation and a systematic review of the existing data, WHO issued a statement upholding its previous guidance on hormonal contraceptive use and re-emphasised the importance of condom use for dual protection. [3]

Renee Heffron presented the results from multiple additional sensitivity analyses examining the robustness of the Partners in Prevention findings. [4] She noted that the findings from this and other observational studies have been inconsistent, are hard to interpret and might have behavioural and/or biological explanations.

In the primary analysis previously reported the investigators used Cox proportional hazards regression, adjusting for age, male partner's viral load, and time-dependent unprotected sex and pregnancy, to compare HIV incidence in women using injectable hormonal contraceptives to women reporting no hormonal method.

The more recent sensitivity analyses examined the possible effects of behaviour, miss-classification of women who switched hormonal contraception during follow-up and the effect of depot medroxyprogesterone acetate (DMPA) compared to other hormonal contraception methods. As information about the brand of hormonal contraception was not collected in the study, in order to isolate the effect of DMPA, data from South African women were censored, as this is the only country with study sites where other methods of hormonal contraception are used.

Dr Heffron reported a persistent increase in HIV acquisition risk of approximately 2-fold across the analyses. When limited to only DMPA users, injectable hormonal contraception was associated with an almost 4-fold increase in risk of HIV acquisition (see Table 1).

Dr Heffron noted that some analyses had diminished power for precision due to decreased sample size of the sub groups but the adjusted hazard ratios always suggested a trend towards increased risk. She concluded that these results must be balanced with the unequivocal benefits of injectable contraception. She added that more high quality studies of hormonal contraception and HIV risk are needed and stressed the importance of integrating reproductive health and HIV prevention programmes.

Following this presentation Chelsea Polis from USAID, Office of Population and Reproductive Health, Washington showed results from a systematic review of the epidemiological literature on the association between hormonal contraception and HIV acquisition, including articles published or in press by December 15, 2011. [5]

Table 1. Results from sensitivity analyses of HIV incidence in women using injectable contraception versus no hormonal contraception

Analysis	aHR	95% CI	p-value
Number of sex acts	2.06	1.04 – 4.07	0.04
Male report of unprotected sex*	2.03	0.95 – 4.35	0.07
Women who reported unprotected sex*	2.29	0.70 - 7.53	0.17
Restricting to periods prior to HC method switch	2.62	0.93 – 7.33	0.07
DMPA users	3.39	1.38 – 11.22	0.01

Adjusted for age, baseline viral load of HIV-positive partner and time dependent report of pregnancy

* Adjusted for the above covariates and the other partner's report of unprotected sex

The investigators identified twenty relevant studies, eight of which met minimum quality criteria. Only one study found a statistically significant association between use of oral contraceptive pills and HIV acquisition.

None of the studies reported statistically significant associations between use of norethisterone enantate (Net-En) and HIV acquisition, but the investigators noted that these data were limited. For DMPA, the data available at the time of review neither established a clear association nor definitely ruled out the possibility of an effect on HIV acquisition.

In order to look at disease progression in HIV positive women, Sharon Phillips from the WHO showed findings from a similarly conducted systematic review. [6]

This review revealed twelve reports of eleven studies meeting the inclusion criteria. One randomised controlled trial found increased risk of a composite endpoint of CD4 decline or death in hormonal contraceptive users versus copper IUD users. Ten observational studies reported no increased risk of HIV disease progression, as determined by death, time to CD4 below 200, time to initiation of antiretroviral therapy, increased viral load, or decline in CD4 with use of hormonal contraception versus non-use.

The investigators noted that although one randomised controlled trial found that hormonal contraceptive use was associated with increased risk of HIV disease progression it had important methodological shortcomings. None of the cohort studies found an association between hormonal contraceptive use and HIV disease progression compared with non-use of hormonal contraceptives.

They concluded that, "the preponderance of evidence indicates that HIV positive women can use hormonal contraceptive methods without concerns related to HIV disease progression".

C O M M E N T

In the first systematic review conducted for the WHO consultation and presented here, findings are mixed and conflicting. None of the studies reviewed were designed to assess HIV transmission risk and, like all observational findings have many potential confounders.

Eight of 20 relevant studies reviewed met minimum quality criteria - related to use of multivariate analysis, low loss to follow up and clear definition of hormonal contraceptive use. Only one study of sex workers in Kenya showed an association between oral contraception and 46% elevated HIV transmission risk. [7] The Heffron et al study described above showed elevated point estimates but this was not significant.

No studies reported statistically significant associations between use of norethisterone enantate (Net En) and elevated transmission risk, but only three gave estimates specific to this method.

Three of eight studies had statistically significantly increased relative risks with DMPA or unspecified injectable methods, including double the risk in Heffron 2012, 73% increase (and narrower confidence intervals) in Baeton 2007 and 48% increase in risk with marginal structural modelling in Morrison 2010 (but not with Cox proportional model in a previous analysis). [8,9] Other studies had non-significant increased and decreased relative risks. This heterogeneity did not appear to be explained by differences in HIV incidence, purpose of data collection, size of study population, approach to pregnancy, number of seroconverters or overall statistical approach. Differences in manner of handling condom use, length of inter-survey interval and analysis of serodiscordant couples need further consideration and concerns about the potential for residual confounding remain.

The systematic review and the WHO expert consultation concluded that the body of evidence on injectable contraceptives does not establish a clear casual association with HIV acquisition nor does it rule out the possibility of an effect.

The medical eligibility criteria (MEC) for use of contraception offers guidance on the safety of use of different methods for women and men with specific characteristics or known medical conditions and is used by policy-makers, programme managers, and the scientific community, to support national programmes in preparing service delivery guidelines. The MEC did not change following the WHO consultation and there are no restrictions on the use of any hormonal contraceptive method for women living with HIV or at high risk of HIV, although the following clarification was added: "Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition, other studies do not show this association. A WHO expert group reviewed all

the available evidence and agreed that the data were not sufficiently conclusive to change current guidance. However, because of the inconclusive nature of the body of evidence on possible increased risk of HIV acquisition, women using progestogen-only injectable contraception should be strongly advised to also always use condoms, male or female, and other HIV preventive measures. Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection is essential. These recommendations will be continually reviewed in light of new evidence”.

It is important to note however that a numbering system such as this one cannot reflect nuance, uncertainty (and the complexity of discussion) involved.

Women living with HIV and activists involved in the expert consultation and a subsequent one to discuss the associated operational considerations have stressed the critical importance of clear information for women using hormonal contraceptives and health workers.

References

1. Hormonal contraception and HIV: an evolving controversy. 19th International AIDS Conference 22-27 July 2012. Washington, DC. Session WEAC02. <http://pag.aids2012.org/Session.aspx?s=287>
2. Heffron et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infectious Diseases*, Volume 12, Issue 1 January 2012.
3. WHO upholds guidance on hormonal contraceptive use and HIV. Geneva. February 2012. http://www.who.int/mediacentre/news/notes/2012/contraceptives_20120216/en/index.html
4. Heffron R et al. Association of injectable contraception and risk of HIV-1 acquisition in women in HIV-1 serodiscordant partnerships: persistence of effect in multiple sensitivity analyses. 19th International AIDS Conference 22-27 July 2012. Washington, DC. Oral abstract WEAC0202.
5. Polis C et al. Hormonal contraception and HIV acquisition in women: a systematic review of the epidemiological evidence. 19th International AIDS Conference 22-27 July 2012. Washington, DC. Oral abstract WEAC0203.
6. Phillips S et al. Hormonal contraception and HIV disease progression: a systematic review of the epidemiological evidence. 19th International AIDS Conference 22-27 July 2012. Washington, DC. Oral abstract WEAC0203.

Towards an HIV cure: Early developments reported at IAS, part 2

Muirgen stack, HIV i-Base

The announcement of the IAS Towards an HIV Cure scientific strategy at the 3rd IAS pre-conference symposium, held this year from 20-21 July, gave a new emphasis to advances in the field of cure research. [1]

The strategy outlines seven important areas of research where advances needed to be made if a cure (functional or sterilising) is to be realised:

- Why does HIV persist: immune and viral factors
- Where does HIV persist: tissue and cell reservoirs
- Immune activation and dysfunction on ART
- Natural models of HIV/SIV control
- How to measure persistent infection
- How to reverse latency: treatments
- Immune approaches, gene therapy, vaccine

Fortunately, some promising cure-related research was presented at AIDS 2012 – something that is hopefully sustained and expanded upon at further meetings.

Novel therapeutic approaches

A greater understanding of viral latency and persistence alongside an expansion of existing therapies is only likely to be one part of any future HIV cure (see Part 1 of this report published in the previous issue of HTB). The creation of novel treatments may be just as essential if targeting viral production and/or replication in sanctuary and/or reservoir sites.

Carolina Garrido and colleagues from UNC Chapel Hill, North Carolina presented a poster on using gold nanoparticles to target viral reservoirs in the brain. [2]

Early research from this group showed that fluorescently labelled (TAMRA) gold nanoparticles successfully enter lymphocytes, macrophages, astrocytes and human brain microvascular endothelial cells (HBMECs) after 24-hours incubation. FACS analysis showed up to 15% of CD4+ T-cells contained TAMRA. Moreover, the ability of the nanoparticles to cross the blood-brain-barrier was confirmed in vivo by intravenous tail injection in mice. Mouse brain gold content reached up to 869 ppb/gram of tissue, and was also observed by microscopy. The nanoparticles were then conjugated to a raltegravir derivative to assess antiviral activity. This reduced viral replication to 25–38% by day 5 compared to 100% HIV replication in media alone. Unfortunately, this was not compared to an unconjugated raltegravir derivative or other ARVs. Nevertheless, these preliminary findings showed initial efficacy and targeting specificity for nanomedicine-based approaches to HIV treatment – although any implications for accumulating gold nanoparticles in brain tissue with chronic treatment were not addressed. [3]

Frauke Christ from the University of Leuven, Belgium, presented pre-clinical data on a new class of integration inhibitors, known as LEDGINS. [4] LEDGINS bind allosterically to a site on integrase where the cellular co-factor LEDGF/p75 attaches. LEDGF/p75 acts to anchor the viral DNA to the host chromatin, before integration. LEDGINS have previously been shown to inhibit HIV replication in vitro via this mechanism. [5]

In the current study, the researchers evaluated the ability of LEDGINS to block the catalytic activity of integrase directly, reporting further inhibition of HIV replication in MT2 and PBMC cells, as well as activity over a broad range of viral clades, and even with viruses containing mutations conferring resistance towards other integrase inhibitors.

Although still in their developmental infancy, there at least appears possible future use for LEDGINS – either on their own or concomitantly with other integrase inhibitors. However, whether they will retain their pre-clinical efficacy in animal and human clinical trials remains to be seen.

Targeting the integrated virus and immunotherapies

Helga Hofmann-Sieber from the Heinrich Pette Institute, Hamburg, presented research, which directly addressed an HIV cure (functional or sterilising) by creating a system that can remove integrated HIV proviral DNA from infected human cell cultures. [6] This approach uses a viral LTR-specific recombinase (Tre-recombinase) that the researchers have previously shown to excise HIV-1 proviral DNA from infected human cell cultures. Tre-recombinase is an enzyme based on the bacterial cre-recombinase, which removes sections of DNA that are flanked by a specific series of nucleotides called loxP. Unfortunately HIV proviral DNA does not contain any loxP sequences. So, the researchers chose a mutant cre-recombinase that could recognise a sequence of nucleotides in the LTRs of integrated HIV.

Applying the technique to HIV positive humanised mice meant creating an advanced lentiviral self-inactivating (SIN) vector that expressed Tre-recombinase conditionally in HIV-infected cells. Both human CD4+ T-cells and CD34+ haematopoietic stem cells (HSC) were successfully transduced prior to engraftment in HIV-1 positive Rag2-/-gammac-/- mice. The pronounced antiviral activity via the Tre-recombinase system was not associated with undesired cytopathic effects in the transduced cells from Tre-recombinase over expression.

Excising integrated HIV-1 DNA would theoretically allow for the eradication of HIV-1 from the body. However, transducing all latently infected cells with Tre recombinase in the many viral reservoirs found in the body remains infeasible. Therefore, the Tre system needs to be modified to allow easier administration before it can be considered for clinical trials like other “anti-latency” drugs such as the histone deacetylase (HDAC) inhibitor vorinostat. [7] First however, the researchers must address a question raised at the end of the presentation which highlighted the Tre-recombinase system to be dependent on the transcription of the viral protein TAT. Unfortunately, disruption of the expression of TAT is a marker of latency, meaning that the Tre-recombinase system would have minimal efficacy on excising proviral DNA from latently infected cells. [8] However, this does make the Tre-recombinase system redundant and perhaps by pairing with other equally novel lentiviral vectors that deliberately over stimulate TAT, the system could continue to be advanced. [9]

Shifting away from novel molecular therapeutics, Lydia Trautmann from VGTI, Florida gave an interesting presentation on possible advances in immunotherapies. [10] She focused on better characterising the differences between HIV-specific CD8+ T cells before and during ART. Her findings included that under low HIV antigen loads (caused by viral suppression from ART), the dominant HIV-specific CD8+ T cell clonotype gained poly-functionality - recognising more epitopes of HIV antigens. This led to a small but efficient clonotype developing under ART. Dr Trautmann concluded that if ways were found to expand these high-affinity HIV-specific CD8+ T cells in vivo, they might be able to control the virus without ART.

Fortunately, an oral abstract by Scott Kitchen from the UCLA AIDS Institute, Los Angeles covered this topic. [11] After recognising the cytotoxic CD8+ T lymphocyte (CTL) response as a critical component in controlling HIV infection, the researchers set out to enhance and expand CTLs' effects in vivo. They utilised molecularly cloned HIV-specific T-cell receptors (TCRs) derived from CD8+ T-cells, which were then used to genetically transduce human haematopoietic stem cells (HSCs). The transduced cells were then introduced into a humanised mouse and were allowed to differentiate into mature human CD8+ CTLs. Mice expressing the transgenic HIV-specific TCRs were compared to control mice after both were infected with HIV-1.

They observed successful differentiation into mature CTLs and migration into multiple anatomic sites. They also crucially saw significant reduction in plasma HIV RNA levels, which correlated with both levels of reconstitution with cells bearing the HIV-specific TCR and antigen-driven T cell expansion.

These early findings from a humanised mouse model demonstrated the importance of the CTL response and how it can be expanded and improved. By relying on the CTLs own ability to transverse to multiple compartments in the body, it could also potentially override some of the difficulty ARVs may have in reaching sanctuary sites.

Stem cell transplantation

Taking host immune system modification even further, Timothy Henrich from Brigham and Women's Hospital, Boston presented two case reports of allogeneic stem cell transplantation in two HIV positive individuals. [12] Both had haematological malignancies and had previously undergone autologous stem cell transplant. The patients remained on ART and were given a reduced-intensity conditioning (RIC) form of allogeneic stem cell transplant. Immunosuppressive therapy was eventually given in the form of prednisone or tacrolimus/sirolimus to treat chronic graft-versus-host disease (GVHD) after the transplant.

Total HIV-1 DNA was still seen up to 2 months after transplant in patient A (87 copies/million PBMCs) and up to 3 months after transplant in patient B (281 copies/million PBMCs). However after 8 and 9 months respectively, total HIV-1 DNA and 2-LTR HIV-1 DNA (copies/million PBMCs) became undetectable. This was also true for plasma HIV-1 RNA, which due to the sensitivity of the assay can only be shown to be <3 copies/ml.

Parallels will naturally be drawn to the “Berlin patient” (Timothy Brown) who received a stem cell transplant from a donor homozygous for the CCR5 delta-32 mutation. [13] However, the stem cells received by both patients A and B were from donors with normal CCR5 expression. Whether, this undermines the CCR5 delta-32 mutation being necessary as a mechanism to explain Timothy Brown being labelled as “cured” is unclear.

The authors proposed multiple possibilities to explain why HIV could not be detected; namely, GVHD and/or the effect of cytotoxic therapies given to treat it. However, a fuller understanding will have to wait until further samples are analysed to see if any HIV can be detected. More information can be found in a recent interview with the co-researcher Dan Kuritzkes from Harvard Medical School, Boston where he hints at the protective role of ART - acting as "PrEP on a cellular level". [14]

It is clear that cure research covers many different areas and that any likely successes may involve a combination therapy approach. These are tentative stages of cure science, but there are still reasons for optimism. The most obvious being the open nature of cure research, which stresses the importance of collaboration between scientists in the field and is endorsed by the "Towards an HIV cure" working group. This leaves an update of cure-related advances at the 20th international AIDS conference (AIDS 2014) in Melbourne, Australia as an appealing prospect. [15]

References

Unless stated otherwise, all references are to the Programme and Abstracts for the 19th International AIDS conference 22-27 July 2012, Washington.

1. International AIDS Society (IAS). Towards an HIV Cure: Global Scientific Strategy. July 2012
www.iasociety.org/Web/WebContent/File/HIV_Cure_Full_recommendations_July_2012.pdf
2. Garrido C et al. Gold nanoparticles to improve drug delivery to the central nervous system: targeting HIV reservoirs in the brain. Poster exhibition THPE014.
<http://pag.aids2012.org/EPosterHandler.axd?aid=19162>
3. Alkilany A and Murphy C. Toxicity and cellular uptake of gold nanoparticles: what we have learned so far? J Nanopart Res (September 2010) 12 (7): 2313-2333.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2988217/>
4. Christ F et al. Pre-clinical evaluation of HIV replication inhibitors that target the HIV-integrase-LEDGF/p75 interaction. Oral abstract TUAA0301.
<http://pag.aids2012.org/Abstracts.aspx?AID=10849>
5. Christ F et al. Rational design of small-molecule inhibitors of the LEDGF/p75-integrase interaction and HIV replication. Nat Chem Biol (June 2010) 6 (6):442-448.
<http://www.ncbi.nlm.nih.gov/pubmed/20473303>
6. Hofmann-Sieber H et al. Towards HIV eradication: excision of HIV-1 proviral DNA by Tre-recombinase in HIV-positive humanized mice. Oral abstract TUAA0302.
<http://pag.aids2012.org/abstracts.aspx?aid=11812>
7. Archin N et al. Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. Nature (26 July 2012) 487: 482-485.
<http://www.nature.com/nature/journal/v487/n7408/full/nature11286.html>
8. Karn J. The molecular biology of HIV latency: breaking and restoring the Tat-dependent transcriptional circuit. Curr Opin HIV AIDS (January 2011) 6 (1):4-11.
<http://www.ncbi.nlm.nih.gov/pubmed/21242887>
9. Macias D et al. A lentiviral vector that activates latent human immunodeficiency virus-1 proviruses by the overexpression of tat and that kills the infected cells. Hum Gene Ther (November 2009) 20 (11):1259-1268.
<http://www.ncbi.nlm.nih.gov/pubmed/19604078>
10. Trautmann L. Novel approaches: treatment and HIV pathogenesis. Immunopathogenesis and its treatment. Symposia Session. 23 July 2012, 2.30-4.00pm, Washington.
<http://pag.aids2012.org/flash.aspx?pid=1677>
11. Kitchen S et al. In vivo suppression of HIV antigen specific T cells derived from engineered hematopoietic stem cells. Oral abstract TUAA0303.
<http://pag.aids2012.org/Abstracts.aspx?AID=19110>
12. Henrich T et al. Long-term reduction in peripheral blood HIV-1 reservoirs following reduced-intensity conditioning allogeneic stem cell transplantation in two HIV-positive individuals. Oral abstract THAA0101.
<http://pag.aids2012.org/Abstracts.aspx?AID=6016>
13. Allers K et al. Evidence for the cure of HIV infection by CCR5delta32/delta32 stem cell transplantation. Blood (10 March 2011) 117 (10):2791-2799.
<http://bloodjournal.hematologylibrary.org/content/117/10/2791.full>
14. A Barton. Paths to a cure: Dr. Dan Kuritzkes discusses experiences of two patients. 16 August 2012.
<http://sciencespeakblog.org/2012/08/16/paths-to-a-cure-dr-dan-kuritzkes-discusses-experiences-of-two-patients/#axzz27OactI7>
15. The 20th International AIDS conference 20-25 July 2014 Melbourne, Australia.
<http://www.aids2014.org/>

Online video interviews between researchers and activists

Simon Collins, HIV i-Base

The US activist Fred Schaich has for many years persuaded leading researchers and other activists attending key medical meetings to step away from the main meeting and spend 10-20 minutes being interviewed for short web cast videos.

The informal discussions complement the main programme and more than 15 interviews have been posted online.

<http://www.ifarablog.org/>

Selected highlights include:

- Daniel Douek, Senior Investigator at the US NIH discusses cure research and the development of therapeutic and prophylactic vaccines for HIV with activist Jeff Taylor.

<http://www.ifarablog.org/2012/07/ias-2012-daniel-douek.html>

- Jens Lundgren, from the University of Copenhagen talks about the early associations between elevated biomarkers such as IL-6, D-dimer and increased risk of serious complications in the SMART and ESPRIT studies, and why these results while exciting are not yet ready for clinical use. Also, earlier testing and the currently ongoing START study, which will produce randomised data to inform the decision on when to start ART.

<http://www.ifarablog.org/2012/07/ias-2012-jens-lundgren.html>

- Judith Aberg, Chair of the HIV Medicine Association (HIVMA) discusses the ways in which the organisation educates the US Congress about science that drives the benefits of ART and the differences between increased health complications associated with HIV and ageing and the differences between this and the common sound-bite of “premature ageing”.
<http://www.ifarablog.org/2012/07/ias-2012-judith-aberg.html>
- Myron Cohen discusses treatment as prevention, a future with new and easy-to-take drugs, the potential for a “virtual cure”, and patient treatment, and reflects on how clinical practice is never fixed - developing over decades of research.
<http://www.ifarablog.org/2012/07/ias-2012-myron-cohen.html>
- Antu Dey from Novartis vaccine development programme in Massachusetts, discusses HIV vaccine development, human vs. animal trials, monoclonal antibodies, and prevention.
<http://www.ifarablog.org/2012/07/ias-2012-antu-dey.html>
- Sheila Tlou, Director, Regional Support Team for Eastern and Southern Africa, UNAIDS, discusses her long and distinguished history in HIV in Eastern and Southern Africa and expectations for expanding treatment access by 2015.
<http://www.ifarablog.org/2012/07/ias-2012-sheila-tlou.html>
- Enid Vasquez on Treatment as Prevention, difficulties for sex workers to attend the IAS meeting, new drugs and PrEP.
<http://www.ifarablog.org/2012/08/ias-2012-enid-vasquez.html>

ANTIRETROVIRALS

FDA approves Quad in US: price may prohibit UK access

Simon Collins, HIV i-Base

On 27 August 2012, both the US Food and Drug Administration (FDA) and Gilead Sciences issued news releases confirming the approval for a single pill boosted integrase inhibitor fixed dose combination for adult HIV treatment.

Developed under the name Quad and with a new tradename Stribild, the combination contains elvitegravir, a new pharmacokinetic booster called cobicistat, FTC and tenofovir. The indication is for treatment-naïve patients with estimated creatinine clearance (CrCl) of >70 mL/min. [1, 2]

The two large phase 3 studies on which approval was based compared Quad to Atripla (efavirenz/FTC/tenofovir) and to atazanavir/ritonavir plus separate FTC/tenofovir. Both studies concluded that Stribild was non-inferior to the comparator arms with 88-90% rates of undetectable viral load at week 48 compared to 84% with Atripla and 87% with boosted atazanavir.

The press release summarised nausea and diarrhoea as common side effects and new or worsening kidney problems, decreased bone mineral density, fat redistribution and changes in the immune system (immune reconstitution syndrome) as serious side effects. Stribild's label gives advice to health care providers on how to monitor patients for kidney or bone side effects.

Stribild needs to be taken with food. This is based on increased mean exposure of elvitegravir and tenofovir by 34% and 24% respectively with a light meal (373 kcal, 20% fat) and by 83% and 23% respectively with a higher fat meal (~800 kcal, 50% fat). [3]

Of note, the US DHHS guidelines have already issued an update that recommends Stribild as an alternative rather than preferred option for first-line therapy. This decision was based on “a significant potential for drug-drug interactions, the availability of only 48 weeks of safety data, usage limited to individuals with pre-treatment CrCl >70 mL/min, a possible increased risk of proximal renal tubulopathy, limited data in patients with advanced HIV disease and in women, and the need for the drug to be taken with food”. [4]

C O M M E N T

This decision was expected after the FDA advisory panel voted 13:1 in May 2012 [5] based on the 200-page briefing document summary of preclinical and clinical studies. [6]

But the expected welcome for an important new option for treatment is tempered by a US price more than a third higher than Atripla (approximately \$28,500 vs \$21,000 for the US annual wholesale list price). Although the European decision on approval is not expected until later this year, and drug pricing is complex, a similar differential in the UK would severely restrict prescribing. [7]

While Quad offers potential advantages to some current options, these were not demonstrated in the clinical trials that led to approval based on finding it is “not likely to be worse” than current treatment, based on a non significant 4% difference in the percentage of patients with undetectable viral load after 48 weeks of treatment.

Unless Stribild is a cost neutral option compared to Atripla, this potentially important new drug is likely to be rarely used in the UK. Without a cost-neutral price compared to boosted atazanavir or boosted darunavir, it is likely to be rarely used in second-line therapy,

or as a switch option based on a better side effect profile compared to efavirenz. If the price is not cost-neutral compared to raltegravir, it is unlikely to be widely used in patients with multidrug resistance.

The cost differences are likely to widen further when efavirenz comes off patent in 2013, with costs savings from generic formulations expected to be sufficient to routinely switch patients from Atripla to efavirenz and separate tenofovir/FTC.

While switching between brand and generic formulations is a basic tenet of NHS healthcare, switching between classes is not.

Gilead have stated that this is a competitive price for the US market and that they have set up patient access programme. Gilead in the UK do not want to comment on European pricing prior to EU licensing.

References

1. Gilead press release: FDA Approves Gilead's Stribild, a Complete Once-Daily Single Tablet Regimen for Treatment-Naïve Adults with HIV-1 Infection. (27 August 2012). http://www.gilead.com/pr_1728981
2. FDA press release: FDA approves new combination pill for HIV treatment for some patients. (27 August 2012). <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm317004.htm>
3. Gilead. US Product information label for Stribild. Section 12.3 Pharmacokinetics, page 25. (August 2012). http://www.gilead.com/pdf/stribild_pi.pdf
4. HHS Panel Statement. HHS panel on antiretroviral guidelines for adults and adolescents recommends a fixed-dose combination product of elvitegravir/cobicistat/tenofovir/emtricitabine as an alternative regimen in antiretroviral treatment-naïve Individuals with HIV-1 infection. (18 September, 2012). http://aidsinfo.nih.gov/contentfiles/AdultARVStatementOnEVG_COBL_TDF_FTC.pdf (PDF file)
5. FDA advisory panel vote 13:1 for approval of Quad. HTB, June 2012. <http://i-base.info/htb/16640>
6. Elvitegravir/Cobicistat/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen (EVG/COBI/FTC/TDF, QUAD STR) for treatment of HIV-1 infection in adults. Antiviral Drugs Advisory Committee Meeting Briefing Document. (11 May 2012). <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM303397.pdf>
7. Quad approved in US: cost may limit use in Europe. Online comment. <http://i-base.info/gilead-price-quad/>

Merck acquires CMX157 and EFdA and starts phase 2 study for new NNRTI

Simon Collins, HIV i-Base

On 24 July 2012, a press release from Merck announced that the company had signed licensing agreement for the development of two new nucleoside analogues and is about to launch a phase 2 study for its in house NNRTI. [1]

CMX157 is a nucleoside analogue in development at Chimerix that reported promising phase 1 results over four years ago and has been waiting for a financial backer since. [2] The compound is a prodrug of tenofovir (tenofovir diphosphate as the active moiety), with an improved pharmacokinetic profile to tenofovir and initial results suggesting a potential for once-weekly dosing. The in vitro resistance profile includes sensitivity to K65R with some but not all thymidine analogue mutations. This was a compound that was expected to be picked up several years ago.

EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine) is a compound in development with the Japanese biotech division of the Yasama Corporation (who have a history that includes brewing soy sauce since the time of the English civil war) and which has been studied with amFAR and US NIH support. A poster presented at the 19th IAS conference in Washington this summer reported a significantly stronger in vitro resistance profile compared to tenofovir following multiple passaging with a mixture of 11 multinucleoside resistant viral mutations.

Merck also used the opportunity to announce its in-house NNRTI compound MK1439 is about to enroll treatment naive patients into a phase 2 dose-finding study (from 25 mg to 200 mg) using efavirenz as a comparator and tenofovir/FTC as background nukes.

C O M M E N T

It is promising news that Merck is developing an active programme of research for new HIV drugs to in parallel to development of integrase inhibitors.

Although less well publicised, Merck is also one of the companies investing in cure research.

References

1. Merck press release. Merck signs two deals for novel HIV drug candidates and initiates phase II clinical trial of MK-1439 for HIV. (24 July 2012). http://www.merck.com/newsroom/news-release-archive/research-and-development/2012_0724.html
2. Lanier ER et al. Hexadecyloxypropyl tenofovir (CMX157) has enhanced potency in vitro against NRTI resistant HIV relative to tenofovir and a favorable preclinical profile. XVII IHDRW 2008, Sitges. Poster 4. <http://i-base.info/htb/598>
3. Maeda K et al. Delayed emergence of HIV-1 variants resistant to 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA): comparative sequential passage study with tenofovir, emtricitabine and raltegravir. 19th IAC, 22-25 July 2012, Washington. Poster abstract TUPE017. <http://pag.aids2012.org/abstracts.aspx?aid=18620>
4. A dose-ranging study to compare MK-1439 plus Truvada versus efavirenz plus Truvada in human immunodeficiency virus (HIV)-1 infected participants (MK-1439-007 AM5). <http://clinicaltrials.gov/ct2/show/NCT01632345>

Roche to discontinue production of nelfinavir and saquinavir 200 mg hard capsules

Roche communication

Roche Laboratories have announced that they intend to discontinue the production of nelfinavir powder and tablets globally when the European patent ends on 23 January 2013.

The decision has been made due to the extremely low use together with the availability of alternative treatments with improved risk/benefit profiles.

Less than 200 people are estimated to still be using the Roche product globally.

Additionally, the 200 mg formulation of saquinavir (Invirase hard capsules) will no longer be available in the UK.

The company will continue to manufacture the 500 mg film-coated tablet formulation of saquinavir and also continue to produce T-20 (enfuvirtide, Fuzeon), irrespective of the current low level of usage.

Source

Press letter from Roche/Genentech. (20 July 2012).

<http://www.nelm.nhs.uk/en/NeLM-Area/News/2012---August/02/Roche-to-discontinue-production-of-Viracept-nelfinavir-mesilate-in-2013/>

TREATMENT ACCESS

FDA approval of generic ARVs

Since the last issue of HTB, the US Food and Drug Administration (FDA) has granted full and tentative approval for the following new generic ARV products.

Drug and formulation	Manufacturer, Country	Approval date
AZT/3TC/nevirapine FDC scored tablets (60 mg/30 mg/50 mg) for oral suspension, for children weighing 5 to 25 kg.	Strides Arcolab, India	21 Sep 2012

* full approval; FDC: Fixed Dose Combination

"Tentative Approval" means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, but because of existing patents and/or exclusivity rights, it cannot yet be marketed in the United States. Tentative approval does, however make the product eligible for consideration for purchase under the PEPFAR program for use outside the United States.

Fixed Dose Combinations are reviewed for PEPFAR under the FDA guidance titled "Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously approved Antiretrovirals for the Treatment of HIV". This document was developed to clarify what regulatory requirements apply to such applications, what issues might be of concern, and how these issues should be addressed. The guidance is intended to encourage sponsors to submit applications for combination and co-packaged products, and to facilitate submission of such applications to FDA.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079742.pdf>

Effective patent dates are listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book:

<http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>

An updated list of generic tentative approvals (now at 140) is available on the FDA website:

<http://www.fda.gov/oa/pepfar.htm>

Source: FDA list serve:

<http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm>

Free HIV treatment in the UK for all, irrespective of residency status

UK Department of Health

From 1 October 2012, an amendment to the NHS (Charges to Overseas Visitors) Regulations means that HIV treatment will no longer chargeable to any overseas visitor.

This guidance sets out:

- The background to the policy change.
- Definitions of HIV treatment and care.
- Prescribing of antiretroviral therapies.
- The role of the Overseas Visitor Manager.
- How the Department of Health will monitor the change.

HIV often presents with other healthcare needs that may be chargeable unless they too are exempt from NHS charge. This guidance supports implementation of the change in England.

C O M M E N T

These changes take immediate effect and should be widely publicised. They will hopefully contribute to earlier diagnosis and access to care and remove the previous fear associated with seeking treatment.

References

HIV treatment for overseas visitors: Guidance for the NHS (September 2012).

<https://www.wp.dh.gov.uk/publications/files/2012/09/DH-Guidance-HIV-and-NHS-Charging-iFORMATED.pdf>

Robin Hood Tax begins in France

Rebecca McDowall, HIV i-Base

The Robin Hood Tax campaign are celebrating victory after a 0.2% financial transaction tax (FTT) came in to effect in France on 2 August 2012.

This was just days after the campaign featured strongly in the March to end AIDS in Washington France became the first country to implement this new type of taxation.

Former French President Sarkozy first announced plans to introduce a 0.1% financial transaction tax in January. This was later doubled by his successor President Hollande. The tax is expected to raise half a billion euros in the first year, with a pledge from President Hollande that a part of the revenue will go towards combating AIDS.

The Robin Hood Tax campaign hopes that this step by the French President will act as a signal to other countries, including the UK, to rethink their position on the FTT.

For further information, and to support the campaign, visit the Robin Hood Tax website:

<http://robinhoodtax.org.uk/>

Novartis case enters Indian Supreme court

Rebecca McDowall, HIV i-Base

The long running Novartis legal challenge to India's patent law entered the Supreme Court in New Delhi, on September 11.

This is a final bid by the company in a six-year attempt to undermine India's pro public health patent laws, and has been met by protests across the world.

The Swiss pharmaceutical company Novartis has been engaged in a legal battle over a part of India's patent law (known as Section 3d) which says that a new form of a known medicine can only be patented if it shows significantly improved therapeutic efficacy over existing compounds; this is a provision to stop the common industry practice of extending, or 'evergreening,' their patent monopolies for routine modifications of known compounds.

Section 3d, which is in line with international trade rules, formed the basis for Novartis not being granted a patent for its cancer drug imatinib mesylate (marketed as Gleevec) in 2006. Novartis' patent application was on a new form of the imatinib molecule already described several years previously in patents in the US and other developed countries.

MSF flashmob brings Novartis protest to Geneva

On Wednesday 19 September, at noon, 200 people froze in the streets of Geneva to protest against Novartis. The group included an ambulance, removing a patient on a stretcher, emphasising the potential impact for access to healthcare from the case. "If Novartis wins,

everything stops. Millions of people around the world will no longer have access to affordable medicine. We therefore urge Novartis to drop the case in India". (MSF protestor) [2]

Act-Up Paris protesters arrested outside of Novartis

In order to coincide with the start of the trial, Act-Up Paris activists gathered at Novartis HQ in order to deliver a petition of 18,000 signatories condemning the case, which led to the entire group being arrested. The activists were detained separately for 48 hours whilst being prevented from accessing medical care, basic hygiene facilities, lawyers or phone calls. One HIV positive activist was denied access to HIV treatment for the duration of his detention. [3]

Stop AIDS Campaign demands Novartis drops the case

The UK based Stop AIDS Campaign held protests outside the Swiss Embassy and Novartis' UK offices. Lotti Rutter, from the Stop AIDS Campaign said: "This case is about a cancer drug, but the result will have a much wider impact on the health of poor people all around the world. If they win, the change will make it easier for drug companies to get unjustifiable extensions to their monopolies, and make it more difficult for generic companies to produce and sell the affordable generic medicines health care providers across the developing world rely on." [4]

References

1. MSF press release. Novartis' six-year legal challenge against India's pro-health patent law heads to Supreme Court (11 September 2012)
<http://www.msfast.org/about-us/media-room/press-releases/novartis%E2%80%99-six-year-legal-challenge-against-india%E2%80%99s-pro-health>
2. MSF Geneva video. STOP NOVARTIS: Flashmob in Geneva (20 September 2012).
<http://www.msf.ch/fr/news/articles/detail/proces-novartis-action-de-protestation-a-geneve/>
3. Act Up-Paris press release. Un ressortissant français, détenu en Suisse, privé de médicaments contre le sida pendant 48 heures (14 September 2012).
<http://www.actupparis.org/spip.php?article4957>
4. Stop AIDS Campaign press release. Novartis: stop strangling the supply of affordable medicines from India (19 September 2012).
<http://stopaidscampaign.org/2012/09/novartis-stop-strangling-the-supply-of-affordable-medicines-from-india/>

India: Bayer stay order against compulsory licence denied

MSF Press Release

On 17 September 2012, India's Intellectual Property Appellate Board (IPAB) dismissed pharmaceutical company Bayer's request for a stay order against the compulsory licence granted by the Patent Controller to a generic manufacturer earlier this year.

In its appeal before the IPAB, Bayer alleged that the CL decision of the Indian Patent Controller is illegal and unsustainable, and had filed for an immediate stay until the appeal could be heard. This has now been rejected by IPAB.

Interest of public health

"This decision once again affirms that courts can and should act in the interest of public health in the case of pharmaceutical products," said Leena Menghaney, of Médecins Sans Frontières/Doctors Without Borders (MSF)'s Access Campaign.

"The high prices caused by patents in India are a growing problem that needs to be grappled with: one year's treatment costs over US\$1,700 for one of the newer HIV medicines we use in our project in Mumbai, and will be needed across the developing world. This price needs to come down, and we hope that the routine use of compulsory licensing may be one way of making this happen."

Affordable access to patented medicines

India's first compulsory licence is seen as a prospective watershed for affordable access to patented medicines, by potentially opening the way for other life-saving drugs - such as the newest drugs used to treat HIV - now patented in India and priced out of reach to be produced by generic companies for use across the developing world at a fraction of the price.

The CL brought the price of the patented anti cancer drug, sorafenib tosylate, down from over US \$5,500 per month to \$175 per month; a price reduction of 97 percent.

MSF had welcomed the grant of a compulsory licence issued in March this year to allow a more affordable version of liver and kidney cancer drug, sorafenib tosylate, to be produced. Bayer is being paid a six per cent royalty on sales by Natco, the generic manufacturer who received the licence.

Reference

MSF Press Release. India: Bayer stay order against compulsory licence denied (17 September 2012).
http://www.msf.org.uk/Bayer_patent_case_India_20120903.news

SIDE EFFECTS & COMPLICATIONS

Increased incidence of ischemic stroke amongst HIV positive cohort

Muirgen Stack, HIV i-Base

A retrospective analysis performed by Felicia Chow and colleagues published in the 1st August issue of the Journal of AIDS showed a significant increase in the incidence of ischemic strokes within an HIV positive cohort compared to HIV negative controls matched for age, gender and race. The relative increase in stroke rates was highest amongst women and younger patients. [1]

Whilst HIV infection has become established as a risk factor for developing such non-AIDS defining illnesses as cardiovascular disease (CVD) and osteoporosis (and increased fragility-fracture risk), analysis of stroke in this context has so far languished. [2,3] However, although a recent study has shown a higher ratio of strokes being attributed to HIV-infected persons, this was not a direct comparison of stroke incidence between persons with and without HIV. [4]

A total of 4308 HIV positive patients were analysed from the Research Patient Data Registry (RPDR) clinical care database from Massachusetts General Hospital and Brigham and Women's Hospital (US) between 1996 and 2007. International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes were used to ascertain HIV status and ischemic stroke (from the category of ischemic cerebrovascular disease). If multiple strokes were reported as per ICD-9-CM codes, only the first was included. A control group of 32,423 was generated by matching HIV negative patients from the RPDR to patients in HIV cohort in a 10:1 ratio on the basis of age, gender and race.

Primary demographics between the two study groups were well matched: mean age of 41.6 vs 40.8, percentage of women 31% vs 35%, race; white 53% vs 52%, black 21% vs 22% and hispanic 17% vs 17% for HIV positive and HIV negative respectively.

Within the HIV positive cohort: mean (SD) CD4 count and CD4 nadir were 473 (+/-317) cells/mm³ and 271 (+/-252) cells/mm³, respectively. The percentage of patients with a viral load below 400 HIV RNA copies/mL was 73% and percentage of patients with CNS infection/malignancy was 4%. Previous ARV use included 95% NRTI, 56% NNRTI and 67% PI use (from the N= 2105 patients with antiretroviral therapy (ART) data).

The proportion of HIV-infected patients with traditional stroke risk factors including hypertension, diabetes mellitus, dyslipidemia, smoking, cardiomyopathy, left sided valvular heart disease, coronary heart disease (CHD) and heart failure was significantly higher than in the HIV negative cohort (P < 0.001 for all comparisons).

The incidence rate (IR/1000 patient years) of ischemic stroke was 5.27 vs 3.75 in the positive vs negative groups respectively, resulting in an unadjusted hazard ratio (HR) of 1.40 (95% CI: 1.17 to 1.69, P < 0.001). In these unadjusted incidence rates, HIV infection was associated with higher rates of stroke amongst those younger than 50. Between 18-29 years the IR was 3.87 vs 0.88 giving an incidence rate ratio (IRR) of 4.42 (95% CI: 1.56 to 11.09, p=0.004), between 30-39 years the IR was 3 vs 1.02 giving an IRR of 2.96 (95% CI: 1.69 to 4.96, p < 0.001) and between 40-49 years the IR was 4.02 vs 2.62 giving an IRR of (95% CI: 1.06 to 2.17, p=0.02) in the positive vs negative groups respectively. For men specifically however, only HIV positive patients between 30-39 years had elevated stroke rates that remained significant: IR of 2.84 vs 1.28 giving an IRR of 2.23 (95% CI: 1.07 to 4.26, p=0.022) in the positive vs negative groups respectively. Once age, gender, race and the traditional stroke risk factors were accounted for, HIV infection remained an independent predictor of stroke with a hazard ratio (HR) of 1.21 95% CI: 1.01 to 1.46, P = 0.043.

Within the HIV cohort, age (HR: 1.06 per year, 95% CI: 1.03 to 1.09, p < 0.001), female gender (HR: 1.76; 95%CI 1.24 to 2.52, p=0.002), a higher log-transformed viral load (HR: 1.10, 95%CI: 1.04 to 1.17, P = 0.001), and a history of CNS infections or malignancy (HR: 2.75, 95% CI: 1.26 to 6.03, p=0.011) were associated with an increased risk of stroke. Conversely, longer duration of any ART use was associated with a significantly decreased risk of stroke (HR: 0.79, 95% CI: 0.71 to 0.88, p < 0.001). Most recent CD4 cell count and nadir value were not associated with stroke risk.

C O M M E N T

Careful interpretation is needed to distinguish the causality from traditional risk factors (which were more common in the HIV-infected cohort) and what may be an indication of HIV specific aetiology i.e. high viral load increasing stroke risk.

The increased stroke risk in HIV-infected women is also notable, and may in part be attributable to "lower baseline risk for stroke in women, amplifying the relative impact of an HIV-specific effect" as speculated by the authors.

Finally, the role of HIV increasing stroke risk in younger people (18-49 years) is intriguing, as the effect from traditional risk factors on stroke risk tends to increase with age. However, before inferring a more pronounced effect of HIV infection on stroke risk in younger persons, it is important not to make a more general underestimation of stroke incidence in persons below 45 years. [5]

References

1. Chow F et al. Comparison of Ischemic Stroke Incidence in HIV-infected and Non-HIV-Infected Patients in a US Health Care System. JAIDS (1 August 2012) 60:351-358.
http://journals.lww.com/jaids/Fulltext/2012/08010/Comparison_of_Ischemic_Stroke_Incidence_in.3.aspx
2. Currier J et al. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. Circulation (June 2008) 118:e29-35.
<http://circ.ahajournals.org/content/118/2/e29.full>
3. McComsey G et al. Bone Disease in HIV infection: A Practical Review and Recommendations for HIV Care Providers. Clin Infect Dis (15 October 2010) 51 (8):937-946.
<http://cid.oxfordjournals.org/content/51/8/937.long>

4. Ovbiagele B et al. Increasing incidence of ischemic stroke in patients with HIV infection. *Neurology* (1 February 2011) 76:444-450.
<http://www.neurology.org/content/76/5/444>
5. Marini C et al. Incidence of Stroke in Young Adults: A Review. *Stroke Research and Treatment* (2011) 2011:535-672.
<http://www.hindawi.com/journals/srt/2011/535672/>

HIV PATHOGENESIS

Discord controllers: characterising a new viremic controller phenotype

Muirgen Stack, HIV i-Base

The results from this study suggest more evidence for the role of immune activation in disease progression, including in the subset of patients who experience decline of CD4+ T cells yet maintain low plasma RNA-loads.

Groves and colleagues from Queen Mary's School of Medicine and Dentistry and Barts and The London NHS Trust Department of Virology analysed a subgroup of HIV-1 viraemic controllers, which presented with both unusual immunology and clinical uncertainty (published on 16 August ahead of print in the *Journal of AIDS*). [1]

Viraemic controllers are defined as HIV positive individuals who maintain HIV suppression level without the use of ARVs. They are distinguished from normal progressors in having HIV RNA-loads below 2000 copies/ml and CD4+ T-cell counts of >450 cells/mm³ (as defined by the International HIV Controller Consortium). This review covers the complex mechanism that might explain these responses. [2] Therefore, the identification of a new subset of patients that seem to show a mixture of traits convergent to both viraemic controllers and progressors is extremely important in the broader context of elucidating how immunopathophysiology contributes to disease progression. [3]

Patients were recruited from outpatient clinics at Barts and The London and Homerton University Hospital Trusts. Of 3000 clinic attendees, 82 were identified as HIV-1 viraemic controllers, divided into 64 "typical" controllers (HIV RNA-loads below 2000 copies/ml and CD4+ T-cell counts of >450 cells/mm³) and 18 "discord" controllers (HIV RNA-loads below 2000 copies/ml and CD4+ T-cell counts of <450 cells/mm³) thus representing 2.7% and 0.6% of patients respectively. The two controller cohorts were compared against progressors (HIV RNA-loads above 10,000 copies/ml and CD4+ T-cell counts of <450 cells/mm³) and in some cases HIV negative patients.

The authors quantified CD4+/CD8+ T-cell subsets, HIV RNA-loads, HIV DNA-loads and analysed viral clade. Demographics identified in the controller cohort included age, gender and ethnicity. Of note, 13 patients (3 discord and 10 typical controllers) were treated with ART during pregnancy but controlled plasma RNA-load for at least 12 months before and after. Two other typical controllers with low RNA-loads for 3.7 and 3.5 years subsequently showed a significant rise in RNA-loads whilst maintaining good CD4+ T-cell counts (geometric means of 732 and 708 cells/mm³, respectively). All of the mentioned patients were included in the patient characteristics and clade analysis, but were not used for DNA-load and T-cell analysis.

In the controller cohort, average age was median 37.5 (IQR 32-43 years) vs 38.5 (32.5-49 years), percentage of cohort of female gender was 54.7% vs 61.1%, plasma RNA-load (log₁₀ copies/mL) was median 408.5 (IQR 160.7-1000) vs median 428.6 (100.3-1043) and CD4+ T-cell count (cells/mm³) was median 699.3 (IQR 550.4-843.1) vs median 347.2 (298-406.6) for typical and discord controllers respectively. The only statistically significant difference between the groups was discord controllers having a lower %CD4 T-cells than typical controllers, median 22.3 (IQR 17.6-26) vs median 33.7 (IQR 23.8-40, p<0.0001).

Of the n=15 discord controllers where clade data was available, 40% were positive with subtype CRF02_AG compared to 19.5% of typical controllers. As the clade distribution of the study population was diverse (East London), any inference from this is currently unclear.

Despite an extensive T-cell subset analysis, statistical significance for comparisons between controllers, progressors and HIV negative patients is lacking. Unfortunately, this remained true for CD8+ T-cell subset populations and levels of CD4+/CD8+ T-cell activation. However, this should not wholly detract away from the researcher's findings, as discord controllers only seem to represent a very small proportion of patients in the wider population.

Discord controllers appear to share many characteristics with progressors namely, depleted naive CD4+ T cells and increased CD4+ T cell activation levels. However, discord controllers appear to have more similarities to typical controllers than progressors in both their CD8+ T-cell activation pattern and preservation of CD8+ naive T-cell pool.

Both discord and typical controllers had much lower plasma HIV RNA-loads than viraemic noncontrollers (p<0.0001) yet, discord controllers are then distinguished from typical controllers by having higher HIV-1 DNA loads (p=0.002).

C O M M E N T

Although more clarification on the defining features of discord controllers is needed, the identification of this subset is important for two reasons. Firstly, it provides evidence of sub-clinical disease progression despite maintaining low plasma viral load. This may be an indicator for more regular analysis of HIV DNA-loads and/or CD4+ T-cell activation levels in patients who present with a seemingly anomalous decreasing CD4+ T-cell count.

Secondly, the authors offer multiple explanations for the disease progression seen in discord controllers, with most possibilities aligning alongside the effects of aberrant immune activation/dysregulation. [4] Whilst these may be valid, it still remains unclear why high cellular HIV DNA levels do not result in higher-level plasma RNA viral load in discord controllers - perhaps suggestive of increased levels of ongoing replication in vivo.

Finally, a concern when characterising new subsets of patients is that it may just be a failure to account for natural variation in the population, in this case lower "normal" CD4+ T-cells counts. However, during the study five patients in the discord controller group started ART and all saw modest gains in their CD4+ T-cell counts. This should hopefully help to define discord controllers as patients who can respond well to treatment even if they appear to be somewhat managing the virus without ARVs.

References

1. Groves K et al. Disease progression in Human Immunodeficiency Virus-1 infected viremic controllers. JAIDS (16 August 2012) [Epub ahead of print]. http://journals.lww.com/jaids/Abstract/publishahead/Disease_Progression_in_Human_Immunodeficiency.98428.aspx
2. Gaardbo J et al. Thirty years with HIV infection-nonprogression is still puzzling: lessons to be learned from controllers and long-term nonprogressors. AIDS Res Treat (2012) 2012: 161584. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3368166/>
3. Deeks S. HIV infection, lymphoid fibrosis, and disease. Blood (30 August 2012) 120 (9):1753-1754. <http://bloodjournal.hematologylibrary.org/content/120/9/1753.full>
4. Hunt P et al. HIV-specific CD4+ T cells may contribute to viral persistence in HIV controllers. Clin Infect Dis (1 March 2011) 52 (5):681-7. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3060894/>

DRUG INTERACTIONS

Ritonavir significantly increases exposure to colchicine (gout)

www.hiv-druginteractions.org

The pharmacokinetic interaction between ritonavir (100 mg twice daily) and colchicine (0.6 mg single dose) was investigated in 24 HIV negative subjects.

Ritonavir increased colchicine C_{max} and AUC by 170% and 240% compared to colchicine alone. There was no apparent increase in the incidence of adverse events during coadministration.

Colchicine doses should be adjusted when administered with ritonavir to avoid the risk of colchicine-related toxicities.

C O M M E N T

Colchicine is a herbal medicine used to treat gout and has a wide range of potential interactions including with antibiotics, antifungals, statins and other HIV protease inhibitors. [2]

Source: hiv-druginteractions.org (31 July 2012).

<http://www.hiv-druginteractions.org>

References

1. Wason S et al. Clinically significant drug interaction between colchicine and ritonavir in healthy adults. 14th International Workshop on Comorbidities and Adverse Drug Reactions in HIV, Washington, July 2012. Abstract P22.
2. British National formulary http://www.medicinescomplete.com/mc/bnf/current/bnf_int483-colchicine.htm

Ritonavir interaction with quinine is clinically insignificant but may warrant caution

www.hiv-druginteractions.org

Coadministration of ritonavir (100 mg twice daily) and quinine (105.3, 162, 210.6 or 648 mg single doses) was studied in 4 groups of HIV negative subjects (n=20 per group).

Quinine did not have a significant effect on ritonavir T_{max} or C_{max}, but increased AUC from 9.2 ± 2.21 ug.h/ml to 11.1 ± 3.96 ug.h/ml.

Similarly, ritonavir had no significant effect on quinine pharmacokinetics (C_{max} 4.3 ± 1.07 vs 3.9 ± 0.88 ug/ml, AUC 78.9 ± 26.78 vs 68.4 ± 22.29 ug.h/ml, alone vs with ritonavir). Although the increased ritonavir exposure and decreased quinine exposure are unlikely to be of clinical significance, caution should be exercised if coadministered.

Source: hiv-druginteractions.org (31 July 2012).

<http://www.hiv-druginteractions.org>

Ref: Wason S et al. Lack of clinically significant pharmacokinetic interactions between quinine and ritonavir in healthy adult participants. International Workshop on Comorbidities and Adverse Drug Reactions in HIV, Washington, July 2012. Abstract P21.

Case report: fluticasone, fluconazole and ritonavir interactions

www.hiv-druginteractions.org

This case report further highlights the well documented interaction of a ritonavir-boosted PI and inhaled fluticasone but also describes an added interaction issue with the introduction of fluconazole for oral candidiasis.

Within days of discontinuing fluticasone and initiating fluconazole, the 52 year old man was confirmed with exogenous Cushing's syndrome and secondary adrenal insufficiency. The authors propose that fluconazole inhibits adrenal steroidogenesis and thereby has an adrenal inhibitory effect.

Source: [hiv-druginteractions.org](http://www.hiv-druginteractions.org) (27 July 2012).

<http://www.hiv-druginteractions.org>

Ref: St Clair K, Maguire JD. Role of fluconazole in a case of rapid onset ritonavir and inhaled fluticasone-associated secondary adrenal insufficiency. *Int J STD AIDS*, 2012, 23(5): 371-372.

<http://www.ncbi.nlm.nih.gov/pubmed/22648897>

TREATMENT GUIDELINES

UK Standards for HIV Care online for comment

In order to help with the planning of HIV services and to ensure that HIV positive people receive access to the appropriate levels of treatment and service, the British HIV association (BHIVA) have drafted "Standards of Care for People Living with HIV".

It is hoped that the document will be used during and after the proposed national changes in NHS reorganisation and be used for planning both national and local services.

A first draft of this report is now online for comments, with the consultation period ending on 7th October. Feedback on all aspects of the document is encouraged. The draft was compiled by a wide range of stakeholders, including doctors, nurses, pharmacists, community advocates and HIV positive people.

Further information on process of producing the standards, together with links to download PDF files for each of the twelve standards and to make online comments is on the BHIVA website.

<http://www.bhiva.org/standards-of-care-2012.aspx>

The final document will be published on Thursday 29 November 2012 at a formal launch event to mark World AIDS Day.

The recommendations are covered in 12 major areas of care.

1. Diagnostic Testing for HIV
2. Access to, and retention in, HIV treatment and care
3. Provision of outpatient treatment and care for HIV, and access to care for complex co-morbidity
4. Safe ARV prescribing: Effective Medicines Management
5. Inpatient care for people living with HIV
6. Psychological care
7. Sexual health and secondary HIV prevention
8. Reproductive Health
9. Self management
10. Service user engagement / involvement
11. Competencies
12. Data, Audit and Research

HIV in England to remain as nationally commissioned specialist service

A report by the Clinical Advisory Group for Prescribed Services (CAG) has been published, recommending which specialised services for people with rare conditions should be commissioned nationally in England.

This report, running to over 200 pages confirms that HIV care and treatment services will be commissioned by the NHS Commissioning Board (see pages 75-76 and 88-90 for adult and paediatric care respectively).

References

Clinical Advisory Group for Prescribed Services: Final Recommendations. (June 2012).

<http://www.dh.gov.uk/health/2012/09/cagreport/>

PDF download:

<http://www.dh.gov.uk/health/files/2012/09/Clinical-Advisory-Group-for-Prescribed-Services.pdf>

US guidelines include Stribild (Quad) as alternative rather than preferred option for treatment naive adults

Shortly after FDA approval of the new once-daily single-pill formulation of elvitegravir/cobicistat/tenofovir/emtricitabine (Stribild) the US HHS guideline panel issued a statement on how this combination has been assessed in its recommendations for treatment naive adult patients.

The included the recommendation for elvitegravir 150 mg / cobicistat 150 mg / tenofovir 300 mg / emtricitabine 200 mg once daily (with food) as an “alternative” regimen for ART-naive HIV-infected patients with CrCl >70 mL/min. The recommendation was rated BI (moderate strength recommendation, based on results from randomised clinical trials).

Factors behind the decision not to make this a “preferred” option included “a significant potential for drug-drug interactions, the availability of only 48 weeks of safety data, usage limited to individuals with pre-treatment CrCl >70 mL/min, a possible increased risk of proximal renal tubulopathy, limited data in patients with advanced HIV disease and in women, and the need for the drug to be taken with food”.

References

HHS Panel Statement. HHS panel on antiretroviral guidelines for adults and adolescents recommends a fixed-dose combination product of elvitegravir/cobicistat/tenofovir/emtricitabine as an alternative regimen in antiretroviral treatment-naive Individuals with HIV-1 infection. (18 September, 2012).

http://aidsinfo.nih.gov/contentfiles/AdultARVStatementOnEVG_COBI_TDF_FTC.pdf (PDF file)

IAS USA update adult ARV treatment guidelines

An update of the International Antiviral Society-USA (IAS-USA) recommendations for adult HIV treatment as an open access article in the Journal of the American Medical Association (JAMA).

The document is written by an international panel of doctors and the update is based on a systematic review of conference presentations and published research from the previous two years.

Changes since the previous edition include:

- Offering ART to all patients regardless of CD4 cell count.
- Changes in therapeutic options (including both tenofovir/FTC and abacavir/3TC as first-line background nucleoside analogues).
- Recognising the protective benefit of treatment in reducing the risk of transmission.
- Cited new evidence that untreated HIV can also lead to a range of other conditions, including cardiovascular disease and kidney disease, and some cancers.
- Modifications in the timing and choice of ART in the setting of opportunistic illnesses such as cryptococcal disease and tuberculosis.

C O M M E N T

These guidelines are a briefer document than the US DHHS guidelines which have a more significant reach and influence.

Although criteria for membership of the panel includes not participating in pharmaceutical industry sponsorship, this is only for the duration of the period on the panel. As with many treatment guidelines, extensive conflicts of interest are declared for most if not all panel members.

References

Antiretroviral Treatment of Adult HIV Infection 2012: Recommendations of the International Antiviral Society–USA Panel. JAMA. 2012;308(4):387-402. (25 July 2012).

TUBERCULOSIS COINFECTION

Costs for rapid TB test reduced by 40%

USAID press release

On 6 August 2012 a USAID press release announced that an agreement that reduces the cost of a rapid TB diagnostic test in 145 high-burden and developing countries. [1]

Under the arrangement, organised by PEPFAR, USAID, UNITAID, and the Bill & Melinda Gates Foundation, the price of Xpert MTB/RIF cartridges will be reduced from \$16.86 to \$9.98 and will not increase before 2022.

To date, the high unit cost of Xpert MTB/RIF cartridges produced by the medical device manufacturer Cepheid has proven a barrier to their introduction and widespread use in low- and middle-income countries. The new agreement will immediately reduce the cost of cartridges used to diagnose TB by more than 40%.

In December 2010, the World Health Organization (WHO) recommended the Cepheid product, known as Xpert MTB/RIF assay, which is run on Cepheid's GeneXpert platform. Until Cepheid developed the Xpert MTB/RIF assay, the only method used in most laboratories in developing countries was smear microscopy, a technique first developed in the 1880s by the German bacteriologist Robert Koch that requires visual detection of the TB bacterium under a microscope.

Smear microscopy is particularly insensitive for diagnosing TB in patients who are co-infected with HIV. It also does not help clinicians detect the presence of drug-resistant strains of TB. The limitations of traditional smear microscopy, along with the cost and long delays to receive culture results, have limited the ability to diagnose and treat TB and drug-resistant forms of the disease.

Xpert is a molecular diagnostic system that can detect TB disease in patients co-infected with HIV and resistance to the antibiotic rifampicin - a widely accepted indicator of the presence of multi-drug resistant TB - in less than two hours. The system also can be used outside of conventional laboratories because it is self-contained and does not require specialized training.

Because TB is the leading cause of death among people living with HIV in Africa, greater access to the Xpert test offers a significant advance in the capacity of health care workers to diagnose TB quickly and help reduce TB transmission, the development of TB disease, and premature TB deaths.

The capacity of the Xpert MTB/RIF assay to yield a rapid and accurate diagnosis has the potential to improve TB diagnosis and treatment in rural clinical settings. A large percentage of people with TB disease fail to start treatment promptly because of the long wait for results of older conventional tests and the need for them to return to the clinic, which may be far from where they live. Using the Xpert system, clinics in poor and rural settings can deliver rapid diagnosis and immediately start patients on appropriate treatment, including second-line drugs in cases of drug-resistant.

Research suggests that the incremental scale up of Xpert in countries with high TB burdens could allow for the rapid diagnosis of 700,000 cases of TB disease and save health systems in low- and middle-income countries more than U.S. \$18 million in direct health costs.

C O M M E N T

The demands for lower cost access to this test have been widespread since the technology was first developed.

Even though \$10 remains a significant cost in many settings, this news was widely welcomed.

Dr Lucica Ditiu, Executive Secretary of the Stop TB Partnership said "This agreement will translate into life-saving TB care for people affected by TB" and Dr Mario Raviglione, Director of the WHO Stop TB Department said "We see innovation happening in real time - scientific evidence rapidly translated into policy, policy quickly adapted into practice, and scale-up significantly accelerated by innovative funding mechanisms effectively addressing cost and affordability." [2]

The capacity for machines range from 4 to 100 tests and the cost was reduced from \$60,000 to \$17,000 when in 2007 when the price of cartridges for low and middle-income countries was initially reduced to \$17 per test. [3]

Source:

1. USAID press release. Public-private partnership announces immediate 40 percent cost reduction for rapid TB test. (6 August 2012). <http://www.usaid.gov/news-information/press-releases/public-private-partnership-announces-immediate-40-percent-cost>
2. Stop TB Partnership. Cost of Xpert cartridges to drop 40 percent. (6 August 2012). http://www.stoptb.org/news/stories/2012/ns12_051.asp
3. Non-technical review on Gene Xpert <http://www.tbonline.info/posts/2011/10/3/gene-xpert/>

Important advances in TB drug development

Nathan Geffen, CSSR

Three recent studies have significantly advanced TB drug development.

Delamanid for MDR TB

Delamanid (formerly known as OPC-67683) is a nitroimidazole and is one of two new drugs in this class used to treat TB. It inhibits the synthesis of mycolic acid, a component of the TB bacterium cell wall. It is being developed by the Japanese pharmaceutical company, Otsuka.

In June the company published the results of a large Phase II trial in the *New England Journal of Medicine*. The trial took place in Philippines, Peru, Latvia, Estonia, China, Japan, Korea, Egypt, and the United States. Patients were randomly assigned to receive a standard background MDR TB drug regimen plus either delamanid 100mg twice daily (n=161), delamanid 200 mg twice daily (n=160) or placebo twice daily (n=160) for eight weeks in hospital. Delamanid is taken with food.

All participants had been diagnosed with multi-drug resistant TB. Nearly all were HIV-negative. The median age was 35. Baseline BMI was 19.6. Nearly 70% of participants had lung cavities. All patients had been previously treated for TB. Of the 481 patients, 402 were sputum-positive using MGIT.

One patient died of TB. Eighteen, 14 and 15 people withdrew from the delamanid 100mg, delamanid 200mg and control arms respectively. Fourteen patients, evenly distributed across the arms, discontinued the study drug because of adverse events.

Except for QT interval, there were no significant differences in adverse events between the arms. QT interval was higher in the 200mg group (13.1%) than in the 100mg group (9.9%), which was higher than the placebo group (3.8%). There were no clinical events associated with QT interval.

Delamanid exposure increased less than proportionally with the dose. The half-life plasma concentration of delamanid was 38 hours after patients stopped taking the drug.

The main finding of the study was that patients who received delaminid 100mg and 200mg had a 45.4% and 41.9% sputum conversion rate (using MGIT) respectively after two months compared to 29.6% in the placebo arm (p=0.008 for the 100mg and p=0.04 for the 200mg comparisons).

The authors explain that a second large, randomised, controlled trial of six months of treatment with delamanid as part of a full background drug regimen and including patients with HIV on ART has started. It is designed to provide data on 30 months of follow-up of patients.

Possible shorter TB regimen using PA-824

One of the aims of the TB Alliance is to develop shorter, more effective and safer TB treatment regimens. But there are many possible drug regimens, especially with several new agents in the pipeline, and each can take years to test. Iteratively adding single agents to the standard regimen and testing these in clinical trials would be an extremely costly and time-consuming way to identify an optimal new regimen. The question then is how to identify the most promising regimens for large, long, expensive trials.

Andreas Diacon of Stellenbosch University and a team from several research institutions published an article in the *Lancet* describing a phase 2a trial. This has received wide publicity because it has provided a clever way forward for identifying new TB regimens to take into large trials. [2]

TB patients at hospitals in Cape Town were randomised to several regimens. The effect of the regimens was measured using 14-day early bactericidal activity (EBA). This was done to identify the most promising regimen (or regimens) to test further. EBA was measured using MGIT from sputum samples collected daily from patients.

To be included patients had to be 18 to 65 years old. They had to weigh 40 to 90kg, be smear-positive, have a chest radiograph consistent with TB and be able to produce sputum.

The following regimens were tested:

1. Bedaquiline 700mg on day 1, 500mg on day 2 and 400mg daily thereafter.
2. The same as above plus PA-824 200mg daily.
3. The same as the bedaquiline alone regimen plus pyrazinamide 25mg/kg daily.
4. PA-824 200mg daily plus pyrazinamide 25 mg/kg daily.
5. PA-824 200mg daily, pyrazinamide 25 mg/kg daily and moxifloxacin 400mg daily.
6. Standard isoniazid, rifampicin, pyrazinamide, ethambutol regimen dosed according to body weight.

PA-824 is a new TB drug being developed by the TB Alliance. Like delamanid, it is a nitroimidazole.

Of the 173 patients screened, 85 were included in the trial. Of these 15 were randomly allocated to each arm, except for the standard regimen, to which 10 were allocated.

Half the patients reported adverse events, though most were mild and not drug-related. Fourteen patients completed their regimens in arms 1 to 4, 12 completed regimen 5 and all 10 completed the standard regimen. Five of the seven withdrawals were due to elevated ALT. One PA-824-moxifloxacin-pyrazinamide patient had a QT interval that met withdrawal criteria. One had an altered consciousness experience due to newly diagnosed neurocysticercosis. All of these (except the patient with neurocysticercosis) withdrawals were asymptomatic.

All patients had TB that was susceptible to the treatment regimens they were on.

The key finding of the trial was that the mean 14-day EBA of the PA-824-moxifloxacin-pyrazinamide regimen (0.233, standard deviation 0.128) was significantly higher than the bedaquiline regimens (bedaquiline 0.061 [SD: 0.068], bedaquiline-pyrazinamide 0.131 [SD: 0.102], bedaquiline-PA-824 0.114 [SD: 0.050]).

The PA-824-moxifloxacin-pyrazinamide EBA was not significantly different from the PA-824-pyrazinamide (0.154 [SD: 0.040]) and standard regimen (0.14 [SD: 0.094]).

The authors conclude that the PA-824-moxifloxacin-pyrazinamide regimen is potentially suitable for treating drug-sensitive and MDR TB. They propose further clinical trials for this regimen. But they also state that the bedaquiline-PA-824 and PA-824-pyrazinamide had comparable EBAs with the standard regimen and therefore “could become important building blocks of future regimens”. They make the important point that, a “regimen not containing isoniazid and rifampicin would represent a substantial step towards a new regimen with low interaction potential suitable for both fully drug-susceptible and MDR tuberculosis. With this study the path to the construction of new regimens becomes clearer.”

PNU-100480

Sutezolid (PNU-100840) is a new oxazolidinone. This is the same class of drug as linezolid. These drugs prevent bacterial proteins from being made by interfering with an enzyme that binds with bacterial ribosomes. [3]

The 2012 i-Base/TAG Pipeline Report explains that sutezolid appears to be more potent against TB than linezolid in vitro, in ex vivo whole blood cultures, and in mice. The report also explains that a whole-blood study predicted that sutezolid, SQ109 and bedaquiline, would be additive and should be tested as part of a novel combination regimen. [4]

The results of a phase 2 study conducted in South Africa were described in an oral abstract by Robert Wallis of Pfizer and colleagues at the IAS 2012 conference. Sputum positive patients were randomly assigned to, either sutezolid 600mg twice daily (n=25), 1200 mg once daily (n=25), or the standard South African first-line regimen (isoniazid, rifampicin, ethambutol and pyrazinamide, n=9) for the first 14 days of treatment. Only 7% of the patients were HIV positive (not yet on ART) and 20% were women. [5]

All volunteers completed the trial. There were no treatment-related serious adverse events. There was also no effect on the QT interval. Seven patients on the sutezolid arms had transient asymptomatic ALT elevations.

At baseline, the mean log colony forming units per millilitre (CFU/ml) was 6.95. The mean time to detection using MGIT was 116 hrs. Using 90% confidence intervals, all three treatment arms reduced colony forming units and increased time to MGIT detection significantly, but the standard regimen improvements were significantly greater. The actual reductions are depicted graphically in the abstract and so the exact values are not given. These appear to be approximately as follows:

- Time to MGIT detection: approximately 75 hours longer for the sutezolid regimens versus 160 hours for the standard regimen.
- CFU/ml reduction: approximately 1.2 log for sutezolid versus 2.8 log for standard.

The authors concluded that further studies of the drug are warranted.

C O M M E N T

This is one of the most exciting and fast-moving periods in TB drug development since the 1960s. Delamanid has arguably leapfrogged bedaquiline to the front of the new drug pipeline. But both are important. Both drugs must be put swiftly through the remaining studies needed for regulatory approval, which includes providing plans for paediatric development, and both drugs must be made available for pre-approval access to patients with drug-resistant TB who are being treated at well-run TB facilities. They also need to be tested together. The Global TB Community Advisory Board has written to Otsuka raising these issues and Otsuka has replied in detail with their plans. [6, 7]

Except for delamanid, the regimens and drugs discussed here are several years away from coming to market. The pace from drug discovery to market for new TB drugs is far too slow. Bedaquiline has been in development since at least 2004 and is still not approved anywhere. According to the Working Group on New TB Drugs the current annual budget for sutezolid is tiny, \$250,000 to \$1,000,000. The annual budget for PA-824 is significant, \$10 million, but nothing close to what would be spent on a blockbuster drug.

Although the TB drug development pipeline has improved, diseases that almost exclusively affect poor people continue to receive dramatically reduced investment from pharmaceutical industry and research institutions compared to medicines that can be more profitably marketed in richer countries.

References

1. Gler MT et al. 2012. Delamanid for Multidrug-Resistant Pulmonary Tuberculosis. *N Engl J Med.* 2012 Jun 7;366(23):2151-60.
<http://www.nejm.org/doi/full/10.1056/NEJMoa1112433>
2. Diacon A et al. 2012. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet.* 2012 Jul 20.
<http://www.ncbi.nlm.nih.gov/pubmed/22828481>
3. Shinabarger D. 1999. Mechanism of action of the oxazolidinone antibacterial agents. *Expert Opin Investig Drugs.* 1999 Aug;8(8):1195-202.
<http://www.ncbi.nlm.nih.gov/pubmed/15992144>
4. Clayden et al. 2012 Pipeline Report.
<http://www.pipelinerreport.org/browse/tb-treatments/sutezolid-pnu-100480>

5. Wallis RS et al. 2012. Safety, tolerability and early bactericidal activity in sputum of PNU-100480 (sutezolid) in patients with pulmonary tuberculosis. Oral abstract THLBB02. 19th International AIDS Conference July 22-27, Washington DC.
<http://pag.aids2012.org/abstracts.aspx?aid=20755>
6. Clayden P et al. 2012. Letter by Global TB CAB to Otsuka.
<http://www.tbonline.info/archive/document/94/>
7. Carlevaro P. 2012. Response to open letter by Global TB CAB.
<http://www.tbonline.info/archive/document/103/>

OTHER NEWS

Jerome Horwitz dies at 93

Jerome Horwitz, the chemist who first synthesised AZT, d4T and ddC while a researcher at Wayne State University's cancer research center in Detroit in the early 1960's, died on 6th September, aged 93.

His obituary in the New York Times noted that when AZT failed as a potential treatment for cancer based on lack of biological activity in murine studies, it was shelved, and Horwitz told colleagues that he had developed "a very interesting set of compounds that were waiting for the right disease."

Dr Horwitz neither patented the drug nor earned income from developing these compounds, even though as the first approved successful treatment it went on to eventually generate billions of dollars for Burroughs Wellcome (later GlaxoSmithKline). The development and patents for ddC and d4T went to Roche and Bristol Myers-Squibb, respectively.

The development of dideoxythymidines later provided the basis for treating HIV, hepatitis and herpes.

Although Burroughs Wellcome donated \$100,000 to the Karmanos Cancer Institute, the research center affiliated with Wayne State, to establish a chair in his name, this "gift" was not enough to cover the cost of an endowed professorship. He said the size of the gift, given the profits earned, made him angry for a while. But he got over it, saying in a 2005 interview "If I was ever bitter, it's long since passed".

Source: Vitello P. New York Times. Jerome Horwitz, AZT creator, dies at 93. (20 September 2012).

<http://www.nytimes.com/2012/09/21/health/jerome-p-horwitz-creator-of-azt-dies-at-93.html>

FUTURE MEETINGS

Conference listing 2012/13

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.

3rd International Workshop on HIV and Ageing

5 – 6 November 2012, Baltimore, USA.

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

11th International Congress on Drug Therapy in HIV

11 – 15 November 2012, Glasgow.

<http://www.hiv11.com>

43rd Union World Conference on Lung Health

13 – 17 November 2012, Kuala Lumpur

<http://kualalumpur2012.worldlunghealth.org>

20th Conference on Retroviruses and OIs (CROI) 2013

3 – 7 March 2013, Atlanta, USA.

<http://retroconference.org>

19th Annual (BHIVA) 2013

16th – 19th April 2013, Manchester.

<http://www.bhiva.org>

14th International Workshop on Clinical Pharmacology of HIV Therapy

22 – 24 April 2013, Liverpool, UK.

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

48th International Liver Congress (EASL 2013)

24 – 28 April 2013, Amsterdam.

<http://www.easl.eu>

7th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2013)

30 June – 3 July 2013, Kuala Lumpur, Malaysia.

<http://www.ias2013.org>

53rd ICAAC

10 – 13 September 2013, Denver, USA.

<http://www.icaac.org>

14th European AIDS Conference (EACS)

16 – 19 October 2013, Brussels, Belgium.

<http://www.europeanaidscinicalsociety.org>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website: 2012 update for PDA access

The i-Base website has been recently redesigned to meet access standards for PDA, iPad, tablet, Windows 8 and touch screen access.

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

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

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

Publications and regular subscriptions can be ordered online.

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

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

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

The advocacy resources include an online training manual with eight 2-hour modules that include questions and evaluation. Training modules start with basics, including CD4, viral load and other monitoring tests, combination therapy and side effects, and include overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment.

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

Non-technical treatment guides

i-Base treatment guides

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

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

- Introduction to combination therapy (April 2012)
- HIV testing and risks of sexual transmission (February 2012)

- HIV and quality of life: side effects & complications (July 2012)
- Guide to changing treatment and drug resistance (February 2011)
- Guide to HIV, pregnancy & women's health (September 2011)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)

Publications and reports

HIV Treatment Bulletin (HTB)

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

HTB South

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

HTB Turkey

HIV Tedavi Bülteni Türkiye (HTB Turkey) is a Turkish-language publication based on HTB and produced three times a year by an independent group of Turkish doctors, activists and health care workers.

Why we must provide HIV treatment information

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

Translations of i-Base publications

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

In addition, PDF files of some of the translated publications are available online.

Please be aware that some of these translations are from earlier editions of the treatment guides, and check the publication date before relying on these editions.

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

Languages include: Bosnian, Bulgarian, Chinese, Czech/Slovak, Croatian, French, Greek, Hindi, Indonesian, Italian, Kosovo, Macedonian, Nepali, Polish, Portuguese, Romanian, Russian, Serbian, Spanish and Turkish.

Advocacy resources

Online treatment training for advocates

<http://i-base.info/ttfa>

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

Additional support material is included on how to understand aspects of science that might be new to a lay reader.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community advocates from across the UK that has been meeting since 2002. It now includes over 480 members from over 120 organisations. The CAB has a separate website, where reading material, reports and presentations from all meetings are posted. Membership is free.

<http://www.ukcab.net>

Phoneline and information services

Treatment information request service - 0808 800 6013

i-Base runs a specialised treatment information service.

We can provide information by phone, email and online based on the latest research.

For further details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm. All calls are in confidence and are free within the UK.

Online Q&A service

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

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

Other resources

Treatment 'Passports'

Booklets for HIV-positive people - whether newly diagnosed or positive for a long time - to record health and treatment history. Like other publications, they are available free as single copies, or in bulk.

Generic clinic forms

A set of generic clinic forms, developed with the Royal Free Centre for HIV Medicine, which may be a useful resource for other hospitals.

These PDF files include record sheets to track CD4 and viral load results, cardiovascular risk, hepatitis, first patient visit, patient update, day case and summary notes.

<http://i-base.info/category/publications/clinic-forms>

i-Base can add your hospital or Trust logo to these forms.

Order publications and subscribe by post, fax or online

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<http://i-base.info/order>

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