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EDITORIAL

For this last issue of HTB for 2011 we bring together a diverse range of conference reports, treatment news, research views, global news, prevention updates and even a film review (of the excellent “We Were Here”).

The full contents highlights the breadth of these reports. Even for a publication heavily focussed on HIV treatment and research, this does not exist in isolation.

So along with reports from the EACS, ICAAC and HIV and ageing meetings we include positive news that the Iranian doctors have been released, that the HPA is now recommending wider testing in the UK, and that Richard Jeffreys, who leads on our basics science reporting each issue has successfully stood up to a high profile AIDS denialist. These people still exist. The New York Court summary judgement is a breath of fresh air and important glimpse of sanity.

But in global terms, the announcement by the Global Fund that it has suspended the next round of funding due to donor countries refusing to honour earlier pledges is an unhappy reality that dominates all other news.

There are 200 days to make up this shortfall. Otherwise, the benefits from the last ten years of both treatment and prevention programmes are likely to be quickly reversed and that this will further disrupt healthcare in poor countries and lead to millions of lost lives.

CONFERENCE REPORTS

13th European AIDS Conference (EACS)

12–15 October 2011, Belgrade, Serbia

Introduction

The 13th European AIDS Conference was held in Belgrade from 12-15 October.

Unfortunately abstracts are not yet available online, and although webcasts, podcasts and PowerPoint slides are available these require a login name and password (obtainable by email from the EACS secretariat).

The same login details can also be used to access training resources from a pre-meeting training for doctors and other resources. iPhone and iPad versions are accessible using the free Talks On The Go App.

http://www.europeanaidsclinicalsociety.org/

The following reports are included in this issue.

- European guidelines (EACS) – 2011 update
- Raltegravir achieves superiority over efavirenz after four years
- Higher plasma levels of tenofovir and darunavir but not efavirenz in older patients
- Ritonavir levels reduced with high fat meal (900 kcal)
- Transplacental transfer of raltegravir and delayed plasma clearance in preterm neonates

European guidelines (EACS) – 2011 update

Simon Collins, HIV i-Base

The launch of 2011 guidelines from the European AIDS Clinician Society (EACS), extensively revised and updated, was probably one of the scientific highlights of the conference.

The three guidelines, previously printed separately, have now been collated together in a slightly larger format. This makes the print edition now more comprehensive and also easier to use and reference.

Based on essential bulleted lists, treatment algorithms, and reference tables the guidelines are an excellent format for rapidly reviewing the current best standard of care in three key areas of HIV management:

i) Assessment and monitoring at initial and subsequent visits

ii) ARV treatment in adults

iii) Prevention and management of non-infectious co-morbidities

iv) Clinical management and treatment of hepatitis B and C in HIV-positive patients

Although additional resources have been produced to compliment the guidelines in many important areas of HIV management, these had no yet been posted online when we went to press.

The guidelines (version 6.1) can be downloaded free as a PDF file and print copies can be order on the EACS website:

http://www.europeanaidsclinicalsociety.org/

Print versions can be ordered from EACS:

info@eacsparis.org

Raltegravir achieves superiority over efavirenz after four years

Simon Collins, HIV i-Base

Four year results from a five year, double-blind, randomised, non-inferiority study comparing raltegravir to efavirenz (each with tenofovir plus FTC) in treatment-naïve patients were presented by Jurgen Rockstroh.

The study design, matched baseline characteristics and safety and efficacy results from earlier analyses have already been presented at earlier meetings. The new subgroup analyses (including baseline CD4 <200 copies/mm3, viral load >100,000 copies/mL, hepatitis and demographic responses) focused on virological efficacy with discontinuations related to viral failure included but discontinuations for other reasons excluded and using an observed failure approach.

From approximately 280 patients in each arm at baseline, 223 (79%) and 197 (70%) completed the 192 week analysis, in the raltegravir and efavirenz arms respectively. Discontinuations were all less frequent in the raltegravir arm: virological failure (n=5 vs 8); side effects (n=13 vs 26); and loss to follow-up (n=8 vs 17)

At 192 weeks, the primary analysis of viral suppression to <50 copies/mL (non-completer=failure) saw raltegravir achieve statistical superiority compared to efavirenz [76% vs 67% (difference = +9.0; 95%CI 1.6, 16.4, $p < 0.001$: with the lower limit for non-inferiority set at –12% and superiority being achieved when both confidence intervals became greater than 1.0].

CD4 increases were + 60 cells/mm3 higher in the raltegravir arm (95%CI 24, 95).

Overall clinical events (96% vs 98%, $p = 0.16$), discontinuations due to drug-related events (5% vs 8%, $p = 0.173$) and serious adverse events (18% in each arm, $p = 0.91$) were similar between the two study groups, raltegravir was associated with significantly fewer drug-related events (50% vs 80%, $p < 0.001$).

There were no statistically significant differences in response between groups by gender, age, race/ethnicity, viral load >100,000 c/mL, CD4 > 200 cells/mm3, hepatitis coinfection or HIV sub-type. Raltegravir showed a significantly stronger virological response in the <100,000 c/mL group (93% vs 81%; difference +12; 95% CI 3, 22). Interpretation of a difference in favour of raltegravir when baseline CD4 was 50-<200 cells/mm3 is complicated by a trend to favour efairenz when CD4 counts were <50 cells/mm3.

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These results support durability and safety of raltegravir. they also show that after week 192 raltegravir achieves superiority compared to efavirenz with the difference largely driven by efavirenz-related side effects.

The CD4 difference may also be important for patients with sub-optimal CD4 responses on other HAART combinations.

Ref: Rockstroh JK et al. Long-term efficacy of raltegravir or efavirenz combined with TDF/FTC in treatment-naïve HIV-1-infected patients: week-192 subgroup analyses from STARTMRK. 13th EACS, 12–15 October 2011, Belgrade. Abstract PS 1/1.

Higher plasma levels of tenofovir and darunavir but not efavirenz in older patients

Simon Collins, HIV i-Base

Several studies looked at the association between older age and antiretroviral pharmacokinetics (PK).

Tenofovir

Muge Cevik from the Chelsea and Westminster Hospital London reported results from a PK study suggesting that tenofovir clearance is significantly reduced with increasing age and resulting in higher drug levels (AUC and Ctrough). [1]

This included steady-state plasma levels from 52 men and 2 women (12 of whom were on PI/r-based combinations). Median age was 54 years (range 40–81 years) with only two people younger than 50. Samples were drawn randomly and population pharmacokinetics applied to predict values.

Tenofovir median clearance (CL/F), AUC (24hr) and Ctrough (C24) were 110.0 L/r (27.4–248.3). 2.2 mg.hr/L (1.0–9.0), and 0.06 mg/L (0.01–0.3) respectively.

Increasing age was significantly associated with slower clearance (p=0.0012), higher AUC (p=0.0012) and higher Ctrough (p=0.0017). People older than 60 had significantly lower clearances (p=0.0447) and higher AUC (p=0.0457) than those younger than 60.

No PK differences were seen between PI and NNRTI based combinations (p=0.08).

Efavirenz and darunavir/ritonavir

A similar analysis was presented by Ahmed and colleagues from the same group at Chelsea and Westminster on the PK of efavirenz or darunavir/ritonavir used by older patients (median age was 54 years (range 27-77) and 56 years (28-76), respectively). [2]

In 70 men and 7 women taking efavirenz, no differences were seen in any PK parameter when comparisons were made between people older and younger than 50 (all p-values >0.05 for between age comparisons).

In 33 men and one woman taking darunavir/ritonavir (23 using once-daily) oral clearance was significantly lower in people over 50 years old (10.3 vs 13.0 L/h; p=0.027) with higher AUC (80.9 vs 61.6 mg.h/L; p=0.021) and Ctrough levels (1.9 vs 1.2 mg/L; p=0.008) than those younger than 50.

Once-daily vs twice-daily could not be assessed because of unequal age distribution between the two dosing regimens.

References
1. Cevik M et al. Tenofovir (TFV) pharmacokinetics (PK) in HIV infected individuals over 40 years of age. 13th EACS, 12–15 October 2011, Belgrade. Abstract PS 6/1.
2. Ahmed A et al. Efavirenz and Darunavir Plasma Concentrations in HIV-infected Patients Aged 50 Years or over. 13th EACS, 12–15 October 2011, Belgrade. Abstract PE6.2/1.

Ritonavir levels reduced with high fat meal

Simon Collins, HIV i-Base

Researchers at Makerere University, Kampala and the pharmocology group at Liverpool University reported a significant interaction between high fat meals and ritonavir as a booster in lopinavir/r (Kaletra).

Three meal conditions were studied in an open-label, three part, cross over study in 12 HIV positive people (6 men, 6 women) using lopinavir/r (2 x 400/100 mg tablets) as second-line therapy. Median (IQR) age and weight of patients was 48 (44 - 49) years and 62 (59-68) kgs.

Intensive PK sampling after a moderate (20 g fat) and high (36 g) fat meal (on Day 1 and 8 respectively) were compared to fasted state on Day 15.

Compared to the fasting, administration with a high fat meal resulted in 29% lower ritonavir AUC (geometric mean ratio 0.71; 90%CI 0.61-0.84) and 29% lower Cmax (GM 0.71; 90%CI 0.60-0.84) while C12 increased non-significantly by 12% (GM 1.12 (90%CI 0.94-1.33).

Ref: Lamorde M et al. - Steady-state exposure of ritonavir is reduced by a high fat meal in Ugandan patients receiving lopinavir plus ritonavir co-formulated tablets. 13th EACS, 12–15 October 2011, Belgrade. Abstract PE6.6/1 (BPD1/1).

Transplacental transfer of raltegravir and delayed plasma clearance in preterm neonates

Polly Clayden, HIV i-Base

Preterm birth is common in infants born to HIV positive mothers and is associated with an increased risk of mother to child transmission. Oral drug absorption in infants is unpredictable due to the immaturity of the gastro intestinal tract at this age. Preloading the foetus with maternal nevirapine (NVP) is common in these cases.

Raltegravir (RAL) is pregnancy category C and data to guide its use in pregnancy are limited. However, it has been used to achieve a rapid reduction in viral load before delivery, for preloading the foetus where poor oral absorption is anticipated and in cases where there is resistance or intolerance to other antiretrovirals.

RAL is absorbed rapidly (with a T max of about three hours) it takes two days to reach steady state concentrations and has an elimination terminal half-life of 9 hours. It uses the UGT 1A1 metabolic pathway. About half of the oral dose is excreted unchanged in the stool and 30% in the urine (about a third of which is as unchanged RAL and the remainder as the metabolite). There is considerable inter patient variability in its metabolism.

In an oral presentation, Aseel Hegazi from St Georges University Hospital, London showed three maternal infant case studies in which pregnant mothers of preterm neonates received RAL as part of their prevention of mother to child transmission (PMTCT) regimens. [1] The investigators looked at transplacental transfer of the drug and plasma clearance in the infants.

The same group has previously described the use of RAL in PMTCT regimens in mothers of three term infants. In these cases they found good transplacental transfer with higher concentrations in the infants than the mothers approximately three hours after delivery. [2] They also reported persistence of neonatal concentrations at three days (although below the therapeutic range). They

suggested that poor neonatal and foetal maturity of the UGT-dependent pathways could account for this. And that it is possible that increased activity of UGT1A1, associated with progesterone, observed in pregnant women contributed to the disparity.

In the three cases of RAL use in preterm delivery, paired blood samples were taken as close as possible to delivery and then post partum. Maternal and neonatal RAL plasma concentrations were measured using liquid chromatography and mass spectrometry. Table 1 summarises these cases.

Table 1. Three cases of maternal RAL use in preterm delivery

	Case 1	**Case 2**	**Case 3**
Background ART and clinical context	NNRTI and 3TC resistance. Ritonavir intolerance. Poor adherence. Preeclampsia. Placenta praevia. Small for gestational age. Emergency Caesarean section.	Poor adherence. Small for gestational age. Emergency Caesarean section.	ART naïve. Started on ABC+AZT+3TC in 2nd trimester. Spontaneous rupture of membranes. Multiple fibroids. Emergency Caesarean section.
Time of RAL initiation	22 weeks gestation	14 hours pre-delivery. No repeat dose due to advanced labour and obstetric complications).	25.5 hours pre-delivery. Dose repeated 10.5 hours pre-delivery.
Viral load at RAL initiation (copies/mL)	5030	100	Undetectable
Background regimen	TDF + ATV	ATV/r + TDF + FTC (NVP + IV AZT at delivery)	EFV + TDF + 3TC (NVP + IV AZT at delivery)
Gestation at delivery	33 weeks + 2 days	30 weeks + 3 days	29 weeks + 5 days
Infant birth weight	1510 g	920 g	1365 g
Viral load at delivery (copies/mL)	Undetectable	55	Undetectable
Maternal RAL plasma concentrations (ng/mL)	2318 (6 hours post dose at delivery)	4870 (3.5 hours post dose, 11 hours pre-delivery) 64 (3 hours post dose, 1 hour post delivery)	300 (10.5 hours post dose at delivery)
Neonatal RAL plasma concentrations (ng/mL)	3781 (7 hours post maternal dose, 1 hour post delivery)	120 (16 hours post maternal dose, 2 hours post delivery) 67 (65 hours post maternal dose, 63 hours post delivery)	602 (11 hours post maternal dose, 0.5 hours post delivery)
Neonatal:maternal RAL plasma concentrations	1.6	1.9	2.0

Dr Hegazi concluded that therapeutic RAL plasma concentrations (> 15ng/mL) might be persistent for up to five days in preterm neonates. She noted that this is longer than that observed in term infants and is probably linked to immature UGT1A1 mediated gluronidation. She suggested that maternal RAL preloading might be a good alternative to NVP where oral absorption is unreliable (particularly with preterm infants) and maternal options are limited

C O M M E N T

These case studies are interesting and this use of RAL could prove important. RAL used this way is likely to be mentioned in the next BHIVA guidelines (although data is very sparse so evidence will be weak).

IMPAACT 1097 is a washout (passive) PK and safety study designed to investigate this phenomenon in neontates. It is the first clinical trial of an investigational drug to look at neonatal PK. It is recruiting mothers already receiving RAL in pregnancy and the infants will be sampled at intervals up to 30 to 36 hours after dosing.

After a review of PK and safety data from this and IMPAACT1060 – which is investigating this drug in children in de-escalated age bands with those below two years, receiving a granule formulation, now being studied – the company is planning a study of infants born to HIV positive mothers from immediately after birth until their status has been confirmed.

References

1. Hegazi A et al. Raltegravir in the prevention of mother to child transmission of HIV: effective transplacental transfer and delayed plasma clearance observed in preterm neonates. 13th EACS, 12–15 October 2011, Belgrade. Oral abstract PS 6/7.
2. Mckeown D A et al. High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women AIDS. 24 September 2010. Volume 24. Issue 15. p 2416–2418.

CONFERENCE REPORTS

2nd International Workshop on HIV and Ageing

27–28 October 2011, Baltimore, Maryland

Introduction

Although we were unable to attend this annual workshop we include the following reports thanks to antap.org.

- Statin blocks negative impact of PIs on bone formation in vitro
- HIV linked to frailty in middle-aged IDUs, especially with poor HIV control

Statin blocks negative impact of PIs on bone formation in vitro

Mark Mascolini, natap.org

Ritonavir-boosted or unboosted atazanavir or lopinavir promoted stem cell changes that could lead to decreased bone formation, according to results of cell studies by Jacqueline Capeau and colleagues at Saint-Antoine Hospital in Paris. Exposing the cells to pravastatin blocked these protease inhibitor (PI)-induced changes. [1]

Bone density declines with HIV infection, and that decline can accelerate with antiretroviral therapy. Treatment with certain PIs or tenofovir heightened the risk of osteopenia and osteoporosis in longitudinal studies. SMART trial participants randomised to take antiretrovirals continuously had more bone loss than those randomised to CD4-based treatment interruptions. [2]

Indinavir and nelfinavir–two PIs rarely used today–resulted in poorly functioning osteoblasts, the cells responsible for new bone formation. Capeau and coworkers planned a series of cell studies to see if two currently prescribed antiretrovirals, lopinavir and atazanavir with or without ritonavir, affect cell properties that could promote bone loss in people with HIV.

The researchers used menenchymal bone marrow stem cells from young, healthy donors. They passaged these stem cells every 5 days to simulate ageing. For up to 40 days, they exposed the cells to doses of lopinavir, atazanavir, and ritonavir equivalent to maximum concentrations of those PIs typically attained in people taking them at prescribed doses.

Stem-cell numbers dropped sharply after 10 to 15 days of lopinavir (with or without ritonavir) and after 20 to 25 days of atazanavir (with or without ritonavir). The PIs had no effect on cell survival, a finding suggesting that decreased proliferative capacity accounted for these declines in stem cell number.

Assessing stem-cell senescence by measuring senescence-associated beta-galactosidase activity, the researchers found that both atazanavir and lopinavir significantly induced premature senescence. Increased reactive oxygen species (ROS) production in these cells suggested that oxidative stress may be responsible for cell ageing. Atazanavir and lopinavir also raised levels of superoxide dismutase, an antioxidant enzyme, in these cells. Both PIs increased expression of the cell-cycle inhibitors P16 and P21. Finally, the two PIs induced accumulation of prelamin A, a cell-ageing marker associated with cell senescence.

Mesenchymal stem cells normally differentiate into an even balance of osteoblasts and adipocytes (fat cells). With ageing, differentiation to adipocytes begins to outweigh differentiation to osteoblasts. Age-related bone loss is marked by increased bone marrow fat, which leads to decreased bone formation.

Stem cells pretreated with lopinavir or atazanavir lost their ability to differentiate into osteoblasts, a result Capeau suggested could mean these PIs irreversibly affect the menenchymal stem cell pool in bone marrow. Lopinavir-exposed stem cells also failed to differentiate into adipocytes, while atazanavir-exposed cells promoted increased differentiation into adipocytes. The investigators proposed that atazanavir could lower the number of osteoblasts in treated people by upsetting the balance between adipocytes and osteoblasts in bone marrow.

When Capeau and colleagues exposed stem cells to pravastatin and the study PIs, they found that this statin prevented PI-induced senescence, reduced oxidative stress, and restored the differentiation of stem cells to an even balance of osteoblasts and adipocytes.

The researchers concluded that their cell-study data "show that some PIs can alter osteoblast formation by a direct effect on osteoblast differentiation and also by inducing premature senescence of the bone marrow progenitors."

References

1. Hernandez-Vallejo S et al. Some HIV protease inhibitors induce premature senescence and alter osteoblastic cell fate determination of human bone marrow mesenchymal stem cells. 2nd International Workshop on HIV and Aging. October 27-28, 2011. Baltimore, Maryland. Abstract: O_14.
2. Grund B et al for the INSIGHT SMART Body Composition Substudy Group. Continuous antiretroviral therapy decreases bone mineral density. AIDS. 2009;23:1519-1529.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2748675/?tool=pubmed.

HIV linked to frailty in middle-aged IDUs, especially with poor HIV control

Mark Mascolini, natap.org

Comparing HIV-positive and negative injection drug users (IDUs) in a large Baltimore cohort, researchers determined that HIV infection independently raised the risk of objectively defined frailty and prefrailty. Frailty and prefrailty risks were highest in people with a CD4 count below 350 and a detectable viral load. [1]

Frailty boosts chances of hospital admission, disability, and death in older people without HIV.

In the Multicenter AIDS Cohort Study of HIV-positive and negative gay men. HIV infection raised the odds of earlier frailty [2], and frailty before combination antiretroviral therapy begins independently predicted AIDS or death [3]. But the impact of HIV on frailty risk and clinical outcomes is still in an early phase of study.

In this analysis Johns Hopkins University researchers focused on 1206 current or former IDUs with or without HIV infection seen from 2005 through 2009 in a prospective observational cohort. All cohort members were at least 18 years old and made twice-yearly visits for follow-up. The Hopkins team defined frailty (by the Fried system) as meeting 3 or more of 5 criteria: weakness determined by grip strength, slowed walking speed, weight loss, low physical activity, and exhaustion. They defined prefrailty as one or two of these criteria.

Of the 1206 IDUs assessed, 345 (29%) had HIV infection. Median age stood at 48 years, and one third in both the HIV-positive and negative groups were women. Higher proportions in the HIV group were African American (95.7% versus 87.6%), had less than a high school education (65.2% versus 57.0%), and were hepatitis C positive (93.3% versus 81.0%) ($P < 0.05$ for all comparisons). Lower proportions of HIV-positive cohort members were recent injectors (36.2% versus 47.4%), actively used alcohol (48.3% versus 56.8%), abused prescription drugs (6.4% versus 12.9%), or had a spouse or common-law partner (4.7% versus 8.8%) ($P < 0.05$ for all).

HIV-positive people had a median CD4 count of 290, a median CD4 nadir of 138, and a median viral load of 3.1 log (about 1250 copies). Half (51%) were taking combination antiretrovirals, and 21.7% had an AIDS diagnosis.

Overall frailty prevalence stood at 8.3%, with rates of 10.7% in the HIV group and 7.3% in the HIV-negative group; 59% of cohort members met prefrailty criteria. Through 4652 person-visits, both frailty and prefrailty proved more common in older IDUs, women, those with less than a high school education, people without a spouse or partner, those who abused prescription drugs, and those with depressive symptoms. African-American cohort members had a lower risk of prefrailty. Adjusting for all these factors, the researchers determined that HIV infection raised the prefrailty risk 28% (adjusted odds ratio [AOR] 1.28, 95% confidence interval [CI] 1.06 to 1.53), while raising the frailty risk 75% (AOR 1.75, 95% CI 1.27 to 2.39).

Compared with HIV-negative IDUs, HIV-positive cohort members had a higher risk of prefrailty or frailty with worse HIV disease status, as noted by the AORs (and 95% CIs) in Table 1.

Table 1: AORs (95%CI) for prefrailty and frailty by CD4 and viral load

	Prefrailty	Frailty
CD4 >350, VL <50 c/mL	1.14 (0.81 to 1.62)	1.13 (0.65 to 1.97)
CD4 <350, VL <50 c/mL	1.37 (0.97 to 1.95)	1.75 (1.02 to 2.98)
CD4 >350, VL >50 c/mL	1.14 (0.79 to 1.63)	1.8 (1.00 to 3.21)
CD4 <350, VL >50 c/mL	1.49 (1.17 to 1.89)	2.26 (1.51 to 3.39)

The Hopkins teams evaluated frailty as a predictor of new hospital admissions in all 1206 cohort members from July 2005 through December 2009. During that time there were 374 hospital admissions, and the admission rate was significantly greater in frail than in nonfrail people ($P = 0.006$).

Compared with nonfrail cohort members, prefrail people did not have an independently higher risk of hospital admission, but frail people had a 60% higher risk (adjusted hazard ratio [AHR] 1.59, 95% CI 1.10 to 2.30). Female gender made hospital admission 66% more likely, homelessness raised the odds by 42%, active alcohol use by 32%, hepatitis C by 90%, and prescription drug use by 56%. Compared with HIV-negative people, HIV-positive people with a CD4 count under 350 and a detectable viral load had a doubled risk of hospital admission (AHR 2.12, 95% CI 1.61 to 2.79).

The Johns Hopkins investigators concluded that HIV infection boosts the risk of prefrailty and frailty in current and former IDUs. They proposed that "early identification of frail and prefrail IDUs may provide opportunities for arresting progression to adverse clinical states."

References

1. Piggott D et al. Frailty and incident hospitalization in a cohort of HIV-infected and uninfected injection drug users (IDUs). 2nd International Workshop on HIV and Aging. October 27-28, 2011. Baltimore, Maryland. Abstract O_06.
2. Desquilbet L et al. HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. J Gerontol A Biol Sci Med Sci. 2007;62:1279-1286.
3. Desquilbet L et al. A frailty-related phenotype before HAART initiation as an independent risk factor for AIDS or death after HAART among HIV-infected men. J Gerontol A Biol Sci Med Sci. 2011;66:1030-1038.

CONFERENCE REPORTS

51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

17–20 September 2011, Chicago

Introduction

The annual ICAAC conference in recent years has had a reduced focus on HIV research but still includes studies that are interesting to highlight.

Unfortunately the conference restricts public access to this research. Although abstracts available online (for a short time) the database to access abstracts is not very user friendly and the long URLs often change, making referencing problematic.

Also, few, if any studies are supported by webcasts or the option to view slides or full PDF posters.

The following studies are largely thanks to natap.org.

- Monitoring kidney function change with cobicistat
- Intracellular raltegravir concentrations better with twice-daily than once-daily dosing

Monitoring kidney function change with cobicistat

Simon Collins, HIV i-Base

Cobicistat is a pharmacokinetic (PK) booster currently in phase 3 studies that unlike ritonavir has no direct antiretroviral activity. This Gilead booster might facilitate a wider range of coformulated boosted medicines: with elvitegravir and Quad (boosted elvitegravir plus Truvada) and with products developed by other companies (darunavir and atazanavir).

An early caution is that cobicistat produces significant reductions in estimated glomerular filtration rate (eGFR). These do not indicate clinically significant changes but will pose a problem for interpretation of routine monitoring tests where clinical changes in eGFR are a concern.

If average actual GFR (aGFR) is used to monitor cobicistat, determined by iohexol clearance (a probe drug excreted almost exclusively by glomerular filtration), no changes are observed.

At ICAAC, Gilead researchers presented results from a placebo controlled study in 36 HIV negative participants with normal renal function (eGFR >80 mL/min) and 18 HV negative participants with mildly impaired renal function (eGFR 50-79 mL/min).

Participants with normal function were randomised (12 per group) to one of three groups: 150 mg cobicistat + placebo; 100 mg ritonavir + placebo; or double placebo for 7 days, with both eGFR and aGFR measured at baseline, day 7 and day 14 (following a 7 day washout). All participants with reduced renal function took cobicistat for seven days with similar monitoring.

Independent of baseline eGFR, volunteers taking cobicistat experienced significant average reductions in eGFR by day seven which resolved seven days after discontinuation, with but showed no significant changes in aGFR (see Table 1). Similar changes were seen using either Cockcroft-Gault or MDRD to calculate eGFR. Participants taking ritonavir or placebo showed no significant changes in either measure.

Table 1: Changes in aGRF and aGFR (mL/min) in HIV negative people using cobicistat for 7 days

	aGFR		eGFR (Cockcroft-Gault)	
Baseline eGFR	day 7	day 14	day 7	day 14
>80 mL/min	-2.7 (NS)	-2.5 (NS)	-9.9 ($p<0.05$)	+1.4 (NS)
50-79 mL/min	-3.6 (NS)	-5.8 (NS)	-11.9, $p<0.05$	-2.2 (NS)

The researchers interpret these findings to show that true GFR is not affected by cobicistat which affects proximal tubular secretion of creatinine.

While these results are reassuring in terms of clinical impact of cobicistat it is unclear how patients using other medications that affect eGFR would be managed in order not to misinterpret a genuine impact on real GFR.

Source: Mascolini M. Kidney Function Change With Cobicistat Calculated in HIV-Negative Volunteers. NATAP.org

http://www.natap.org/2011/ICAAC/ICAAC_66.htm

Ref: German P et al. Effect of cobicistat on glomerular filtration rate (GFR) in subjects with normal and impaired renal function. 51st ICAAC, 17-20 September 2011, Chicago. Abstract H2-804.

Intracellular raltegravir concentrations better with twice-daily than once-daily dosing

Mark Mascolini, NATAP.org

Intracellular concentrations of raltegravir stayed above the 95% effective concentration (EC95) in higher proportions of people taking this integrase inhibitor twice daily than in those taking it once daily, according to results of a 13-person study [1]. The average intracellular-to-plasma ratio was 0.37.

Raltegravir is licensed for adults at a dose of 400 mg twice daily with or without food. A randomised trial of twice- versus once-daily raltegravir for antiretroviral-naive people found that 318 of 382 (83%) in the once-daily group versus 343 of 386 (89%) in the twice-daily group had a viral load below 50 copies/mL after 48 weeks, a significant difference (-5.7%, 95% confidence interval -10.7 to -0.83, P = 0.044) [2]. The investigators concluded that "despite high response rates with both regimens, once-daily raltegravir cannot be recommended in place of twice-daily dosing."

The study of plasma and intracellular raltegravir concentrations involved 12 people taking 400 mg of raltegravir twice daily and 1 taking 800 mg once daily for more than 1 week [1]. People on the twice-daily dose who had a viral load below 50 copies were offered a switch to once-daily dosing for at least 3 days so the investigators could assess raltegravir after once-daily dosing. Six people agreed.

In the twice-daily group, the researchers collected 26 paired samples of plasma and peripheral blood mononuclear cells (PBMCs) 2, 4 or 6, and 12 hours after dosing. In the once-daily group they collected 12 paired samples over the 24-hour dosing interval. Among people taking raltegravir twice daily, 3 had a detectable viral load; 2 of these were considered blips, and one load of 2649 copies came during the first 6 weeks of treatment.

No one taking raltegravir twice daily had a plasma trough concentration below the EC95 (14 ng/mL). Three of 12 had an intracellular trough below the EC95, at 7, 11.1, and 13.3 ng/mL.

Two of 6 people taking raltegravir once daily had a plasma trough below the EC95, at 7 and 13.8 ng/mL. Three of these 6 had an intracellular trough below the EC95, at 1.56, 4.06, and 6.56 ng/mL.

The mean ratio of intracellular-to-plasma concentrations was 0.37 and did not change over time. The ratio was higher than reported previously, probably because cell-wash steps in older methods flushed out some intracellular drug.

The researchers proposed that the high plasma and intracellular troughs with twice-daily raltegravir "may contribute to the efficacy observed with this regimen."

UK researchers just published results of a 24-person study comparing plasma and intracellular raltegravir concentrations with once- and twice-daily dosing, with or without darunavir/ritonavir [3]. Study participants were taking 400 mg of raltegravir twice daily for at least 21 days. They added 800/100 mg of darunavir/ritonavir once daily for 14 days. During that 14-day period, people were randomised to continue twice-daily raltegravir (group 1) or to switch to 800 mg once daily (group 2).

Geometric mean ratios (and 90% confidence intervals) of raltegravir area under the concentration-time curve without and with darunavir/ritonavir for group 1 were 0.90 (0.73 to 1.44) in plasma and 1.02 (0.81 to 1.67) in cells and for group 2 were 1.21 (1.03 to 1.77) in plasma and 1.27 (1.07 to 1.94) in cells. These researchers concluded that "no remarkable interactions between darunavir/ritonavir and raltegravir in plasma or cells were seen."

References

1. Sandkovsky US, Swindells S, Robbins BL, Nelson SR, Acosta EP, Fletcher CV. Measurement Of plasma and intracellular concentrations of raltegravir in patients with HIV infection. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). September 17-20, 2011. Chicago. Abstract A1-1738b.
2. Eron JJ Jr, Rockstroh JK, Reynes J, et al. Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial. Lancet Infect Dis. 2011 Sep 19.
http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(11)70196-7/fulltext
3. Jackson A, Watson V, Back D, et al. Plasma and intracellular pharmacokinetics of darunavir/ritonavir once daily and raltegravir once and twice daily in HIV-infected individuals. J Acquir Immune Defic Syndr. 2011 Sep 15. Epub ahead of print.
http://www.ncbi.nlm.nih.gov/pubmed/21926632

ANTIRETROVIRALS

Rilpivirine (Edurant) and rilpivirine/FTC/tenofovir FDC (Eviplera) approved in Europe

In September 2011 the EMA recommended for approval for the NNRTI rilpivirine and a fixed dose combination (FDC) of a single pill formulation of rilpivirine/teneofovir/FTC. Approval has now been confirmed for rilipivirine and the 3-in1 FDA, which were launched in the UK on 1 December 2011. [1]

Rilpvirine (tradename Edurant) has a European indication for use as part of a combination for treatment-naïve patients with viral load <100,000 copies/mL.

The 25mg tablet must be taken with food and in Phase 3 studies had a tight relationship between adherence and efficacy. Low milligram medications are often vulnerable to a lower pharmacological safety buffer above the minimum effective concentration (MEC) at the end of the dosing period.

The license for rilpivirine stresses that it needs to be taken at the same time each day.

Additionally, patients who have experienced virological failure while taking rilpivirine can develop NNRTI cross-class resistance including to nevirapine and efavirenz.

The list price for rilripirine is £200.27 per month (for 30 tablets).

A more detailed summary of the data from Phase 3 studies was included in the August edition of HTB, with announcement of approval in the US. [2]

The FDC formulation (tradename Eviplera in Europe and Complera in the US) based on a similar indication to rilpivirine. The list price for Eviplera is £618.77 for 30 tablets.

References and links:

1. Patient information and Summary of Product Characteristics for Edurant will be published to the EMA website.

   http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

2. FDA approve new NNRTI rilpivirine (Edurant) in the US. HTB August 2011.

   http://i-base.info/htb/15538

FDA updates US label for darunavir for serious rash

On 19 October 2011 the FDA approved updates to the darunavir (Prezista) package insert to include 192-week results from the Phase 3 registrational studies.

In addition, section 5.3 Severe Skin Reactions now includes the following text about combinations that include darunavir/ritonavir plus raltegravir:

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing darunavir/ritonavir + raltegravir compared to subjects receiving darunavir /ritonavir without raltegravir or raltegravir without darunavir /ritonavir. However, rash that was considered drug related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

Source: FDA HIV/AIDS Update - Prezista label update includes 192-week safety, resistance and efficacy data (21 October 2011).

FDA updates US label for raltegravir due to serious rash

On 2 November 2001 the US Food and Drug Administration (FDA) approved updates to the package information and patient leaflet for raltegravir (Isentress).

Postmarketing reports have included cases of severe, potentially life-threatening, and fatal skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure.

Patients should be advised to immediately contact their healthcare provider if they develop rash. They should discontinue raltegravir (with medical supervision) and other suspect agents immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema).

Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping raltegravir treatment or other suspect agents after the onset of severe rash may result in a life-threatening reaction.

Cerebellar ataxia and drug rash with eosinophilia and systemic symptoms have been added as side effects.

Patients should understand that if severe rash occurs, they will be closely monitored, laboratory tests will be ordered and appropriate therapy will be initiated.

Source: FDA HIV/AIDS Update - Isentress (raltegravir) package insert updated, (02 November 2011).

Lopinavir concentrations suboptimal at reduced dose of lopinavir/ ritonavir 200/50 mg twice daily

Polly Clayden HIV i-Base

An article published online ahead of print in JAIDS, November 2011, shows findings from a pharmacokinetic (PK) study to evaluate a lower dose of lopinavir/ritonavir (LPV/r) than that currently approved.

Reshmie A Ramautarsing and HIV-NAT colleagues from Thailand and the Netherlands performed a two-arm crossover study including 20 HIV-positive Thai patients. Participants receiving a PI-containing regimen (virlogically suppressed <50 copies/mL for at least 4 weeks at enrollment) were randomised receive branded or generic LPV/r dosed at 200/50mg twice daily, in addition to an NRTI backbone.

Due to a compulsory license, Abbott only markets the paediatric formulation (100/25 mg) of LPV/r in Thailand. The Indian generic company, Matrix, has developed a 200/50 mg tablet formulation of LPV/r, which is currently used at the standard dose (400/100 mg twice daily).

Following sampling for PK analysis at week 2, all participants crossed over from their initial study arm to the other. A second sampling was performed at week 4. Participants continued with their study regimen until week 12, when they resumed their pre-study regimen.

There were 10 participants in each arm with a median age, weight and CD4 count of 38.6 (IQR 34.4 – 47.5) years, 59.8 (52.9 – 62.0) kg and 578 (476 – 795) cells/mm3, respectively. The majority (n=17) received standard dose LPV/r and the remainder saquinavir containing regimens prior to the study. None were lost or discontinued their medication during follow up.

The investigators reported comparable bioequivalence for the generic and branded formulations, with point estimates and 90% CI of the geometric mean ratios of 1.00 (0.92-1.09), 1.01(0.90-1.07) and 0.87 (0.76-1.31) for the AUC0-12, Cmax and Ctrough respectively.

Overall 10/40 (25%) samples had subtherapeutic (<1.0 mg/L) plasma concentrations of LPV. These were detected in 8 patients: 2 had subtherapeutic levels measured with both branded and generic formulations, 4 with branded and 2 generic. The lowest concentration was 0.25 mg/L. The investigators noted that all participants reported >90% rates of adherence and 7/8 reported 100% at the time that subtherapeutic plasma concentrations were found.

A comparison of PK parameters for different doses and formulations of LPV/r, using historical data from the same research group, revealed decreased concentrations at lower doses. When compared to LPV/r soft gel capsule (SGC) 400/100 mg twice daily, a dose of LPV/r SGC 266/66 twice daily resulted in 44.1%, 36.0% and 49.1% decreases in LPV concentrations for AUC0-12, Cmax and Ctrough respectively. Using LPV/r generic tablets 200/50mg twice daily decreased the same parameters by 63.5%, 56.6% and 70.2% respectively.

At week 12 all participants remained virologically supressed <50 copies/mL.

The researchers noted that LPV plasma concentrations are dependent on the RTV dose to a greater extent than some other PIs and in this study they had reduced both the LPV and RTV dose, which may explain the subtherapeutic LPV concentrations. They wrote that other dose reduction studies suggest that 200 mg of LPV is sufficient if there is a sufficient boosting dose of RTV (100 mg).

The researchers also noted that this bio-equivalence analysis of LPV/r, although not using the approved 400/100 mg twice-daily dose, demonstrated that the generic and branded tablets result in comparable PK parameters. They wrote: “These data are particularly important for clinicians working in settings where the branded tablets are not available due to compulsory licensing or cost. The availability of safe and effective generic alternatives to branded second line treatment will play an important role in the scaling up of second line treatment in low- and middle-income countries.”

C O M M E N T

That the generic and originator products are bioequivalent is important.

Previous PK trials have shown that the dose of ritonavir affects LPV levels. In the first dose-ranging trial by Abbott, the dose with the best efficacy and safety profile was 200/100 mg twice daily. If we had 50 mg ritonavir tablets (see below), we could get back to this dose and it may be worth doing more studies.

However, the WHO and Clinton Foundation are more interested in ATV/r and DRV/r, which showed better efficacy and safety profiles than LPV/r (in the CASTLE and ARTEMIS trials, respectively).

Ref: Ramautarsing RA et al. Neither branded nor generic lopinavir/ritonavir produces adequate lopinavir concentrations at a reduced dose of 200/50mg BID. J Aquir Immune Defic Syndr. Publish ahead of print. DOI: 10.1097/QAI.0b013e3182ba736.

Switching to 50mg ritonavir dose for selected protease inhibitors

Polly Clayden HIV i-Base

Although not appropriate for LPV (see previous article), a 50mg boosting dose of RTV may be sufficient for selected PIs, argue researchers from the University of Liverpool and Chelsea and Westminster in a letter to the editor published in the December 15 2011 edition of JAIDS.

Lower doses of RTV may be better tolerated, cheaper and easier to co-formulate with PIs than the current dose.

Andrew Hill and colleagues identified four crossover PK studies evaluating 50 vs 100mg of RTV. These included boosting once daily atazanavir (ATV), 300/50 vs 300/100mg and once daily darunavir (DRV) 800/50 vs 800/100mg. The other two studies indentified by the researchers were with saquinavir and amprenavir, which are less commonly used PIs and not preferred options, particularly in resource-limited settings.

These small PK studies – conducted with 13 and 18 participants for ATV and DRV respectively – showed bioequivalent AUC and Cmax concentrations of both drugs using the lower and higher RTV doses. But Cmin concentrations were slightly lower when boosted with the 50 mg dose of RTV. See Table 1: PK parameters of ATV and DRV boosted with 50 and 100mg of RTV.

Table 1: PK parameters of ATV and DRV boosted with 50 and 100mg of RTV

PI (Ref)/dose	Cmax mg/L	AUC mg.h.L	Cmin mg/L
ATV 300/50 mg	5.07	47.1	0.59
ATV 300/100 mg	5.19	50.6	0.79
DRV 800/50 mg	6.14 (1.32)	68.5 (20.5)	1.67 (0.64)
DRV 800/100 mg	6.17 (1.27)	77.2 (23.5)	2.12 (0.80)

Mean PKs of boosted PI (SD)

The researchers explained that the clinical significance of the lower Cmin levels was not known and this would need to be investigated in larger studies including efficacy endpoints. They added that small differences in RTV boosting doses might have different consequences in treatment naïve and experienced patients.

They noted that as RTV is only marketed as a 100 mg tablet, these studies were conducted using the liquid formulation. If a 50mg heat stable tablet of RTV could be manufactured or 50 mg coformulated with either PI, new bioequivalence trials would be needed to ensure the boosting effects were similar to those achieved with the liquid.

A 50mg RTV tablet would also be very useful for paediatric dosing, as the liquid is expensive, impractical (particularly for resource limited settings) and tastes dreadful.

They concluded that if lower doses of RTV are able to achieve bioequivalence there is a strong justification for the development of a 50mg tablet and/or coformulations of RTV with these PIs.

C O M M E N T

Once again, the 50 mg RTV tablet really would be useful in paediatrics.

The generic companies should be able to make 50 mg tablets and get approval by showing that 2 x 50 mg tablets are bioequivalent to an Abbott 100 mg tablet.

Ref: Hill A et al. Should we switch to a 50mg boosting dose of ritonavir for selected protease inhibitors? J Acquir Immune Defic Syndr. Volume 58. Number 5. December 15, 2011.

http://journals.lww.com/jaids/Citation/2011/12150/Should_We_Switch_to_a_50_mg_Boosting_Dose_of.18.aspx

New formulations, acquisitions and company announcements

Simon Collins, HIV i-Base

The last two months have been a lively time for pharmaceutical industry announcements concerning Fixed Dose Combinations (FDCs) and new compounds in the HIV and hepatitis pipelines.

Integrase FDC Quad submitted to the FDA

At the end of October, Gilead submitted a new drug application (NDA) to the US regulatory agency (FDA) for its four-drug formulation of elvitegravir, cobicistat, tenofovir and FTC (Quad). This is based on 48-week data from two Phase 3 studies.

Three weeks later Quad was also filed with the European Medicines Agency (EMA).

If these applications are given a fast track review a decision will be made by both agencies within six months.

Reference: Gilead press release: Gilead Submits New Drug Application to U.S. FDA for Once-Daily, Single-Tablet "Quad" HIV Regimen (27 October 2011).

Planned co-formulations of cobicistat with atazanavir, darunavir and darunavir/FTC/GS7340

On 26 October, Bristol-Myers Squibb (BMS) announced that it has entered an agreement to develop and market an FDC of its protease inhibitor atazanavir (Reyataz) with a pharmacokinetic booster cobicistat, currently in development with Gilead. [1]

Phase 2 and 3 studies of atazanavir using cobicistat boosting are ongoing in treatment-naïve patients.

Cobicistat has a similar inhibitory impact on cytochrome P450 3A (CYP3A) and similar side effect profile to ritonavir.

Earlier this year a similar agreement was reached between Gilead and Tibotect to produce an FDC of darunavir with cobicistat. [2]

The press release also referred a further collaborate to produce an FDC of darunavir plus FTC together with cobicistat plus the new tenofovir prodrug (GS7340).

References

1. Press release: Bristol-Myers Squibb and Gilead Sciences announce licensing agreement for development and commercialisation of new Fixed Dose Combination pill for People Living with HIV. (26 October 2011).
2. Press release: Gilead Sciences announces agreement with tibotec Pharmaceuticals to develop and commercialise a new fixed-dose combination of cobicistat and darunavir (Prezista). (28 June 2011).

Gilead license integrase inhibitor compounds from Boehringer Ingelheim

Gilead acquired a license for exclusive worldwide rights for the research, development and commercialisation of its novel non-catalytic site integrase inhibitors (NCINIs) for HIV. This includes the lead compound BI 224436, which has been evaluated in a Phase 1a dose-escalation study to assess bioavailability and pharmacokinetics in healthy volunteers.

NCINIs inhibit HIV integrase by binding to a novel site, distinct from the catalytic site used by the current class of integrase inhibitors, and therefore may possess a differentiated resistance profile from raltegravir or elvitegravir.

Ref: Press statement: Gilead and Boehringer Ingelheim Sign License Agreement for Novel HIV Non-Catalytic Integrase Inhibitors. (05 October 2011).

Gilead spends $11 billion to buy Pharmasset

Finally, on 21 November 2011, Gilead announced that it would acquire Pharmasset for the not insignificant cost of $11 billion from 'cash on hand, bank debt and senior unsecured notes'.

Pharmasset currently has three clinical-stage product candidates for the treatment of chronic hepatitis C virus (HCV) advancing in trials in various populations.

- The lead product compound, PSI-7977, an unpartnered uracil nucleotide analogue, has recently been advanced into two Phase 3 studies in genotype 2 and 3 patients. Both studies use 12 weeks of treatment with PSI-7977 in combination with ribavirin. Comparitor arms include pegylated : 'interferon/ribavirin in treatment-naïve patients, and placebo in interferon- intolerant/ineligible patients. A third Phase 3 study in genotype 1 patients will be initiated in the second half of 2012.
- PSI-938, an unpartnered guanosine nucleotide analogue, is being tested in a Phase 2b interferon-free trial as monotherapy and in combination with PSI-7977 in subjects with HCV of all viral genotypes.
- Mericitabine (RG7128), a cytidine nucleoside analogue, is partnered with Roche and is being evaluated in three Phase 2b trials. Roche is responsible for all aspects of the development of mericitabine.

Ref: Press statement: 'Gilead Sciences to acquire Parmasset Inc for $11 billion'. (21 November 2011).

Abbott to separate treatment from medicinal products in company split

Abbott, the research-based company responsible for developing lopinavir/ritonavir (Kaletra) and ritonavir (Norvir) which has a annual revenue close to $18 billion dollars announced that it plans to divide into two separate companies: one focused on research and treatment and the other on diversified medical products.

The press statement listed immunology, Multiple Sclerosis, chronic kidney disease, Hepatitis C, women's health and oncology, but not HIV, as future research priorities.

Ref: Press statement: 'Abbott to Separate into Two Leading Companies in Diversified Medical Products and Research-Based Pharmaceuticals'. (19 October 2011).

US guidelines (DHHS) update recommendations for first-line combinations (October 2011)

In October the US Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents were updated and posted online to the AIDSinfo web site.

This revision to the guidelines is focused on What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient. Additions and key changes to the section are outlined below. More detailed discussion of the rationale for changes can be found in the updated section. Related tables have also been updated.

Table 1: Key changes to DHHS guidelines (October 2011)

NNRTI-based combinations	
Rilpivirine	Added as an alternative NNRTI option for initial therapy in treatment-naive patients.
Nevirapine-based combinations (NVP)	All reclassified as acceptable for naive patients (women with CD4 count <250 cells/mm3 or men with CD4 count <400 cells/mm3). Previously, NVP+ AZT/3TC was an alternative regimen and NVP + abacavir/3TC and NVP + tenofovir/FTC were 'acceptable but should be used with caution'.
PI-based combinations	
Darunavir/ritonavir + abacavir/3TC	Reclassified as an alternative regimen (BIII) - was 'acceptable but needed more data (CIII)'.
Unboosted fosamprenavir	Removed as a PI option for naive patients (inferior potency and potential for cross-resistance to darunavir).
Raltegravir-based combinations	
Raltegravir + abacavir/3TC	Reclassified as an alternative regimen (BIII) - was 'acceptable but needed more data (CIII)'.
Dual NRTI options	
AZT/3TC	Reclassified to 'acceptable' from 'alternative' because of greater toxicities compared with tenofovir/FTC and abacavir/3TC and twice-daily dosing. However, AZT+3TC remains as the preferred dual-NRTI during pregnancy.
ddI/3TC	Removed for initial therapy due to poor data and higher toxicity.
abacavir	Discussion on the association between abacavir use and the risk of a cardiovascular event updated.

In addition to the changes highlighted above, the following tables are updated with information relevant to rilpivirine:

- Tables 14, 15b, and 16b – Drug interaction tables
- Appendix B, Table 2 – Drug characteristic table
- Appendix B, Table 7 – Dosing recommendation for patients with renal or hepatic insufficiency

The DHHS guidelines are online in PDF and html page formats. The PDF file helpful highlight all recent changes in yellow.

http://www.aidsinfo.nih.gov/guidelines/

TREATMENT ACCESS

Global Fund cancels Round 11 and introduces new rules for grant renewals

Global Fund Observer (GFO)

The Global Fund Board has cancelled Round 11 in light of the Global Fund's financial difficulties. This difficult decision was made at a stressful two-day Board meeting in Accra, Ghana, that ended yesterday evening, 22 November. The Board also announced new rules for grant renewals in an attempt to find savings that can be applied to funding new proposals.

The original decision to launch Round 11 in August 2011 was made at a Board meeting in December 2010. At its meeting in May 2011, the Board did not make any changes to its plans for Round 11, having been told by the Secretariat that sufficient funding (an estimated $1.6 billion) would be available for that round. But the estimate of funds available for Round 11 declined to $0.8 billion in September 2011, and then to a negative amount this month. The decline was caused primarily by some donors changing their minds regarding their so-called pledges, and other donors saying that they would delay payment of their pledges.

The Global Fund has long had a policy that the financing of Phase 2 renewals of existing grants has a higher priority than the financing of new grants. As a result, the Board concluded that almost all of the $8.2 billion in revenues that is now projected to arrive by the end of 2013 will be needed for renewals, leaving no money for Round 11.

The next replenishment period will be 2014-2016. Given that there is no money for Round 11, the next opportunity for countries to apply for new grants will be during the 2014-2016 period. They will be able to do so using a new funding model that is called for in the Fund's new Strategy 2012-2016, also approved at this Board meeting.

Some countries have existing grants that will reach the end of Phase 2 well before 2014. Many of those countries have been hoping to be approved for Round 11 grants. Because that will not be possible now, the Board has agreed to put in place a Transitional Funding Mechanism that will provide for continuation of essential prevention, treatment and/or care services by current grantees. Details of this mechanism will likely be announced in the coming weeks.

However, even with the cancellation of Round 11, the Global Fund did not have enough money to pay for the Transitional Funding Mechanism, and for some Round 10 grants, unless further savings could be found. (The Fund stopped signing Round 10 grant agreements about a week ago because of its financial problems.)

The Board decided to find some of the required savings in the following ways:

The one-year Grace Period provision for changes in country income classification will be rescinded. (See explanation in GFO 80.)

The "counterpart financing" and "focus of proposal" requirements that already apply to new grants will also apply to Phase 2 renewals. (See description in GFO 146.)

Instead of Phase 2 financial commitments being made in two tranches (i.e., the first two years, and then the third year), they will be made one year at a time ("1+1+1").

But even more money had to be freed up. The Board discussed two options for this. One was to say that all eligibility rules that apply to new proposals would also apply to Phase 2 renewals. The other was to say that countries are not eligible for Phase 2 renewal of their current grants if they are Group of 20 (G-20) upper-middle-income countries "with less than an extreme disease burden." Following a difficult discussion, the Board chose the second option. This means, for example, that Argentina, Brazil, China, Mexico and Russian Federation will not be eligible for Phase 2 renewal. (South Africa is a G-20 country, but it has an "extreme" disease burden, so it will be allowed through.)

China is, by far, the country that will suffer most from this decision, because China had been expecting to be eligible for some $880 million in grant renewals.

Now that the above measures have been agreed, the Fund will temporarily be able to resume signing Round 10 grant agreements. However, because the signing of new grant agreements can only be done when the required funds have been received by the Global Fund from its donors, and because Phase 2 renewals take priority over new grants, it is always possible that the signing of Round 10 agreements will be put on hold again. It all depends on whether donors deliver their 2011 pledges during 2011, and whether at least some of them deliver their 2012 pledges earlier rather than later in 2012.

C O M M E N T

There are 200 days to make up the current shortfall, driven by underpayment by US, Italy, Germany (paid since), Japan, Spain and EC.

The significance of capped funding cannot be overestimated. Years of progress with strategies to combat HIV – including testing and prevention programmes - have been and continue to be dependent on increasing access to effective treatment.

Source: GFO issue 167 – 23 November 2011.
http://www.aidspan.org

Documents from the Global Fund Board meeting and the related decisions are online.
http://www.theglobalfund.org/en/board/meetings/twentyfifth/

FDA approval of generic ARVs

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

Drug and formulation	Manufacturer, Country	Approval date
AZT/3TC/nevirapine FDC tablets 300/150/200 mg	Hetero Labs, India	18 November 2011
atazanavir/ritonavir 300/100 mg FDC tablets	Matrix, India	18 November 2011

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 is available on the FDA website:

http://www.fda.gov/oia/pepfar.htm

Source: FDA list serve:

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

We need the Patent Pool to work

Joint statement by TAC, TAG, HIV i-Base, EATG and SECTION27

The exorbitant price of AIDS medicines, especially antiretrovirals, has been one of the main barriers to people with HIV accessing them, especially in developing countries. As activist organisations we have been at the forefront of many of the struggles to make medicines affordable.

A patent gives a pharmaceutical company the exclusive right to manufacture and market a medicine. The patent lasts for 20 years from the date of filing the patent application. Companies typically patent medicines that they develop, they buy patents from other companies or they enter into exclusive licensing arrangements with universities or small companies that have developed medicines but do not have the capacity to bring them to market.

The purpose of patents is to encourage research and development into new medicines. The problem is that patents ordinarily create monopoly conditions which allow companies to charge exorbitant prices. Over the last 15 years, some developing world governments and activists have battled pharmaceutical companies to reduce medicine prices. They have won many hard-fought concessions that have brought down the prices of life-saving drugs and allowed millions of people to go onto antiretroviral treatment. But new generation patented drugs that have fewer side effects, are easier to take or offer treatment alternatives to people resistant to current regimens, are mostly unaffordable. Yet they will soon be needed by millions of people. Furthermore, the struggles for lower medicine prices have to a large degree depended on country-specific laws and the capacity of activists in those countries to organise. Crucially, it is not sustainable to fight drug-by-drug, country-by-country for concessions from the pharmaceutical industry.

One of the initiatives that has resulted from these struggles is the Patent Pool. This is an initiative by activists and UNITAID [1] to negotiate concessions from the pharmaceutical companies on an international scale to license their products through the patent pool. Multiple generic producers will then be able to access these licenses, stimulating sufficient competition between generic producers to drive down prices. The pool also aims to spur the production of generic combinations of medicines, where patents on medicines are held by a number of different companies.

There is no guarantee the Patent Pool concept will work. It ultimately depends on pharmaceutical companies entering into voluntary agreements that dilute the monopolies that patents give them. Getting pharmaceutical companies to the negotiating table requires ongoing activist pressure and protests. It requires co-ordinated strategies to monitor prices and patents, pressure governments to use the powers they have under TRIPS [2] to license essential medicines and campaigns to expose profiteering from health.

The Patent Pool has not been without teething problems and this has led to questions and criticism from activists around the world. It needs to improve its consultation mechanisms. We are pleased that it has begun to do so by meeting with key HIV civil society organisations around the world and by putting together an expert advisory group that will recognise the expertise and experience that members of civil society may bring.

So far only one antiretroviral patent-holding company, Gilead has signed an agreement with the Patent Pool. Gilead has agreed that the Patent Pool can license some of its antiretrovirals to generic companies in over 100 countries. The drugs include tenofovir (TDF), cobicistat (COBI), elvitegravir (EVG), and the Quad, a fixed-dose combination of TDF-COBI-EVG-emtricitabine. Gilead has also committed to not enforcing its exclusive rights on emtricitabine (FTC). It will also not stop companies from making fixed-dose combinations involving these compounds. [3]

The Gilead agreement has shortcomings. For example, Brazil, Thailand, China, Botswana, Namibia and Ukraine, all countries with significant numbers of people with HIV, and many other middle-income countries are excluded from part or all the agreement. Botswana, Thailand and Namibia are included in the TDF license, but excluded from the COBI one. The current agreement also unnecessarily restricts the sub-licensees to Indian generic manufacturers only.

Nonetheless these licenses are the most far-reaching of the concessions obtained from pharmaceutical companies on AIDS drugs. Millions of people can benefit and we must keep up pressure to ensure that all people do. That is why we demand that Gilead re-open negotiations with the Patent Pool to extend the licenses to include all the above countries and others in all aspects of the

agreement. Also, the excluded countries can still access products produced by licensed companies if they make use of their TRIPS flexibilities; we therefore call upon them to do so.

We also demand that other pharmaceutical companies join the Patent Pool and make their essential HIV medicines available for voluntary licensing. In particular, we call on ViiV, Merck, Johnson & Johnson and Abbott to conclude agreements with the pool so that the antiretrovirals dolutegravir (still in clinical trials), raltegravir, darunavir, etravirine, rilpivirine and lopinavir and ritonavir become more accessible.

If these companies join the Patent Pool, the prices of these drugs are likely to drop substantially. Hundreds of thousands, perhaps millions, more people with HIV will therefore have access to these life-saving medicines.

Today six million people are alive and receiving antiretrovirals. Nine million more are in need. In some countries however, access to treatment is reducing rather than increasing. The unaffordable price of medicines is one of the reasons for this. We maintain the view that patents should not be used to make essential medicines unaffordable and that governments should play a much greater role in research and development of medicines. Access to essential medicines cannot be left to the market and the private sector; these cannot meet people's needs.

We call on activists globally to unite and once again build powerful campaigns against pharmaceutical company profiteering so that access to antiretrovirals as part of the human right to the highest attainable standard of health, can be universally realised.

Joint Statement by Treatment Action Campaign, Treatment Action Group, HIV i-Base, European AIDS Treatment Group and SECTION27, 16 November 2011.

Notes

1. UNITAID is a WHO initiative. Its mission is "to contribute to scaling up access to treatment for HIV/AIDS, malaria and tuberculosis, primarily for people in low-income countries, by leveraging price reductions for quality diagnostics and medicines and accelerating the pace at which these are made available."
2. The WTO's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) was negotiated in the 1986-94 Uruguay Round. While imposing intellectual property regimes on countries that did not previously have them, it does contain some flexibilities.
3. TDF is an important drug because it can be used for first-line antiretroviral treatment instead of an older drug called stavudine which has much worse side-effects. Cobicistat, which is not yet approved, is potentially important because there is currently only one other drug that serves a similar purpose, i.e. to boost other antiretrovirals. The Quad is a four-in-one once daily pill that is not yet approved, but is hopefully going to be an excellent first-line antiretroviral regimen. Elvitegravir is also being tested. It will likely be useful for people who are resistant to other antiretrovirals.

PAEDIATRIC CARE

Efavirenz under-dosing in children

Polly Clayden HIV i-Base

An article in the December 1 2011 edition of JAIDS describes efavirenz (EFV) exposure in African children in the ARROW trial, dosed according to the 2006 WHO weight bands, which are similar to the manufacturer's recommendations (the current approved paediatric doses).

ARROW is an open label randomised trial comparing routine laboratory to clinical monitoring (a paediatric version of DART) in children in Uganda and Zimbabwe. It also compares different ART strategies. Quirine Fillekes and colleagues from the trial team conducted a pharmacokinetic (PK) sub study in Ugandan children aged 3-12 years. The children evaluated had received twice daily lamivudine plus abacavir (3TC+ABC) with once daily EFV and participated in a crossover study comparing twice to once daily 3TC+ABC.

EFV was dosed according to WHO 2006 weight bands. Doses were 200, 250, 300 and 350 mg for children weighing 10 to <15, 15 to <20, 20 to <25 and 25 to >30 kg respectively. The children received 200/50mg capsules or halved 600mg tablets.

At week 36 from initiating treatment (once daily EFV plus NRTIs), 12 hour PK sampling was performed, pre-dose and at 1, 2, 4, 6, 8 and 12 hours post dose. The children were switched to once daily NRTIs at 36 weeks. Intensive PK sampling was repeated at 40 weeks, including an extra PK sample at 24 hours post dose.

A total of 41 (24 girls and 17 boys) were enrolled in this sub study. Of these, 4 children increased weight bands between the first and second PK sampling but were included in the analyses and 2 were excluded due to implausible time concentration curves (believed to be labeling errors).

Eighteen of the children were age 3 to 6 years and 23 children were 7 to 12 years. The majority were moderately stunted and wasted. Five, 16, 17 and 3 children were in the 10 to <15, 15 to <20, 20 to <25 and 25 to >30 kg weight bands respectively, at the first PK sampling.

Doses in mg/kg were highest in the 15 to <20 kg (median 14.7 mg/kg) and lowest in the 20 to <25 kg (median 13.0 mg/kg) weight bands. The median dose received overall was 13.6mg/kg.

The geometric mean EFV plasma concentrations time curves obtained at the first and second samplings were similar. Six children at the first sampling and 7 children at the second had subtherapeutic (<1.0 mg/L) plasma concentrations at 8 hours and/or at 12 hours; 7/41 (17%) at either sampling. At the second sampling 15/39 (38%) of children had subtherapeutic levels at 24 hours. Ten (24%) children at the first sampling and 11 (28%) at the second had potentially toxic levels >4 mg/L at 8 hours and/or at 12 hours; 12/41 at either sampling.

Overall the EFV Cmax, Cmin and AUC0-24 were respectively 15%, 36% and 10% lower than those observed in adults receiving the 600mg tablet.

The authors observed wide intersubject but modest intrasubject variability across EFV PK parameters. There was no evidence of significant differences across the four weight bands for all PK parameters evaluated (suggesting no major effect of using divided tablets) however, with only 41 children in total the sub study was rather underpowered to show this.

They wrote that these data (and that of two previous studies) strongly suggest that children should receive EFV doses higher than the WHO 2006 recommendations or the manufacturers daily dose in the leaflet (50mg higher only for children weighing 14 to <15 kg and 30 to 32.5 kg).

More recent 2010 dosing guidelines have higher EFV doses than evaluated in this study for children weighing 14 to <20, 25 to <30 and 35 to <40 kg. The authors noted that these higher doses were not only selected in response to concerns about under doing but to remove the 50 mg tablets from dosing tables as these were being discontinued.

They expressed concern that although these data suggest that higher doses should lead to greater exposure and in turn better virological efficacy, the trade off is that more than one-third of children will be exposed to potentially toxic EFV levels.

Reference
Fillekes Q et al. pediatric underdosing of efavirenz: a pharmacokinetic study in Uganda. J Acquir Immune Defic Syndr. Volume 58. Number 4. December 1, 2011.

Treatment response and duration of first line treatment in European infants

Polly Clayden HIV i-Base

Investigators from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group in EuroCoord evaluated response to antiretroviral therapy (ART) and predictors of switching or interrupting treatment in children starting in infancy up to 5 years from treatment initiation. Findings from this study were reported in the 28 November 2011 edition of AIDS.

The study evaluated data from nine observational cohorts in 13 European countries. A total of 437 HIV-infected, ART naïve infants, less than 12 months of age, born between 1996 and 2008 were included.

The infants started ART at a median of 3.7 (IQR 2.1-5.8) months. About 40% were from UK/Ireland and 20% each from France and Italy. About half were black and half female. Just over a third had been exposed to maternal antiretrovirals in pregnancy and just under a third neonatal prophylaxis. One third were breast-fed.

The median duration of follow up after starting ART was 5.9 (IQR 2.3 – 7.6) years. During this time 20 children died and 32 were lost to follow up. The median CD4 percentage and viral load at treatment initiation of were 29% (IQR 17 - 39%) and 5.7(IQR 4.9 – 5.9) log10 copies/mL respectively.

The majority (76%) started ART before 6 months of age. Twenty four percent started on an NNRTI plus 2 NRTIs, the most common backbone being ddI/d4T from 1996 – 1999 and AZT/3TC from 2000 onwards. Four drug regimens, most frequently NNRTI plus 3NRTIs, were used more often in the later time period (18% compared to 3%) and in UK/Ireland. Boosted PIs were used only from 2001 onwards (34% 2004-2008). Nelfinavir use declined over calendar time.

Just over half (53%) the infants initiating ART in 1996 – 1999 had viral load <400 copies/mL by 12 months, this increased to 57% in 2000 – 2003 and 77% in 2004 – 2008, but the difference was not statistically significant, p=0.09. Infants aged 6 -12 months at ART initiation were more likely to be suppressed than those aged <3 months AOR 1.98 (95% CI 0.92 – 4.25), but again, this difference did not reach statistical significance, p=0.06.

Four-drug NNRTI regimens were associated with significantly better viral load suppression; AOR 3.00 (95% CI 1.24 – 7.23) compared to three drug NNRTI (reference) regimens, p<0.001. But boosted PI plus 2 NRTI regimens performed similarly to the reference regimen, AOR 1.39 (0.62 – 3.13). Higher baseline viral load was associated with less likelihood of virological suppression, AOR 0.67 per log10 copies/mL (95%CI 0.50 – 0.89), p=0.01.

For infants with data available, median baseline and 12 month CD4 count, CD4 percentage and CD4 z-score were 520 (IQR 271 – 1340) cells/mm3, 6% (-6 to 16%) and 0.92 (-0.14 to 2.34), respectively. Median CD4 z-score increase was 2.29 in infants receiving four-drug NNRTI regimens compared to 0.65 in those receiving three-drug NNRTI regimens and 0.91 for boosted PI regimens, p=0.04.

Eighteen percent of infants switched to second line treatment. The cumulative incidence of switching was 10.2% (95% CI 7.5 – 13.4) and 16.7% (13.0 – 20.7%) by 2 and 5 years respectively. Children starting treatment with a four drug NNRTI or boosted PI-based regimen were slower to switch; AHR 0.41 (95% CI 0.15 – 1.14) and AHR 0.26 (95% CI 0.06 – 1.19) respectively, p=0.03. Although the investigators noted data were sparse.

Twenty eight percent of children experienced at least one treatment interruption of more than 14 days, no factors predicted interruption.

Sixty five percent of children remained on treatment without interruption at last follow-up. Of these 36% had been treated for at least 5 years. The estimated probability of remaining on first-line ART without interruption was 79.3% (95% CI 75.1 – 83.1%) and 63.8% (95% CI 58.7 – 68.9%) by 2 and 5 years from starting ART respectively.

C O M M E N T

That boosted PI-based regimens performed similarly to NNRTI-based is contradictory to findings from IMPAACT 1060 that showed 20% higher rates of failure at 24 weeks in children aged 2 months to 3 years receiving NNRTI-based regimens compared to PI-based (whether or not they had been NNRTI exposed through PMTCT). Although IMPAACT 1060 was an RCT and these are cohort data – the difference in length of follow up is considerable.

That four drug NNRTI-based regimens did well is notable and induction/maintenance strategies in young children remain under explored.

Ref: European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group in EuroCoord. Early antiretroviral in HIV-1 infected infants, 1996-2008; treatment response and duration of first-line regimens. AIDS: 25(18):2279-2287, 28 November 2011.

OIs AND COMPLICATIONS

US guidelines for management of older people living with HIV

The American Academy of HIV Medicine (AAHIVM), the American Geriatrics Society (AGS) and the AIDS Community Research Initiative of America (ACRIA) has released the first clinical treatment strategies for managing older HIV patients: The HIV and Ageing Consensus Project: Recommended Treatment Strategies for Clinicians Managing Older Patients with HIV**.**

The executive summary and full guidelines are both available to download in PDF format.

The report is part of the organisations' HIV and Ageing Consensus Project, developed to assess how the presence of both HIV and common age-associated diseases, alter the optimal treatment of HIV as well as other co-morbidities. The purpose of the report, developed by a panel of experts with experience both in the fields of HIV and Geriatrics, is to provide best practice guidance for HIV practitioners and other health care providers who treat, diagnose and refer older patients with HIV disease.

References

The HIV and Ageing Consensus Project: Recommended treatment strategies for clinicians managing older patients with HIV.

View the executive summary: (direct PDF download)

http://www.aahivm.org/Upload_Module/upload/HIV%20and%20Aging/AAHIVM%20Executive%20Summary%20FINAL%202.pdf

Full report and guidelines: (direct PDF download)

http://www.aahivm.org/Upload_Module/upload/HIV%20and%20Aging/Aging%20report%20working%20document%20FINAL.pdf

New studies on HIV and the diseases of ageing

Richard Jefferys, TAG

The December 1st issue of Clinical Infectious Diseases contains a raft of papers addressing the issue of HIV and ageing.

A report from the Swiss HIV Cohort Study documents that illnesses typically associated with ageing are now the most common causes of morbidity in their cohort, which contains an increasing proportion of individuals aged 50 or older. [1] In contrast, opportunistic infections make only a minor contribution in the current era of effective antiretroviral therapy (ART). An accompanying editorial by Mike Saag highlights the implications for providing appropriate multidisciplinary care to people with HIV as they age. [2]

While there are ongoing debates about whether HIV infection is linked to premature ageing—some studies have suggested the risk of ageing-associated diseases is increased among HIV-positive people compared to age-matched HIV-negative individuals, while other studies have disputed these findings—the Swiss HIV Cohort Study paper emphasises that whether or not they are occurring sooner, these morbidities are now the main concern in the long-term care of people with HIV. In discussing their findings, the authors note that the incidence of cancer, heart attacks and diabetes among members of their cohort aged 50-64 was higher

than described in studies of somewhat comparable HIV-negative cohorts, but they also stress that "a comparison of our results with an age-matched HIV-uninfected population with similar comorbidity or behavior is difficult, because we had no suitable HIV-uninfected control group in our country."

Giovanni Guaraldi and colleagues from the University of Modena and Reggio Emilia in Italy attempted to address this issue in their study, which compared the occurrence of non-infectious co-morbidities (NICMs) and polypathology (the presence of more than one NICM) among HIV-positive people on ART and a matched HIV-negative control group from the general population (from 2002 through 2009). [3]

The NICMs captured in the study included cardiovascular disease, hypertension, diabetes mellitus, bone fractures, and renal failure. The results revealed that prevalence of NICMs and polypathology was higher in HIV-positive individuals across all age categories. The prevalence of polypathology among people with HIV aged 41-50 was similar to the prevalence among HIV-negative controls aged 51-60.

Interpretation of the findings is complicated by the fact that the data from HIV-positive individuals was all derived from a metabolic clinic at Modena. Part of this population is comprised of local people from main HIV clinic at Modena who are automatically referred to the metabolic clinic if they are on ART. However, the population also includes a large proportion of HIV-positive individuals who are referred to the Modena metabolic clinic from neighboring centers due to metabolic issues such as lipodystrophy, and this would appear to account for the unusually high prevalence of this condition among the study cohort (74%). To assess whether this over-representation of people with metabolic issues had biased their results, the study authors compared the incidence of NICMs and polypathology among the local referrals to those from the neighboring centers but—perhaps surprisingly, as Jacqueline Capeau notes in an accompanying editorial commentary—they found no difference. [4]

The authors conclude: "our findings suggest that an aggressive approach to the screening, diagnosis, and treatment of NICMs is warranted as part of routine healthcare for HIV-infected patients. Furthermore, our data suggest that onset of such screening should commence at a substantially earlier age for HIV-infected persons, compared with HIV-uninfected persons, possibly at least a decade in advance. Additional studies are needed to further evaluate the impact of convergent age-related NICMs on age-related functional status, frailty, and disability among ART-experienced HIV-infected persons and to provide insights into accelerated ageing processes that may be associated with chronic HIV infection."

Source: TAG Basic Science web log. (1 November 2011).

References

1. Hasse B et al for the Swiss HIV Cohort Study. Morbidity and ageing in HIV-infected persons: the Swiss HIV Cohort Study. Clin Infect Dis. 2011 Oct 13. [Epub ahead of print]
   http://cid.oxfordjournals.org/content/53/11/1130
2. Saag MS. Editorial commentary: HIV now firmly established in the Middle Ages. Clin Infect Dis. 2011 Oct 13. [Epub ahead of print]
   http://cid.oxfordjournals.org/content/53/11/1140
3. Guaraldi G et al. Premature age-elated comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis. 2011 Oct 13. [Epub ahead of print]
   http://cid.oxfordjournals.org/content/53/11/1120
4. Capeau J. Editorial commentary: Premature Aging and Premature Age-Related Comorbidities in HIV-Infected Patients: Facts and Hypotheses. Clin Infect Dis. 2011 Oct 13. [Epub ahead of print]
   http://cid.oxfordjournals.org/content/53/11/1127

Risk of cataract surgery higher in HIV-positive compared to HIV-negative people

Richard Jefferys, TAG

A population-based study carried out in Denmark to assess the risk of cataract surgery among HIV-positive individuals compared to large group of matched HIV-negative controls.

Risk was found to be greater among the HIV-positive population, with the highest risk among those with CD4 T cell counts below 200 (either on or off ART). Individuals on ART with CD4 T cell counts over 200 still showed a higher risk than both the general population and HIV-positive people with over 200 CD4 T cells who had not yet started ART; the authors note this could reflect a contribution of drug side effects or receipt of ART could be acting as a marker for having reached a stage of illness requiring treatment (which in turn is associated with an elevated cataract risk).

Supporting the latter possibility, no association with specific antiretroviral drugs was found. Although the researchers do not claim that their data represents evidence of accelerated ageing in the HIV-positive population, they acknowledge that such a phenomenon "cannot be excluded as a possible part of the explanation."

Source: TAG Basic Science web log. (1 November 2011).

Ref: Rasmussen LD et al. Risk of cataract surgery in HIV-infected individuals: a Danish nationwide population-based cohort study. Clin Infect Dis. 2011 Oct 13. [Epub ahead of print]

http://cid.oxfordjournals.org/content/53/11/1156

CD4 count <200 independently associated with 5-fold increased risk of fracture

Simon Collins, HIV i-Base

A study published in the July 1st edition of JAIDS by Michelle Yong from The Alfred Hospital, Melbourne, reported a significant association between CD4 count and risk of fractures that was independent of traditional risk factors including corticosteroid use.

The group performed a 1:2 matched case-control study in HIV positive patients attending a single hospital site between 1998 and 2009. Controls were matched on gender, age, and duration of HIV infection.

The overall fracture incidence rate was 0.53 per 100 person-years (95%CI: 0.43 to 0.65) and period prevalence of 3.34 per 100 patients (95% CI: 2.66 to 4.13). There were 73 low trauma fractures in 61 patients. Patients were predominantly male (89%) with a mean age of 49.8 years. Independent risk factors for fragility fracture were a CD4 cell count <200 cells/mm3 (OR 4.91: 95% CI 1.78 to 13.57, p = 0.002), corticosteroids (OR 8.96: 95% CI 1.55 to 51.88, p = 0.014) and anti-epileptic medications (OR: 8.88: 95% CI 1.75 to 44.97, p = 0.008).

No association was found between risk of fracture and HIV viral load (p = 0.18), use of antiretrovirals or class of antiretroviral medication. The majority patients with fracture (88%) had osteopenia or osteoporosis.

References

Yong MK et al. Low CD4 count is associated with an increased risk of fragility fracture in HIV-infected patients. JAIDS, 1 July 2011 - Volume 57 - Issue 3 - pp 205-210

http://journals.lww.com/jaids/Fulltext/2011/07010/Low_CD4_Count_Is_Associated_With_an_Increased_Risk.5.aspx

BASIC SCIENCE

Exercise as immune-based therapy

Richard Jeffreys, TAG

Many studies have reported that regular exercise confers health benefits and that, conversely, a sedentary lifestyle is a major risk factor for morbidity and mortality (particularly from cardiovascular disease). In recent years, researchers have begun to look more specifically at the immunological effects of exercise. The scientist Richard Simpson, formerly at Napier University in Edinburgh and now based at the University of Houston in Texas, has pioneered the exploration of the intersection between exercise and immune senescence. [1, 2] This research is potentially relevant to HIV infection because, as reported in some prior blog posts), senescent immune cells—particularly CD8 T cells—accumulate over time and may persist despite antiretroviral therapy. [3]

Simpson's recent work suggests that exercise mobilises senescent immune system cells from the tissues into the blood and increases their death by apoptosis; [4] if confirmed this may offer both a more practical approach to addressing senescence than the idea of physically removing cells, and could also explain some of the positive contributions of exercise to healthy ageing that have been described in the literature.

Exercise may also have a beneficial impact on inflammation, another problem common to both ageing and HIV infection. In Nature Reviews Immunology, Mike Gleeson and colleagues from Loughborough University in the UK review the mechanisms by which exercise may reduce inflammation, and highlight some of the questions that remain to be answered about which mechanisms are most important in producing beneficial health outcomes. [5]

Finally, in a paper in press at the Journal of the Association of Nurses in AIDS Care, Anella Yahiaoui and colleagues review the literature in an attempt to offer evidence-based exercise recommendations for older individuals with HIV. [6] They conclude that:

"Combined moderate to vigorous aerobic and resistance exercise for 20-40 minutes, 3 times per week, is safe and effective in older adults and has many benefits to decrease symptom burden, decrease disease progression, and increase quality of life."

Additional specifics are included in the paper. The authors also recommend the basic "Exercise Tips for Older Americans" offered on the website of the American Heart Association. [7]

C O M M E N T

Of interest, a study at EACS in HIV positive patients with high cardiovascular risk, reported that an intensive and multidisciplinary intervention on lifestyle led to a significant improvement in lipid profile, quitting smoking and Framingham risk score. [8]

Source: TAG basic science blog (15 August 2011).

http://tagbasicscienceproject.typepad.com/

References

1. Simpson RJ. Aging, persistent viral infections, and immunosenescence: can exercise "make space"? http://journals.lww.com/acsm-essr/Abstract/2011/01000/Aging,_Persistent_Viral_Infections,_and.6.aspx

2. Simpson RJ et al. Senescent phenotypes and telomere lengths of peripheral blood T-cells mobilized by acute exercise in humans. Exerc Immunol Rev. 2010;16:40-55.
http://www.medizin.uni-tuebingen.de/transfusionsmedizin/institut/eir/content/2010/40/article.pdf (PDF)
3. http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/immunosenescence/
4. Spielmann G et al. Aerobic fitness is associated with lower proportions of senescent blood T-cells in man. Brain Behav Immun. 2011 Jul 19. [Epub ahead of print].
http://www.sciencedirect.com/science/article/pii/S088915911100465X
5. Gleeson M et al. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol. 2011 Aug 5. doi: 10.1038/nri3041. [Epub ahead of print]
http://www.nature.com/nri/journal/vaop/ncurrent/full/nri3041.html
6. Yahiaoui A et al. Development of evidence-based exercise recommendations for older HIV-infected patients. J Assoc Nurses AIDS Care. 2011 Jul 29. [Epub ahead of print]
http://www.nursesinaidscarejournal.org/article/S1055-3290(11)00125-7/abstract
7, http://www.heart.org/HEARTORG/GettingHealthy/PhysicalActivity/GettingActive/Exercise-Tips-for-Older-Americans_UCM_308039_Article.jsp
8. Saumoy M et al. Efficacy of an Intensive and Multidisciplinary Intervention on Lifestyle in Cardiovascular Risk and Metabolic Variables in HIV-infected Patients: 96-week Results. 13th EACS, 12–15 October 2011, Belgrade. Abstract PE9.5/4.

Mapping the long genetic road to broadly neutralising antibodies

Richard Jeffreys, TAG

Over the past couple of years, several new antibodies capable of neutralizing a broad array of HIV isolates have been discovered.

As mentioned in prior posts about these discoveries, one common feature of these antibodies is that the B cells that produce them have undergone an unusual degree of somatic hypermutation—a process in which the cell's antibody-producing genetic code is progressively revised in order to increase the affinity of the antibody for its target. The genetic code that the B cell starts out with is called the germline sequence, and it is typically altered by around 5-15% to produce antibodies against common infections, whereas this figure ranges from 19-46% for the broadly neutralising antibodies against HIV that have been identified. Antibodies targeting the part of the HIV envelope that binds to the CD4 receptor, such as the recently discovered VRC01, are at the extreme end of this scale (showing sequence alterations of 40-46%).

In a recent article in Science Express, researchers from the Vaccine Research Center (VRC), the Center for HIV/AIDS Vaccine Immunology (CHAVI) and the International AIDS Vaccine Initiative (IAVI) published the latest results from their collaborative effort to better understand how these antibodies are generated. [1]

The work involves analyses of mind-boggling numbers of B cell genetic sequences, and identifies several new broadly neutralising antibodies from infected individuals that target HIV's CD4 binding site. Of potential importance for vaccine design, the B cell sequences that give rise to the antibodies are not uncommon, and although a similarly extensive degree of somatic hypermutation is involved in their generation, it appears that the mutations do not have to be exactly the same to produce structurally similar antibodies.

The researchers are hopeful that these data can be used as a map for guiding the development of broadly neutralising antibodies using vaccines. [2]

Source: TAG basic science blog (12 August 2011).
http://tagbasicscienceproject.typepad.com/

References

1. Wu X et al. Focused evolution of HIV-1 neutralizing antibodies revealed by structures and deep sequencing. Science (11 August 2011). DOI: 10.1126/science.1207532.
http://www.sciencemag.org/content/early/2011/08/10/science.1207532
2. NIAID Press Release: NIH-Led Team Maps Route for Eliciting HIV Neutralizing Antibodies.
http://www.niaid.nih.gov/news/newsreleases/2011/Pages/HIVAntibodyEvolution.aspx

Monkey viral reservoir study goes for gold

Richard Jeffreys, TAG

A small study of auranofin, a gold-based drug developed to treat rheumatoid arthritis, suggests it may be able to reduce the reservoir of SIV-infected CD4 T cells in macaques on antiretroviral therapy (ART). The paper appears in the 17 July issue of the journal AIDS [1], and previously generated some excitable media coverage when it appeared online-ahead-of-print in April (the researchers issued a press release at the time entitled "Gold-based Drug May Pave the Way to a Cure for AIDS" [2]).

The mechanism of action of auranofin is not fully understood, but it has been shown to inhibit proliferation of CD4 T cells and thus may prevent the expansion of latently infected cells and/or shift these cells from a long-lived to short-lived phenotype. The authors note that there is one published case report on the use of auranofin in an individual with HIV, and it did not show an adverse effect on overall CD4 T cell numbers. [3]

A key issue in interpreting this or any other cure-related research study in rhesus macaques is that there is no consensus regarding the most appropriate way to try and model combination antiretroviral treatment of HIV infection in humans, because not all HIV drugs work against SIV. The researchers in this instance used a new approach that they first described last year, in which macaques are infected with SIVmac251 and treated with the combination of tenofovir+emtricitabine (Truvada) and raltegravir (Isentress). [4]

However, in this initial description of the model, follow-up was for 52 days and viral replication and persistence were only analysed in blood samples, not tissues, making the extent and durability of SIV suppression unclear.

The uncertainty regarding the animal model is thrown into sharp relief by the initial results of the new experiment in which auranofin was added to ART in six macaques: SIV DNA levels declined to undetectable levels after four weeks but rebounded by eight weeks. It is uncertain whether this reflects a transient effect of auranofin or some limitation of the ART combination to fully suppress SIVmac251.

In the second part of the study, the same six macaques had ART intensified by the addition of ritonavir-boosted Prezista (darunavir). Two control macaques on the same ART combination without auranofin were also added to the experiment at this juncture. After around two months of follow-up, the researchers report a trend toward declining SIV DNA levels in the auranofin group but not the controls; however the very small number of controls makes this data hard to interpret. An attempt was then made to see if the compound SAHA could stimulate production of virus in the auranofin-treated macaques. SAHA is a histone deacetylase (HDAC) inhibitor that can induce replication of latent HIV. SIV viral load did not increase after SAHA administration in the auranofin-treated macaques, but it's not clear from the paper if SAHA was given to the two control macaques. Instead the researchers cite two "historical" control macaques treated with ART that showed viral load rebound after SAHA treatment.

Finally, ART was stopped in 5 out of 6 of the auranofin-treated macaques (one animal was spirited away to participate in another study) and both of the real-time controls. There was, on average, a slight delay in SIV viral load rebound in the auranofin group compared to the real-time two controls that just about achieved statistical significance. Set point viral loads were also lower than those documented prior to ART in the same animals, but the statistical significance of this finding was borderline and appeared to be driven by results in one macaque. There was absolutely no evidence that auranofin had led to a cure of SIV infection in any of the treated macaques, as all showed viral load rebounds.

In sum, these experiments may have identified a compound deserving of further evaluation in the context of efforts to deplete the latent HIV reservoir. However, the data are by no means clear-cut due to the use of a new macaque model of ART that is not well characterised, the small numbers of animals involved, and the use of historical controls (issues that likely reflect limitations on funding and access to macaques). Hopefully the publication of the data will help the researchers obtain the support necessary to conduct a larger and more rigorous evaluation of the reservoir-depleting potential of auranofin.

Additional background on the use of the drug in rheumatoid arthritis, along with an excellent potted history of the use of gold in medicine, can be found in a review published in 1997 in the British Journal of Rheumatology (free to access online). [5]

Source: TAG basic science blog (26 Jul 2011).
http://tagbasicscienceproject.typepad.com/

References

1. Lewis MG et al. Gold drug auranofin restricts the viral reservoir in the monkey AIDS model and induces containment of viral load following ART suspension. AIDS: 17 July 2011 - Volume 25 - Issue 11 - p 1347–1356.
http://journals.lww.com/aidsonline/Abstract/2011/07170/Gold_drug_auranofin_restricts_the_viral_reservoir.1.aspx
2. Press release. Gold-based Drug May Pave the Way to a Cure for AIDS.
http://www.hiv-reservoir.net/index.php/Latest-News-on-HIV-Reservoirs-Eradication/gold-based-drug-to-hit-hiv-reservoirs.html
3. http://www.ncbi.nlm.nih.gov/pubmed/8895167
4. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2853490/?tool=pubmed
5. British Journal of Rheumatology, 1997.
http://rheumatology.oxfordjournals.org/content/36/5/560.full.pdf (PDF)

Immune pressure on HIV

Richard Jeffreys, TAG

Several recent papers offer insights into the role of the immune response in shaping the genetic make-up of HIV. In a well-publicised, open access paper by Vincent Dahirela, Karthik Shekhara and colleagues, a complex statistical approach called random matrix theory is used to analyse published HIV sequences and look for groups of sites that evolve collectively. [1]

The method allows the researchers to uncover a region of the Gag protein they dub "sector 3" that is far more constrained in its ability to mutate than surrounding areas. Additional analyses reveal this constraint is likely due to an important role in the formation of the viral capsid. In collaboration with Bruce Walker's group at the Ragon Institute, the researchers show that HIV-specific CD8 T cell responses in elite controllers preferentially target sector 3 of Gag, consistent with prior studies indicating that immune responses in these individuals work partly by compromising viral fitness. The findings suggest that vaccines should attempt to induce T cells against this potentially vulnerable region of HIV. The researchers also recommend using their technique to search for other "multidimensionally constrained" parts of viral proteins.

In a paper published in Blood, Tao Dong and colleagues describe the impact of CD8 T cell responses on HIV diversity in a population of Chinese individuals who were infected with genetically homogenous viruses as a result of plasma donation. [2]

Because of the similarity of the infecting viruses, the cohort offers a unique window into how individual variability in the parts of HIV targeted by CD8 T cells shapes viral evolution, by selecting variants able to escape recognition. Based on analyses of four HIV proteins—Gag, Reverse Transciptase, Integrase and Nef—the researchers find evidence that 24-56% of variable sites were subject to selection by CD8 T cell responses (over approximately 10-12 years since the time of infection). The results offer strong and unusually direct evidence for the key role of virus-specific immune responses in driving HIV diversity.

In a separate paper by the same authors, involving individuals from the same cohort possessing the beneficial HLA B51 immune response gene, CD8 T cell responses targeting specific epitopes from HIV Gag and Pol proteins are investigated in detail. [3]

The researchers show that mutations in these epitopes that abrogate CD8 T cell recognition are associated with higher viral loads and lower CD4 counts, whereas individuals in whom the epitopes are unmutated had higher CD4 T cell counts and lower viral loads. The findings add to the evidence that the beneficial effect of certain HLA genes in HIV infection is mediated by CD8 T cell responses targeting vulnerable parts of the virus.

Lastly, Ingrid Schellens and colleagues compare two groups of HIV-positive individuals who seroconverted in 1985 and 2005/6, respectively, to investigate whether CD8 T cell responses are altering the make-up of circulating HIV over time. [4]

The researchers report that certain HIV epitopes have become significantly less common, and these are epitopes known to be targeted by people with HLA-B alleles associated with slower HIV disease progression (such as HLA B27, B51 and B57). The implication is that HIV is adapting at the population level to avoid the most effective CD8 T cell responses, so HLA alleles that have been shown to be "protective" against disease progression in the past may not always show this association. As a possible example, the authors note that individuals with HLA B57 who seroconverted in 1985 had significantly lower viral loads than individuals lacking this allele, but this was not the case among the 2005/6 cohort.

Source: TAG basic science blog (05 Jul 2011).
http://tagbasicscienceproject.typepad.com/

References

1. Dahirel V et al. Coordinate linkage of HIV evolution reveals regions of immunological vulnerability. Proc Natl Acad Sci U S A. 2011 Jun 20. [Epub ahead of print]
http://www.pnas.org/content/early/2011/06/15/1105315108.long
2. Dong T et al. Extensive HLA-driven viral diversity following a narrow-source HIV-1 outbreak in rural China. Blood. 2011 May 11. [Epub ahead of print]
http://bloodjournal.hematologylibrary.org/content/early/2011/05/10/blood-2010-06-291963.abstract
3. Zhang Y et al. Multilayered Defense in HLA-B51-Associated HIV Viral Control. J Immunol. 2011 Jun 13. [Epub ahead of print]
http://www.jimmunol.org/content/early/2011/06/13/jimmunol.1100316.abstract
4. Schellens IM et al. Loss of HIV-1 derived CTL epitopes restricted by protective HLA-B alleles during the HIV-1 epidemic. AIDS. 2011 Jun 15. [Epub ahead of print]
http://journals.lww.com/aidsonline/Abstract/publishahead/Loss_of_HIV_1_derived_CTL_epitopes_restricted_by.99152.aspx0

Lymphocyte production capacity in HIV: links to immune activation & immune reconstitution on ART

Richard Jeffreys, TAG

A number of studies have documented that the body's machinery for producing new immune system cells is impaired by HIV infection. In a new paper in the journal Blood, Delphine Sauce and colleagues delve into the issue further by analyzing circulating CD34+ hematopoietic progenitor cells (HPC) in over one hundred HIV positive individuals at various stages of disease, compared to both age-matched and elderly (75-96 years old) uninfected controls. [1]

The research reveals significant correlations between the number of HPC and multiple types of immune cells including CD4 T cells, CD8 T cells, B cells, natural killer cells and neutrophils (the strongest correlation being between circulating HPC and CD4 T cells). The number of HPC is found to decline over the course of HIV disease progression such that middle-aged HIV-positive individuals with CD4 T cell counts less than 200 had similar levels of circulating HPCs to the elderly uninfected controls.

Additional analyses show that markers of immune activation such as CD38 expression on CD8 T cells are inversely associated with HPCs; the higher the levels of immune activation, the lower the HPC counts. The researchers demonstrate that among elite controllers with declining CD4 T counts, HPC numbers and functional capacity are diminished despite persistently low viral load, consistent with the link between immune activation and CD4 T cell loss that has been reported in this population. HIV-positive individuals with poor CD4 T cell recovery despite antiretroviral therapy (ART) also show reduced HPC numbers and functional capacity compared to individuals with better immune reconstitution.

The study authors conclude that preservation of lymphocyte production capacity (lymphopoiesis) is important for preventing HIV disease progression and that strategies for enhancing lymphopoiesis should be evaluated in the setting of poor CD4 T cell recovery

on ART. One approach that is currently under evaluation in a clinical trial for people on ART with CD4 T cell counts less than 250 is TXA127 (angiotensin 1-7), a drug formulation of a naturally occurring substance that may stimulate production of HPCs. [2]

Source: TAG basic science blog (28 Apr 2011).
http://tagbasicscienceproject.typepad.com/

References

1. Sauce D et al. HIV disease progression despite suppression of viral replication is associated with exhaustion of lymphopoiesis. Blood, 24 March 2011. doi: 10.1182/blood-2011-01-331306.
   http://bloodjournal.hematologylibrary.org/content/early/2011/03/24/blood-2011-01-331306.abstract
2. http://clinicaltrials.gov/ct2/show/NCT00757250

TRANSMISSION & PREVENTION

International PrEP study (VOICE) discontinues use of tenofovir vaginal gel due to lack of efficacy

Simon Collins, HIV i-Base

On 17 November a large international Phase 2b study looking at interventions to reduce HIV sexual transmission announced that it will discontinue use of a 1% tenofovir vaginal gel and matched placebo gel due to the study's data and safety monitoring board (DSMB) finding no difference in efficacy between these two groups. [1]

In the latest review the DSMB found a 6% HIV incidence rate among participants in both the tenofovir gel group and the placebo gel group. No other safety concerns (other than efficacy) have been reported with any of the studied interventions.

This is the second major change in the US NIH funded VOICE study (Vaginal and Oral Interventions to Control the Epidemic) in two months. In September, we reported in HTB that the use of daily oral tenofovir was discontinued for a similar lack of efficacy. [2]

The study originally enrolled more than 5,000 HIV-negative women at 15 clinical research sites in Uganda, South Africa and Zimbabwe. The study randomised women to one of five groups: daily oral tenofovir, daily oral Truvada, daily oral placebo tablet, daily tenofovir gel or daily placebo gel.

Only the daily oral Truvada and oral placebo arms will continue to be studied, with results expected in 2013.

References:

1. NHI press statement: NIH discontinues tenofovir vaginal gel in 'VOICE' HIV prevention study: product safe but no more effective than placebo. (25 November 2011).
   http://www.niaid.nih.gov/news/newsreleases/2011/Pages/VOICEdiscontinued.aspx
2. DSMB stops oral tenofovir monotherapy arm of VOICE PrEP study due to lack of difference compared to placebo. HIV Treatment Bulletin (HTB), October 2011.
   http://i-base.info/htb/15779

Further information
Statement and Q&A from Microbicide Trials Network (MTN):
http://www.mtnstopshiv.org/node/3909

UK Health Protection Agency (HPA) recommends universal HIV testing in the high incidence regions of the UK

HPA press statement

The number of people living with HIV in the UK reached an estimated 91,500 in 2010, with a quarter of those unaware of their infection, according to Health Protection Agency (HPA) figures published just ahead of World AIDS Day on 1 December.

The report also showed how in 2010, one in five people visiting an STI clinic did not accept an HIV test. This comes as the HPA calls for universal testing for HIV, so that no one leaves an STI clinic without knowing their HIV status.

The HPA is concerned that over half of people diagnosed in 2010 came forward for testing after the point at which treatment for their infection should ideally have begun. Late diagnosis is associated with an increased risk of AIDS and death. Among the 680 people with HIV who died in 2010, two thirds were people who had been diagnosed late. The HPA report recommends that in areas where prevalence of HIV is high, there should be universal testing for the infection in all new GP registrants and patients admitted to hospital so as to reduce late diagnosis.

The HPA's annual "HIV in the UK" report found 6,660 people were newly diagnosed with HIV in the UK. The report confirmed that infections probably acquired within the UK almost doubled in the last decade from 1,950 in 2001 to 3,640 in 2010 and exceed those acquired abroad – 3,020. This rise is mostly due to infections acquired among men who have sex with men, who remain the group most at risk of HIV infection in the UK.

In 2010, over 3,000 gay men were diagnosed with HIV – the highest ever annual number. One in 20 gay men are now infected with HIV nationally with one in 12 in London.

Dr Valerie Delpech, consultant epidemiologist and head of HIV surveillance at the HPA, said: "HIV is an infection which can nowadays be treated and those diagnosed promptly can expect to experience similar life expectancy as an individual without the infection. However, we are very concerned that a large number of people in the UK are unaware of their HIV status and are diagnosed late.

"We want to see increased access to HIV testing routinely offered in clinical settings such as new registrants at GPs and hospital general admissions, in areas of the country where rates of HIV infection are high. We are also urging sexual health clinics to ensure that HIV testing is offered as part of a universal sexual health screen at every new attendance.

"Research by the HPA has shown that routine and universal testing is feasible to undertake and acceptable to patients. Increased testing and greater access will help reduce the number of people who are unaware of their HIV status and increase the chances of early diagnosis, when treatment is more successful."

Dr Delpech added: "Thanks to the development of anti-retroviral treatments and universal access to world class health care through the NHS, HIV is a manageable illness for the vast majority of people affected in this country. But an HIV diagnosis means a lifetime of medication and the costs of providing specialist HIV treatment and care are substantial and accelerating, so avoiding the infection altogether is essential for controlling the epidemic in the UK.

"If you are having sex, using condoms with any new or concurrent partners is the best way to prevent HIV. We encourage all people to take up the offer of an HIV test in whatever health care setting."

Ref: HPA press statement: HPA urges 'universal testing' for HIV as it is revealed more than 21,00 people are unaware they have the infection. (29 November 2011).

http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1317131678707x

OTHER NEWS

Iranian doctors now freed

Two doctors, who raised awareness for testing and treatment of HIV in Iran and who were the focus of a human rights campaign have now both been released. Doctor Arash Alaei and Doctor Kamiar Alaei were detained in June 2008 by Iranian authorities without cause and without charges or trial. [1]

The physicians, who are brothers, were held for over six months before being tried. On 31 December 2008, the brothers were tried as conspirators working with an "enemy government" to overthrow the government of Iran in a one-day, closed-door trial. They were also tried on unspecified other charges which neither they nor their lawyer were allowed to know. [1]

In the autumn of 2010, Kamiar Alaei was released from Evin Prison after serving two years of his three-year sentence. He moved to the US and worked for the release of his brother.

In August 2011, Arash Alaei was also released from Evin Prison after more than three years of a six year sentence. He rejoined his mother and other family members in Tehran and anticipates the resumption of his life-saving work, as well as reuniting with his brother, Kamiar, and sister in the US.

Physicians for Human Rights (PHR) is a campaigning organisation that raised the profile of Drs. Kamiar and Arash Alaei. We included this as a new item in October 2008 as their situation was also highlighted prominently at the IAS conference in Mexico City. [2]

Both doctors received the Jonathan Mann Award for Global Health and Human Rights in June 2011. [3]

A video of the brothers speaking about their detainment and release can be viewed online. [4]

References

1. Dr. Arash is Freed! PHR news feature. (29 August 2011). http://physiciansforhumanrights.org/blog/dr-arash-is-freed.html
2. Free The Iranian HIV/AIDS Doctors! HTB October 2008. http://i-base.info/htb/140
3. Alaeis Honored at Global Health Council Event. PHR news feature. (17 June 2011). http://physiciansforhumanrights.org/blog/alaeis-honored-at-global-health-council-event.html
4. http://physiciansforhumanrights.org/library/multimedia/released-iranian-aids-doctors-share-story.html

New York court rejects AIDS denialist case against leading HIV community activist and journalist

Simon Collins, HIV i-Base

It is with great pleasure, and considerable relief that we report that the New York State Supreme Court Justice Louis B. York granted summary judgment in favor of Richard Jefferys in a defamation lawsuit brought by an AIDS denialist named Celia Farber. [1] Jefferys was represented in the case by Joseph Evall of Gibson, Dunn & Crutcher.

The suit against Jefferys arose out of a May 12, 2008, comment he submitted via the now-defunct website for "Whistleblower Week," conference. [2]

Jefferys was responding to an announcement that one of the conference sponsors was planning invite the AIDS denialists Celia Farber and Peter Duesberg to testify before a "tribunal" (including several Congresspeople), in the guise of whistleblowers.

In his comment, Jefferys asserted that Farber and Duesberg "are not whistleblowers, they are simply liars who for many years have used fraud to argue for Duesberg's long-discredited theory that drug use and malnutrition - not HIV - cause AIDS."

Jefferys wrote that he could provide "many, many examples, including their altering of quotes from the scientific literature, false representations of published papers, etc." He stated that including Farber and Duesberg in this event "will, regrettably, discredit and demean your efforts to support the very real issues of recrimination against legitimate whistleblowers."

Justice York found Farber to be a "limited purpose public figure," which means that a defamation case can only be sustained if the alleged defamatory comments were malicious and knowingly false. Also, since HIV is a matter of public concern and debate, Jefferys would have to be shown to have been grossly negligent regarding the factual accuracy of his statements.

Justice York decided that Jefferys comments reflected his sincere and informed opinions and therefore met neither of these criteria. Justice York's full opinion, which is available on the New York Courts website [3], provides a potted history of the AIDS denialism controversy and Celia Farber's role within that controversy. But this decision is not a judicial verdict on AIDS denialism. Instead, it is a strong defense of freedom of speech on contested questions of public policy.

NY Law School Professor Arthur Leonard wrote: "In effect, Farber was contending that defamation law can be used to stifle criticism of a controversial position on a matter of great public importance."

This report is edited from Arthur S. Leonard's excellent detailed legal analysis of this case. [1]

References

1. New York Court Rejects Journalist's Defamation Claim Against AIDS Activist. (12 November 2011). http://newyorklawschool.typepad.com/leonardlink/2011/11/new-york-court-rejects-journalists-defamation-claim-against-aids-activist.html
2. Whistleblower Week In Washington (May 12-16 2008) http://web.archive.org/web/20080517225306/http://www.w3conference.org/contact.htm
3. Justice York, Supreme Court, New York. (09 November 2011). http://decisions.courts.state.ny.us/fcas/fcas_docs/2011NOV/3001063992009001SCIV.pdf

UK ban on HIV-positive doctors and dentists set to be overturned

On 24 November, The Independent Online reported that ministers are planning to launch a consultation later this year to examine whether it is justified to overturn the 20-year-old prohibition on doctors and dentists with HIV carrying out procedures that might potentially lead to blood contamination. It comes after a study of the evidence presented to the Chief Medical Officer concluded that the risk of transfer during any medical procedure was now negligible.

This is based the reduced infectivity associated with effective treatment together with high levels of infection control that are demanded of medical professionals that has resulted in much of Europe along with Australia and America having removed the restriction.

The article goes on to say that "sources in the medical profession say that even in Britain, where the ban is still in place, hospitals and dental surgeries have long operated a "don't ask, don't tell" policy with regard to practitioners who have HIV. They argue the policy is now clearly discriminatory as it can no longer be justified on public health grounds – despite the emotive nature of HIV."

Apparently the decision to launch the review comes after the Department of Health's Expert working group on AIDS and the UK Advisory Panel for Healthcare Workers Infected with Blood-borne Viruses both concluded that the risks could not justify the ban. They are believed to have told the Chief Medical Officer that the likelihood of any infection was as low as one case every 2,400 years.

Source: The Independent online. 24 November 2011.

http://www.independent.co.uk/life-style/health-and-families/health-news/ban-on-hivpositive-doctors-and-dentists-set-to-be-overturned-6267110.html

FILM REVIEW

We Were Here

Simon Collins, HIV i-Base

This moving documentary interviews five people who lived in San Francisco in the 1970s and who came through the HIV epidemic. It takes you slowly through their involvement and the impact of their experiences on their personal and professional lives.

The interviews are intercut with film, newspaper cuttings, newsreels and stills from hundreds of people who fought before HIV had a name and before there was treatment.

It is important and difficult to remember, that AIDS only happened this way once and involved creating a framework to understand an epidemic that was already widely established before it was discovered. By 1981, it was likely that at least 20% of gay men in San Francisco were already HIV-positive and by the time the first HIV test became available in 1985 this figure was likely to be higher than 50%.

In the 1970s, people moved to San Francisco to escape hatred and isolation of homophobia. As one of the five says “If you had a bus ticket, it had better be going to San Francisco” and “when you arrived you knew you were home”. To understand the film means feeling the optimism shared from finding life and friends and sexuality in a new age when pregnancy was preventable and sexual diseases were treatable.

Against a background, not just of political indifference, but active persecution and hatred, these narratives show the breadth of the human and social responses. Hundreds of examples make up the body of the film. Dancer and florist (Guy) who gave away flowers with gentle dignity to help people bury their friends and lovers. Or the sister of a patient who was unaware of how much she helped a nurse by saying “it makes me feel better knowing that you were with him (her brother) to treat him with respect and to treat his body with love”.

The medical reality of having to help people die rather than treat them back to health is shown by a nurse (Eileen) telling of how she had never before been in a room full of doctors who were sobbing because their patients had all died. “But we did the research because there was nothing else”.

The sole survivor from a study of a compound called surinin (Daniel), tells of how he discontinued the treatment early because it was impossible to tolerate, but also how his lover, a researcher working at a key HIV virology laboratory, had died from liver complications within three months of ending the study.

These histories are time and place specific. Gay men in San Francisco had one of the highest prevalence rates reported (soon after to be superseded by people with haemophilia dependent on blood products) at a time before treatment. It includes the community, social and political responses to fighting AIDS.

Light comes slowly “as people started hanging on” and then as effective treatment became a reality “they found a way through the storm”. This film is moving and it is sad, but it is not depressing. Each person has a gentle eloquence and takes you through their journey so you glimpse how this has lead to a greater understanding of life and a closer connection to people who in other circumstances many of them might never otherwise have known.

AIDS has happened thousands of times for every new country, region or town and in many different populations, each with their own story and against their own background. This film should encourage others to shows their histories. And millions of people have their own story of how HIV has and still does affect them personally, and who despite differences of background and experiences will be touched with each of these stories.

Taken together, the film will affirm and strengthen your own history with HIV. And for those coming to understand HIV for the first time it should give a historical perspective from a setting that is hard to imagine even if you were there. Its humanity should fire a response that recognises the importance of preventing infections in new generations and ensuring effective and affordable treatment for all becomes a global reality.

“We were here” was screened twice at the London Lesbian and Gay Film Festival earlier this year and has been touring festivals to much acclaim since. Six months later, it had its official UK launch, a couple of showings at the ICA in London and a benefit for the THT. If this film doesn’t come to a cinema near you, organise a group screening, or get the DVD, which was released on 5th December.

We Were Here, USA, 2011, 90 minutes.

Directed by David Weissman.

Released on DVD from 5th December on Peccadillo Pictures.

http://wewereherefilm.com/

http://peccapics.com/View/id,245

ON THE WEB

Online reports

Cure research: report from research workshop

A report from a community-initiated workshop on cure research, held in Baltimore in April 2011 is now online in PDF format.

http://www.treatmentactiongroup.org/cure/2011-workshop-report

The meeting included a focus on the following issues:

- If HIV eradication is the goal, how can this be proved when the best currently available tests may still miss the tiny residual amount of the virus that can bring the infection roaring back to life when antiretroviral drugs are withdrawn?
- If treatment interruptions are necessary, how can they be conducted safely in research participants when prevailing data suggest that even relatively short treatment interruptions can be harmful for some?
- If immune control of the virus is the objective, what kinds of changes in the immune system and inflammatory markers will tell us we are on the right track? and
- If early trials require participants to take greater risks with little hope of gain, how can we ensure that studies are ethical and guarantee that those taking the risks are fully informed?

Free full text online articles:

PLoS Medicine

Hallet TB et al. Optimal uses of antiretrovirals for prevention in HIV-1 serodiscordant heterosexual couples in South Africa: a modelling study. PLoS Medicine Volume 8(11) November 2011.

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001123
Timothy Hallett and colleagues use a mathematical model to examine the long-term impact and cost-effectiveness of different pre-exposure prophylaxis (PrEP) strategies for HIV prevention in serodiscordant couples.

Koenig SP et al. Cost-effectiveness of early versus standard antiretroviral therapy in HIV-infected adults in Haiti

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001095
In a cost-effectiveness study, Bruce R Schackman and colleagues compares early versus standard antiretroviral treatment (ART) for HIV, based on randomised clinical trial data from Haiti, revealing that the new WHO guidelines for early ART initiation can be cost-effective in resource-poor settings.

FUTURE MEETINGS

Conference listing 2012

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.

2nd International Workshop on HIV & Women

9–10 January 2012, Bethesda, USA

http://www.virology-education.com

19th Conference on Retroviruses and OIs (CROI)

5–8 March 2012, Seattle

http://retroconference.org

10th European HIV & Hepatitis Drug Resistance

28–30 March 2012, Barcelona, Spain

http://www.virology-education.com

13th Intl Workshop on Clinical Pharmacology of HIV Therapy

16–18 April 2012, Barcelona

http://www.virology-education.com

47th European Liver Conference (EASL)

16–18 April 2012, Barcelona

http://www.easl.eu

18th Annual BHIVA Conference

17–20 April 2012, Birmingham

http://www.bhiva.org

20th International HIV Drug Resistance Workshop

9–13 June 2012, venue tbc

http://www.informedhorizons.com/resistance2012/

7th International Workshop on HIV Transmission

19–20 July 2012, Washington

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

4th International Workshop on HIV Paediatrics

20–21 July 2012, Washington

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

19th IAS World AIDS Conference

22–25 July 2012, Washington

http://www.aids2012.org

11th International Congress on Drug Therapy in HIV

11–15 November 2012, Glasgow

http://www.hiv11.com

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

The i-Base website is designed with portals for healthcare professionals, HIV-positive people and community advocates.

It is fast and easy 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 100,000 pages 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 five booklets that comprehensively cover five important aspects of treatment. Each guide is written in clear non-technical language. All guides are free to order individually or in bulk for use in clinics and are available online in web-page and PDF format.

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

- Introduction to combination therapy (July 2010)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)
- Guide to changing treatment and drug resistance (February 2011)
- Guide to HIV, pregnancy & women's health (September 2011)
- HIV and quality of life: side effects & complications (December 2010)

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.

http://i-base.info/htb

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.

http://i-base.info/htb-south

HTB Turkey

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

http://i-base.info/home/hiv-tedavi-bulteni-htb-turkey/

ARV4IDUs

An electronic publication, Antiretroviral Treatment for Injecting Drug Users (ARV4IDUs) is produced in English and Russian language editions, to provide an overview of research related to IV-drug use and antiretroviral treatment.

http://i-base.info/idu

Treatment information needs of African people in the UK living with HIV

This report by Winnie Sseruma and i-Base includes an analysis from workshops held last year and details African use and experience of current treatment information resources.

http://i-base.info/home/africans-and-treatment-infomation

i-Base Book: "Why we must provide HIV treatment information"

Photography by Wolfgang Tillmans

i-Base has worked as a treatment literacy project for over ten years. Over this time we have always produced copyright-free material and encouraged other organisations to use, translate and adapt our material. Through this work, we have been very lucky to develop links to many other advocacy projects outside the UK.

A meeting, held in Cape Town focused on how to raise the profile of treatment literacy. One result from the meeting is a publication "Why we must provide HIV treatment information".

Text is provided by activists from 25 countries and 50 full 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.

More information about this process is available on the i-Base website.

In addition, PDF files of some of the translated publications are available on the i-Base site.

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

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 and Spanish.

Advocacy resources

Online advocacy training manual

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

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.

http://www.i-base.info/manual/en/index.html

The training manual was previously only available online as a PDF document and has been widely translated. Earlier editions are available in Russian, Portuguese, Hindi and Nepalese as are available as PDF files.

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 380 members from over 120 organisations. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

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 1500 questions online. Questions can be answered privately, or with permission, can be answered online.

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

Recent questions include:

- My CD4 and viral load has risen lately - should I be concerned?
- My CD4 is 350 but my doctor say to wait before starting treatment - should I be worried?

- I have a detectable viral load, should I change treatment ?
- How do I help my partner that infected me?
- Why does my CD4 count change between 175 and 185?
- I'm tired of meds, but people tell me to see a professional?
- My viral load is still detectable after 5 months on treatment
- Why does my CD4 count change over time?
- Will I get any symptoms if I do not take my med regularly?
- What do reactive negative/non-reactive results mean?
- What is the treatment for hepatitis C?
- How old is HIV?
- Can HIV medication cause miscarriage at 1 week?
- Why is my husband HIV negative when I am pregnant and HIV positive?
- Does drinking aloe vera interact with my meds?
- Do I need to continue taking cotrimoxazole prophylaxis?
- I'm just diagnosed with a CD4 count of 41? What does this mean?
- What does it means to measure cell counts in μl?
- Are these cholesterol results ok?
- Can you live with meds?
- Is a viral load "blip" caused by stress?
- Can I die from HIV if I'm on treatment. How long do I have to live?
- What causes my CD4 to drop from 220 to 30 in less than a month?
- I had PCP and my CD4 count has risen from 20 to 230 - can I stop taking prophylaxis meds?
- Are the dark patches on my skin HIV related?
- We are sero different couple - can I infect my negative partner? Does taking PEP helps to reduce infection?
- Is there any dating sites for positive straight men in london?
- Does my CD4 of 1000 means I was misdiagnosed?
- How long can I live without HIV drugs?
- Can my licence be returned because of my HIV status?
- I missed taking my medication for 4 days - can I develop resistance?
- I find it hard to take my meds at work - can I take a late dosage?
- I'm about to start my treatment - what should I do and how long do I have to live?
- Can I get a work visa for Australia if I'm HIV positive?
- Why am I being advised to have a vaginal delivery?

Other resources

Treatment 'Passports'

These popular booklets are for HIV-positive people - whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Like all i-Base 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.

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h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website:
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HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

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