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EDITORIAL

This issue of HTB includes over 25 reports from recent conferences including the recent BHIVA /BASSH conference in Manchester, summaries from the PK workshop in Italy (thanks to the Liverpool drug interaction report) and final reports from CROI held earlier in the year.

We also include news that the large international START study is now open and on the reliance on prompt enrollment into the pilot phase of the trial.

START has the potential to inform our understanding of the pathogenisis of HIV as much as it can answer the primary question of whether initiating treatment above a CD4 count of 500 is better than at 350–500 cells/mm3.

A community statement produced in response to the US DHHS guidelines affirms the importance of this study, and of its safety for participants. We encourgage healthcare workers to inform patients who have CD4 counts >500 when not on treatment, of the option to join this exciting research.

Over news coverage connects the global economic problems with the implications for HIV treatment and prevention programmes. Uganda is one of many countries where treatment programmes are reported to be closing to new patients. Over the last ten years the expansion of treatment access programmes have brought hope that treatments will keep them alive and healthy. These programmes provide the drive behind testing and prevention campaigns, and directly reduced transmission through reducing viral load and risk of infection. Sustainability of these programmes is crucial for treatment that is life-long.

The Global Fund are accepting applications for round ten funding, but this was far from certain earlier in the year. Concern over donor nations maintaining their funding commitments is raised in the report on US funding.

In most countries, HIV-positive people are from sections of the population that are already stigmatised or disenfranchised prior to acquiring HIV. An HIV diagnosis usually increases their vulnerability further. As members of some of the world's poorest and isolated citizens, these people will be most vulnerable to the downturn in the global economy.

Economic restrictions generate pressure that have the potential to inflame and divide societies in other ways.

We include articles about Uganda and Malawi that have both be widely covered in mainstream press, for the discrimination based on sexuality, specifically agsinst gay men, lesbians and transgender people.

Protecting these human rights and refusing to be complicit in this discrimination is inextricably connected with global programmes to provide great equality in access to medical treatment. Where HIV programmes have the opportunity to challenge this, they should use it.

It is timely that, as this issue of HTB went to press, the two men in Malawi had their prison sentences overturned. A concerted campaign will need to insist on similar prinicpals in the future if this single act of compassion is to impact on widespread legislation that continues to maintains broader discrimination.

CONFERENCE REPORTS

2nd Joint Conference of BHIVA with BASHH

20–23 April 2010, Manchester

Summary reports from this meeting include:

- HAART use among women in UK receiving treatment prior to conception
- Duration of ruptured membranes and vertical transmission in the UK
- Significant rates of unplanned pregnancies among young women born with HIV
- Route of HCV transmission in HIV-positive gay men is unlikely to be from semen
- Increase in LGV cases in gay men report in the UK
- 75% HIV-positive children have insufficient levels of Vitamin D
- High rates of osteopenia and osteoporosis: importance of DEXA monitoring
- Summaries of other studies

Abstracts from the conference are published as a supplement to the May 2010 edition of HIV Medicine; Volume 11, Supplement 1.

Until these are posted on the aegis.org conference abstract database, a PDF files abstract is:

http://www.aegis.org/conferences/BHIVA/2010/16BHIVA-2010.pdf

HAART use among women in UK receiving treatment prior to conception

Polly Clayden, HIV i-Base

HIV positive women in the UK are increasingly receiving HAART prior to conception and pregnancy.

BHIVA guidelines recommend that women already on treatment at conception remain on HAART throughout and after their pregnancy.

Some drugs, notably efavirenz (EFV), are not recommended for use during pregnancy.

Loveleen Bansi and colleagues from the UK CHIC Study and the National Study of HIV in Pregnancy and Childhood (NSHPC) analysed clinical and treatment patterns of women conceiving their first child on HAART between 1996 and 2008 using linked data from the two datasets.

The investigators found 1838 matches between the women in the current UK CHIC (n=8,659) and NSHPC (10,912) datasets. Of these, 821 (45%) had received HIV clinical care before their first pregnancy.

The majority of women were infected via heterosexual sex (88%) and over two-thirds (69%) were of black-African ethnicity. Their median age at delivery was 33 (IQR: 28-36) years.

Just over half, 440/821 (54%) women were receiving HAART at the time of conception of their first child.

Their median CD4 count at conception was 389 (IQR 270-554) cells/mm3. Amongst women who had a measurement up to 90 days before conception, 88 (27.9%) had a detectable viral load >50copies/mL.

Of the 440 women, 237 (53.9%) received an NNRTI and for 86 (19.5%) women this was EFV. Most women had not started treatment close to conception, 40.9% had already been on HAART for over 3 years and only 10.9% started less than 6 months before conceiving.

One-third (n=155 (35.2%)) made a switch in their regimen before delivery. The proportions of women switching therapy by 3 and 6 months of conception were 22% and 33%. Of those receiving EFV at conception, 37 (43%) of women switched this drug.

The vast majority (97%) of women receiving HAART at conception were also receiving HAART at delivery. After delivery 286/428 women switched regimen at a median of 15 (IQR 13-18) months.

The proportions of women switching regimen at 6, 12, 18 and 24 months were 27%, 41%, 55% and 61%, respectively. In the year following delivery 13 (13%) of women receiving HAART at delivery discontinued completely.

The investigators wrote; " Adherence support is important after pregnancy to minimise the number who interrupt or stop treatment after delivery."

C O M M E N T

The authors of this poster noted (personal correspondence) that they don't have information on when the woman found out she was pregnant, in relation to conception (or when she told her clinician). So, for women who were already on efavirenz at the time of conception, if they didn't find out they were pregnant until a few months into the pregnancy, it might be argued that any potential damage had already been done, and so there was less reason to switch.

The study also highlights the importance of post natal adherence support.

Ref: Bansi L et al. Use of antiretroviral therapy during and after pregnancy among HIV-infected women already aware of their infection before conceiving. 2nd Joint Conference of BHIVA with BASHH, 20–23 April 2010, Manchester. Poster abstract P154.

Duration of ruptured membranes and vertical transmission in the UK

Polly Clayden, HIV i-Base

Longer duration of rupture of membranes (ROM) was identified as a risk factor for mother to child transmission (MTCT) in the 1990s. Elective caesarean section prior to ROM was found to be protective. However, these studies were conducted before the availability of HAART.

Whether duration of ROM has clinical implications for women on effective HAART is unclear. An increasing number of women in the UK opt to deliver vaginally but, of these, a high proportion, undergo emergency caesarean section. It is likely that concern over ROM contributes to this management decision.

In an oral presentation at the 2010 BHIVA/BASHH meeting, Pat Tookey showed findings from an investigation, using routine surveillance data from UK and Ireland, to explore the association between duration of ROM and transmission. Surveillance of obstetric and paediatric HIV is conducted through the National Study of HIV in Pregnancy and Childhood (NSHPC). Data on ROM have been collected since January 2007.

In this study, the investigators reviewed pregnancies resulting in live singleton births among HIV-positive women reported in 2007-9.

During this period, 2686 births were reported. The majority (95%) of mothers were on HAART; 40% had an elective caesarean section, 34 had vaginal delivery and 26% emergency caesarean section. Almost Three quarters of mothers (74%) had an undetectable viral load and the rate of mother to child transmission was 0.9% (15/1697).

Of the total, 1063/2686 mothers had an elective caesarean and data were missing for 298. There were ROM data for 1325, of which 884 (67%) had ROM prior to delivery and data on duration was provided for 661 (75%). The median duration was 4 hrs (IQR 1.5-8), ≤6hrs for 444 (67%), >6-48 hrs for 217 (33%), this included 16 mother with >48 hrs ROM.

There were 6/421 (1.4%) transmissions overall, among the infants with confirmed HIV status. The rate was similar for infants with ≤ 6 hrs ROM, 2/284 (1.4 compared to those with >6 hours, 2/137 (1.5%), OR 1.0 (95%CI 0.2-5.7, p=1.0)

In the sub group of women with undetectable viral load (<50 copies/mL) near delivery (99.7% on HAART), there was no difference in MTCT (overall 1/341, 0.3%), between those with ROM for >6 hrs compared to ≤6 hrs (0/112, 0.4% vs 1/229, 0.0%, p=1.00). Likewise, among mothers with undetectable viral load who had a planned vaginal delivery (overall 1/203, 0.5%: 0/52, 0% vs 1/151, p=1.0).

Six of the 661 children had confirmed infection at the time of analysis including 3 likely in utero transmissions (positive PCR on Day 1, see Table 1).

Table 1: Six children infected with HIV who were born to women with ROM before delivery

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
ROM (hrs/mins)	12.45	4.00	3.29	5.50	6.50	4.37
Mode of delivery	EMCS	Vaginal	EMCS	EMCS	EMCS	Vaginal (unplanned)
Gestational age (week)	38	40	36	39	40	37
HAART (start week)	Yes (33)	Yes (17)	Yes (17)	Yes (22)	Yes (21)	Yes (32)
Maternal viral load *	330	<40	48,230	71, 500	122,040	23, 460
1st positive PCR	Day 1	16 weeks	Day 1	6 weeks	Day 4	Day 1

* closest to delivery. Note: Patients 1, 5 and 6 had reported adherence issues.

The investigators concluded that although data are sparse to date, so far there is no evidence that among women on HAART longer duration of ROM is associated with an increased risk of MTCT. Larger sample sizes are required and comprehensive data on: ROM and duration of ROM, infant infection status and viral load close to delivery. Continuing monitoring is essential.

Ref: Haile-Selassie H et al. Duration of ruptured membranes and vertical transmission of HIV: data from national surveillance in the UK and Ireland. 2nd Joint Conference of BHIVA with BASHH, 20–23 April 2010, Manchester. Oral abstract O2.

Significant rates of unplanned pregnancies among young women born with HIV

Winnie Sseruma, HIV i-Base

There is little research and information reported on young women growing up with HIV. But a study at the meeting showed some interesting data on the pregnancy outcomes of young women who were born with HIV 10–20 years ago. The study looked at a cohort of 172 women, born with HIV and accessing services in 19 centres across the UK and Ireland.

Overall, there were 36 pregnancies reported in 27 women, with a median age of 18 years at first pregnancy. Of these, 27 (75%) were unplanned, 7 (19%) were planned and 2 were unknown. The women all conceived before September 2009. Seventeen women were on HAART, with a median CD4 count of 244 cells/mm3, but 8 out of the10 women who were not on treatment had CD4 counts below 200 cells/mm3.

Of the reported pregnancies, 86% (31/36) were with regular partners, of whom 22 (61%) reported being unaware of their partners HIV status. The pregnancies resulted in 5 (14%) 1st trimester miscarriages, 9 (25%) elective terminations, 18 (50%) live births and 4 (11%) pregnancies were ongoing.

At the time of delivery, 89% of the mothers were on HAART, with a median CD4 count of 254 cells/mm3 and a median viral load of 79 copies/mL (range <50–580,000). Seven women delivered with viral load <50 copies/mL, four had VL >1,000 copies/mL. Two women were admitted for Directly Observed Therapy and two were non-adherent to HAART at delivery. Mode of delivery was 9 elective and 5 emergency C-sections with 4 vaginal deliveries. 6 (33%) infants delivered at <37/40, five of whom required Neonatal Intensive Care. None of the babies were infected and there were no congenital anomalies were reported. Five of the babies were fostered and 3 have ongoing concerns.

The study showed without a doubt, that prevention of mother to child transmission worked, even though some mothers had advanced HIV and were not well adherent. Additionally, the study also highlighted a worrying high number of unplanned pregnancies, a population with social needs despite access to contraceptive services.

Ref: Williams B et al. Pregnancy outcomes in women growing up with HIV acquired perinatally or in early childhood. 2nd Joint Conference of BHIVA with BASHH, 20–23 April 2010, Manchester. Poster abstract P144.

Route of HCV transmission in HIV-positive gay men is unlikely to be from semen

Simon Collins, HIV i-Base

The mechanism for high rates of hepatitis C (HCV) transmission in HIV-positive gay men is unknown with little data on whether HCV levels in semen had a similar risk factor to HIV viral load, especially during acute infection.

Joanna Turner and colleagues presented a key study to inform this field.

Paired blood and semen samples were collected from 5 acute and 9 chronic HCV cases in HIV-positive men. At baseline 0/5 acute and 2/9 chronic cases had detectable HCV RNA in semen. Of all samples tested 2/10 (20%) of acute cases and 4/23 (17%) of chronic cases (p=NS) had detectable HCV RNA in semen.

However, when detected, HCV RNA viral loads were low: <30 IU/ml (acute cases) and <230 IU/ml (chronic cases) and did not correlate with plasma HCV viral load

Taken together, this lead the researcher to suggests that the quantity of seminal HCV virus is not a significant factor in determining the rate of HCV transmission, even during acute infection. Recruitment to the study is ongoing.

Ref: Turner J et al. Hepatitis C viral load in semen of HIV-positive men during acute and chronic hepatitis C infection. Oral abstract O5

Recent increase in LGV cases in gay men in the UK

Simon Collins, HIV i-Base

The first ever 'late breaker' presentation for a BHIVA meeting was included to report a rapid increase in the number of cases of Lymphogranuloma venereum (LGV) reported to the Health Protection Agency (HPA) over winter 2009/10.

Diagnoses were 91% higher for November 2009 to January 2010 than in the previous three months (88 vs 46 cases), and 115% higher than that seen in the same period in 2008/09 (41 cases).

Since 2004, outbreaks amongst MSM have occurred in major cities in Europe, with 1,070 cases in the UK, mainly in London and to a lesser extent in Brighton and Manchester. LGV, which is caused by the L serovars of Chlamydia trachomatis, is endemic to areas of Africa, Asia, South America and the Caribbean.

The understanding of the epidemiology and mode of transmission of LGV remains poor, with only a small number of asymptomatic cases detected. Urethral infection is uncommon and, whilst infected individuals have high risk sexual behaviour and links to sex toys and sex parties have been described, no definitive associations have emerged.

Unlike other forms of C. trachomatis, LGV is invasive. Most cases seen in the UK have presented with proctitis but symptoms vary according to the site of infection and may include ulcers and inflamed and swollen lymph nodes in the groin (inguinal syndrome). If left untreated symptoms can become more severe and cause lasting damage to health. Treatment with three weeks of doxycycline BD 100 mg is recommended by BASHH.

Information posted to the HPA website, includes the following recommendations for limiting further spread.

- Testing for LGV should be offered during routine clinical care to HIV positive MSM who have symptoms of LGV infection and have a positive test for C. trachomatis;
- MSM should have a full sexual health screen annually. This should include testing for HIV where it is not already diagnosed;
- Behavioural modification is a key component of control strategies. Campaigns that increase awareness and knowledge of STIs and promote safer sex need to be intensified.

Several posters at the conference related to LGV.

Pallawela and colleagues from five clinics in London and Brighton presented results from a six-month pilot screening programme in 98 men who were newly diagnosed with HIV, HCV or syphilis and who were routinely offered testing for urethral and, if indicated, rectal Chlamydia. [2]

Of the 82 men (84%) who were screened within 4 weeks, 40 (49%) were newly diagnosed with HIV, 36 (44%) with syphylis and 8 (10%) with hepatitis C. Rectal Chlamydia was diagnosed in 13/82 (16%), of whom one also had urethral Chlamydia, and two with urethral Chlamydia only. No cases of LGV were found.

Dosekun and colleagues from St Thomas' Hospital, London, which was also one of the five centres reported above, included a case report of pharyngeal LGV in a 26-year old HIV-positive gay man. [3]

He presented in April 2009 with rectal discharge and constipation, but reported no symptoms of urethritis or sore throat. Sexual history included recent protected anal and unprotected oral receptive and insertive sex with casual male partners. He was on antiretroviral therapy with a CD4 count of 627 cells/mm3 and undetectable viral load (<40copies/mL).

On examination he had florid proctitis with haemopurulent exudate. A rectal swab was positive for Chlamydia trachomatis (CT) and pharyngeal swab showed an equivocal CT result. Both specimens had LGV-specific DNA detected in laboratory analysis.

He was treated for proctitis with cefixime 400mg stat and a 21-day course of doxycycline 100mg bd. His rectal symptoms resolved with treatment and a pharyngeal CT test of cure at 6 weeks was negative.

Although most cases have been rectal, the authors reported this as the first documented case of LGV- associated CT DNA detected from the pharynx in the current UK outbreak. Reported risk factors for LGV acquisition suggest that transmission is predominantly rectal-to-rectal via intermediate carriage on hands or fomites. This case highlights possible transmission via orogenital contact.

References:

1. Substantial increase in cases of Lymphogranuloma venereum (LGV) in UK. Oral late breaker.
   See also online HPA report:
   http://www.hpa.org.uk/hpr/archives/2010/news0810.htm#lgv
2. Pallawela S et al. Screening for asymptomatic LGV coinfection in MSM newly diagnosed with HIV, hepatitis C or infectious syphilis. 2nd Joint Conference of BHIVA with BASHH, 20–23 April 2010, Manchester. Poster abstract P187.
3. Dosekun G et al. Case report: asymptomatic LGV detected from the pharynx of a London MSM. 2nd Joint Conference of BHIVA with BASHH, 20–23 April 2010, Manchester. Poster abstract P203.

75% HIV-positive children have insufficient levels of Vitamin D

Simon Collins, HIV i-Base

Although the interpretation of the role HIV and vitamin D deficiency remains a focus in HIV-positive populations in relation to reductions in bone mineral density in adults, the impact on children is potentially more worrying. If HIV-related complications prevent optimum bone development earlier in life (generally until the age of 30), this could result in higher rates of bone complication in later in life.

Atkinson and colleagues presented results of such low vitamin D levels in HIV-positive children that suggest further research should be an urgent priority.

An audit of plasma bone biochemistry, 25(OH) vitamin D and PTH levels in a cohort of 131 HIV-positive children receiving routine clinical care at a single UK centre between January and December 2009. Median age was 12 years (IQR 9, 15); 51% were female and 85% were African/Caribbean. Median CD4 count (%) was 760 (32%) and 104 children (79%) were on HAART.

64 children (49%) were deficient (defined as 25nmol/L) and a further 37 (28%) had insufficient levels (25-50nmol/L). Abnormal PTH (>6.8 pmol/L) was seen in 15/52 children who had these levels (28.9%).

In multivariate analysis 25(OH) vitamin D deficiency was associated with older age (p=0.001), African/Caribbean ethnicity (p=0.04), winter season (0.008) and NNRTI use (P=0.01).

The authors concluded that Vitamin D deficiency and insufficiency is very common in children with HIV. Maximising bone health is increasingly important as this population enter adult life and the role of vitamin D supplementation requires further elucidation.

Ref: Atkinson S et al. Vitamin D deficiency in children with perinatally acquired HIV-1 infection living in the UK. Poster abstract P159.

High rates of osteopenia and osteoporosis: importance of DEXA monitoring

Simon Collins, HIV i-Base

Bone disease was addressed in many of the posters, with the first of these reports coming from Guys and St Thomas' and the remaining three from the Chelsea and Westminster Hospital.

Perry and colleagues from reported results of a cross-sectional study of 175 randomly selected HIV-positive patients who completed lifestyle and general health questionnaires that were compiled with biochemical analyses and DEXA lumber spine and hip. [1]

Baseline characteristics included median age 38 years (IQR 30-43); 64% male, 41% black, 85% ARV-experienced, 31% current smokers.

DEXA results showed 49% patients had reduced BMD, 13% with osteoporosis and 36% with osteopenia. Age increased the association (p=0.007) occurring at a median age of 44.50 years (IQR 38–51 years) but not gender, with osteoporosis diagnosed in approximately 10% of patients aged 40-49 and 20% in those aged >50 years. (See Table 1).

Table 1: BDM results by gender and age

	Men		*Women*	
age	***osteoporosis***	***osteopenia***	***osteoporosis***	***osteopenia***
30-39	***8.3%***	***33.3%***	***0%***	***14.3%***
40-49	***11.8%***	***43.1%***	***8.8%***	***26.5%***
>50	***20.5%***	***34.1%***	***21.4%***	***57.1%***

In multivariate analysis, other risk factors were low BMI (OR 0.87; 95%CI 0.79–0.95; p= 0.003) and ever having been on HAART

(OR 4.43; 95%CI 1.57–12.50; p= 0.005). Gender, ethnicity, HIV viral load, CD4 cell count, CD4 cell count nadir and vitamin D were not statistically associated with abnormal BMD.

In their conclusion the authors highlighted the high proportion of patients with HIV from young age groups, and a significant correlation with HAART and that this may provide a rationale for routine screening for risk factors that predict fracture in HIV, including low BMD.

Stuart-Buttle and colleagues reported results from a retrospective audit of 106 patients who had DEXA scans from 2007–2009. [2]

12% had osteoporosis, 30% had osteopaenia and 58% had normal DEXA scans. Of the 44 patients over 50 (mean age 58.1 ±7.02), 36% had a diagnosis of osteoporosis and 41% had osteopaenia, compared to 28% and 5%, respectively, in the group under 50 years.

While this was a retrospective study, presumably in patients selected for DEXA bone concerns, the researchers concluded that HIV should be considered a risk factor and that including HIV-positive people >50 years need to be included in screening studies. No significant correlation between bone mineral density and CD4 count, calcium or vitamin D levels.

Hughes and colleagues presented results from a new 'over 50s clinic' that was set up in January 2009. Of 54/70 patients with DEXA results (4 patients were excluded due to with diagnosed bone disease), osteopaenia was diagnosed in 24% (13/54) and osteoporosis in 11% (6/54). Of these, 77% (10/13) with osteopaenia and 100% (6/6) with osteoporosis were male. [3]

The mean age was 60 years, 93% (50/54) were male and 85% (46/54) of white ethnicity. All patients were taking ART (100% VL <50, mean CD4 551 cells/mm3).

Low vitamin D levels occurred in 66% (4/6) with osteoporosis, 38% (5/13) with osteopaenia and 49% (17/35) with normal DEXA result. With over one third of this cohort with osteopaenia or osteoporosis, the authors concluded that this supported routine screening in individuals aged over 50.

Finally, Rashid and colleagues, prospectively measured Vitamin D levels (25(OH) vitamin D) in 312 patients in July 2009. [4]

Mean age was 48 years (range 25-83), 88% male, mean duration of HIV infection 12 years (range 0-26). Median vitamin D level was 66nmol/L (range <10-221) with 35% levels low (40-70nmol/L) and 21% deficient (<40nmol/L). Low Vitamin D correlated with non-caucasian ethnicity (p<0.001) and female sex (p<0.001), but not antiretroviral class or specific agent, including efavirenz.

Of note, in 102 patients (33%) who had DEXA scans for unrelated reasons, median vitamin D levels were 71, 71 and 58 nmol/L for those with normal, osteopaenic and osteoporotic results respectively.

The lack of association of low vitamin D levels with DEXA results, and also with alkaline phosphatase levels, suggest the importance of larger definitive studies to inform patient management in this area.

References

All references are to the Abstracts of the 2nd Joint conference of the BHIVA and BASHH, 20–23 April 2010, Manchester.

1. Perry M et al. The relationship of HIV and bone density: implications for screening. Poster abstract P44.
2. Stuart-Buttle C et al. Screening for bone disease in HIV patients. Poster abstract P46.
3. Hughes A et al. Over 50? It's time for a dual energy x-ray absorptiometry (DEXA) scan. Poster abstract P39.
4. Rashid T et al. No association of vitamin D levels with individual antiretroviral agents, duration of HIV infection, alkaline phosphatase levels or bone mineral density findings. Poster abstract P45.

Summaries of other studies

Simon Collins, HIV i-Base

Many other studies at the conference deserve further reporting but can only be briefly summariesed here. For full details please refer to the conference abstracts and contact the lead authors.

Transmission and late diagnosis in older people: half of late diagnoses in people over 50 years old

An oral presentation from the Health Protection Agency highlighted some aspects of how older people are affected by HIV. The number of older adults who are HIV-positive in the UK from 2333 in 2000 to 8268 in 2007, accounting for 16% of adults accessing care in 2007 and 8% of all HIV diagnoses between 2000–2007. [1]

Compared to younger adults, newly diagnosed adults aged 50 years and over were more likely to be men (74% vs. 58%; p<0.001), infected through sex between men (40% vs. 34%; p<0.001) and of white ethnicity (60% vs. 38%; p<0.001). Older heterosexuals adults were more likely to be infected within the UK (16% vs. 12%; p<0.001), with evidence of travel abroad amongst white heterosexual men.

Late diagnosis (CD4 count <200) was significantly higher amongst older adults (48% vs. 33%; p<0.001); with older MSM being twice as likely to present late than younger MSM.

This study estimated that nearly half (48%; 1486) of persons diagnosed between 2000 and 2007 acquired their infection aged 50 and over.

Ref: Smith R et al. Refocusing our efforts – transmission and late diagnosis of HIV among adults aged 50 and over. Oral abstract O3.

Ocular syphilis at first presentation of HIV

Three cases were described where ocular syphilis was the presenting symptom: a 33-year old heterosexual man, a 20-year old gay man, and a 39-year old gay man. The study concluded: "Syphilis should be excluded in cases of uveitis and optic neuritis; other features of secondary syphilis may be absent. All patients had improving visual symptoms after neurosyphilis therapy, and had preceding oral steroids to prevent Jarisch-Herxheimer reaction, as this can worsen ocular symptoms. Early diagnosis is important as ocular syphilis can rapidly cause blindness.

Ref: Dhairyawan R et al. Ocular syphilis as the first presentation of HIV infection. Poster abstract P132.

Perinatally infection diagnosed in late adolescence

Two cases of extremely late diagnosis, in a young man and woman, both 20-year old Ugandan patients, presenting with multiple complications, including HIV-related dementia. These rare cases highlight the importance of family history and HIV testing in children and young adults who were potentially exposed to HIV during pregnancy and at birth.

Ref: Ross S et al. Vertical HIV infection in young adults presenting with HIV-associated dementia. Poster abstract P169.

CONFERENCE REPORTS

11th International Workshop on Clinical Pharmacology of HIV Therapy

7-9th April, 2010, Sorrento, Italy

Introduction

Summary reports from this workshop included below have been selected from a comprehensive report from the Liverpool pharmacology group.

The full report is available in PDF format:

http://www.hiv-druginteractions.org/new/Uploaded_Attachment/82_11%20PKW%20Sorrento.pdf0

Reports in this issue include:

- Atazanavir absorption maximised with food
- Methadone levels reduced moderately by rilpivirine
- Maraviroc 150mg once-daily achieves target concentrations with atazanavir/ritonavir
- Raltegravir and unboosted atazanavir
- Raltegravir dose adjustment not required for patients on dialysis
- Raltegravir and darunavir pharmacokinetics in liver disease
- Tenofovir may require closer renal monitoring in older patients
- Effect of age on atazanavir, darunavir, raltegravir and etravirine
- TDM targets for raltegravir
- Impact on billirubin levels when atazanavir is dosed twice-daily

Selected abstracts and presentations from the 2010 workshop are now on the Virology Education website:

http://regist2.virology-education.com/11th/7_april.html

Atazanavir absorption maximised with food

The impact of food on atazanavir/ritonavir (300/100mg once-daily) was assessed in 12 HIV-positive volunteers. When given without food, atazanavir AUC, Cmax and Ctrough decreased by 41%, 32% and 53%, respectively. Ritonavir AUC and Ctrough decreased by 26% and 53%; Cmax increased by 4%. One patient had atazanavir Ctrough below target (<150 ng/mL), but no patients showed evidence of virologic failure.

C O M M E N T

This study indicates that food maximises the absorption of atazanavir and supports the recommendation to take atazanavir/ritoanavir with food.

Ref: Giguerre P et al. The effect of food on the pharmacokinetics of atazanavir/ritonavir 300/100mg daily in HIV-infected patients. 11th PK Workshop, 2010. Abstract 30.

Methadone levels reduced moderately by rilpivirine

The effect of TMC278 (25 mg once daily) on the pharmacokinetics and pharmacodynamics of methadone was studied in 13 HIV negative volunteers stable on methadone maintenance therapy (60-150 mg/day). TMC278 decreased the AUC, Cmax and Cmin of active R-methadone by 16%, 14% and 22%, respectively. Decreases were also seen in the AUC (16%), Cmax (13%) and Cmin (21%) of inactive S-methadone. Exposure of TMC278 in the presence of methadone was within the expected range. No signs of opiate withdrawal were observed.

C O M M E N T

Although no a-priori dose adjustment of methadone is required, clinical monitoring for withdrawal symptoms is recommended as some patients may require dose adjustment.

Ref: Crauwels HM et al. Pharmacokinetic interaction study between TMC278, a next-generation NNRTI and methadone. 11th PK Workshop, 2010. Abstract 33.

Maraviroc 150mg once-daily achieves target concentrations with atazanavir/ritonavir

The pharmacokinetics of maraviroc (150 mg once daily) and atazanavir/ritonavir (300/100 mg once-daily) were assessed in a pharmacokinetic sub-study of 15 HIV-positive volunteers. All subjects achieved, or exceeded, the targeted maraviroc Caverage of 75 ng/ml. Steady state values for maraviroc AUC, Cmax and Cmin were 4330 ng.h/ml, 650 ng/ml and 37 ng/ml, respectively. Efficacy and safety of this combination are currently being evaluated.

Ref: Vourvahis M et al. Pharmacokinetics of QD maraviroc co-administered as part of a novel NRTI-sparing regimen with atazanavir/ritonavir in HIV treatment-naïve patients. 11th PK Workshop, 2010. Abstract 37.

Raltegravir and unboosted atazanavir

Coadministration of raltegravir (400 mg twice daily) and unboosted atazanavir (300 mg twice daily) was studied in 22 HIV-positive volunteers. Raltegravir pharmacokinetics were compared to historical data from HIV-positive volunteers receiving 10 day raltegravir monotherapy.

Raltegravir geometric mean AUC with atazanavir was 6166 ng.h/ml and was comparable to historical controls (6851 ng.h/ml). Atazanavir exposure showed high inter subject variability with a geometric mean AUC of 14622 ng.h/ml and a CV of 68.3%. Linear regression showed a highly significant correlation between raltegravir AUC and atazanavir AUC: subjects with atazanavir AUC >14622 ng.h/ml had a two-fold increase in raltegravir AUC. A similar trend was observed for trough concentrations.

Overall, unboosted atazanavir did not significantly increase raltegravir exposure, although subjects with higher atazanavir exposure had higher raltegravir concentration.

C O M M E N T

Raltegravir pharmacokinetics are variable and this is a cross study comparison; therefore we need to be cautious in interpreting the data.

Ref: Cattaneo D et al. Exposure-related effects of unboosted atazanavir on the pharmacokinetics of raltegravir in HIV-1 infected patients. 11th PK Workshop, 2010. Abstract 49.

Raltegravir dose adjustment not required for patients on dialysis

The effect of haemodialysis on raltegravir clearance was evaluated in two anuric end stage renal disease HIV-positive patients.

Predialyzer (C_in) and postdialyzer (C_out) blood samples were collected at the beginning and end of a single 4 h dialysis session and the haemodialysis extraction ratio (ER) was calculated using (C_in - C_out)/C_in. Raltegravir dialysis clearance (CLd) in terms of plasma was calculated using ER x Qp, where Qp is plasma flow through the dialyzer.

At the end of the session, raltegravir concentrations decreased by 68% in patient 1 and by 45% in patient 2. However, ER and CLd were only 5.5% and 9.1 mL/min in patient 1, and 9.5% and 19.1 mL/min in patient 2, respectively. Both patients maintained raltegravir concentrations higher than 15 ng/mL at the end of the dialysis session.

C O M M E N T

These results show minimal removal of raltegravir by haemodialysis and dosage adjustments of raltegravir may not be required.

Ref: Molto J et al. Effect of hemodialysis on raltegravir clearance in HIV-infected patients with end stage renal disease.11th PK Workshop, 2010. Abstract 7.

Raltegravir and darunavir pharmacokinetics in liver disease

The pharmacokinetic profiles of darunavir and raltegravir were analysed in five HIV/HCV coinfected patients with moderate to severe liver disease. Based on the ultrasonographic and histological evaluation, two patients had HCV-related chronic active hepatitis, and three patients had a diagnosis of cirrhosis (Child Pugh stage B). Trough concentrations were determined 14 and 30 days after starting a raltegravir/darunavir containing regimen.

Mean raltegravir and darunavir trough concentrations in the hepatic impairment group was 637 (mean Ctrough in control group: 221±217 ng/ml) and 8519 ng/mL (mean Ctrough in control group: 3236±2183 ng/ml), respectively. In a sub-group analysis, patients with cirrhosis had higher mean raltegravir Ctrough than patients with active non cirrhotic hepatitis (665 vs 581 ng/mL). The mean darunavir Ctrough was consistently higher in cirrhotic than non cirrhotic patients (9820 vs 2016 ng/mL).

C O M M E N T

The data suggest special caution in the use of raltegravir, and especially of darunavir, in patients with moderate to severe liver impairment because of the risk of additionally increased toxicity.

Ref: Tommasi C et al. Raltegravir and darunavir plasma pharmacokinetic in HIV-1 infected patients with advanced liver disease.11th PK Workshop, 2010. Abstract 10.

Tenofovir may require closer renal monitoring in older patients

The impact of age on tenofovir-related effects on estimated glomerular filtration rate (eGFR) were explored in a retrospective analysis of 1031 HIV-positive subjects receiving tenofovir as part of their antiretroviral regimen. Serum creatinine values were used to compute eGFR by the MDRD method.

The average eGFR at baseline was 112.7 ml/min and the median age was 43 years.

In a univariate analysis, there was a decrease in eGFR of 0.016 ml/min for each day of tenofovir use, an effect that persisted after controlling for age, baseline MDRD, race and gender. When age was added to a model controlling for days of tenofovir use, eGFR decreased by 0.638 ml/min for each year increase in age.

Individuals >50 years had an average eGFR 16 ml/min lower than individuals <50 years, which reduced to 4 ml/min lower than those <50 years after controlling for baseline eGFR. When subjects were further stratified by age (<30, 30-45, >45 years), individuals aged 30-45 had an average eGFR 9.54 ml/min less compared to those <30; individuals >45 had an average eGFR 11.9 ml/min less than those <30 years, after controlling for eGFR at baseline.

C O M M E N T

The authors of this study concluded that tenofovir may require closer monitoring in older individuals.

Ref: Goeddel L et al. Effect of Age on Renal Function with TDF. 11th PK Workshop, 2010. Abstract 38.

Effect of age on atazanavir, darunavir, raltegravir and etravirine

Trough concentrations of atazanavir, darunavir, raltegravir and efavirenz were compared in HIV-positive volunteers, grouped according to age (A: ≤39, B: 40-49, C: ≥50 years). A total of 249 samples were analysed from 134 subjects (28 ATV/r, 40 DRV/r, 47 RAL, 19 EFV).

Atazanavir mean trough concentrations were lower in group C than group A, but this was not statistically significant (1483 vs 1968 vs 1013 ng/ml, A vs B vs C). Darunavir mean concentrations were similar across the three groups (2633 vs 3077 vs 2581 ng/ml, A vs B vs C), as were raltegravir concentrations (210 vs 263 vs 177 ng/ml, A vs B vs C). Efavirenz mean concentrations were significantly higher in group C (2950 ng/ml) than in group A (2148 ng/ml) or group B (2097 ng/ml).

No linear correlation between age and concentration was found for any drug.

C O M M E N T

There are few data on the metabolism of antiretroviral drugs and it may be important to study people who are older than 60, as CYP450 activity does reduce with age.

Ref: Tommasi C et al. Pharmacological evaluation of new antiretroviral drugs in the elderly HIV-1 infected people. Tommasi C, Nicastri E, Gallo AL, et al. 11th PK Workshop, 2010. Abstract 56.

Proposed approach to measuring TDM for raltegravir

Clinical studies have shown that the virological response to raltegravir is not linked to trough concentrations, but relates to AUC or "GMall" (geometric mean of all concentrations over 48 weeks). However, obtaining a full AUC over the dosing interval is not practicable in clinical practice and so the use of alternative measurements were investigated.

Plasma concentrations and full AUCs were obtained from 47 HIV-negative volunteers receiving raltegravir (400 mg). Trough concentrations were not significantly related to AUC0-12h or GMall. The best single time point correlation with AUC0-12h was found with C2h (R2=0.815), but a stronger correlation (R2= 0.929) was found with AUC0-3h.

C O M M E N T

Assuming AUC to be the important PK parameter for raltegravir, then TDM should preferably use C2h or an abbreviated AUC0-3h to estimate reliably AUC0-12h, but these observations should be tested prospectively in a patient data set.

Ref: Burger D et al. AUC0-3h of raltegravir is correlated to AUC0-12h: a novel approach for therapeutic drug monitoring of raltegravir. 11th PK Workshop, 2010. Abstract 41.

Increased bilirubin levels when atazanavir is dosed twice-daily

The changes in total, conjugated and unconjugated bilirubin were studied in 10 HIV+ subjects who switched from atazanavir 400 mg once daily to atazanavir 200 mg twice daily.

Total bilirubin at Ctrough and AUC24 were slightly increased after switch (31% and 15%, respectively), while maximum total bilirubin was unchanged. Similar increases were observed for unconjugated bilirubin at Ctrough and AUC24, while maximum unconjugated bilirubin was unchanged.

The increases in bilirubin levels related to the switch from once to twice daily dosing were not clinically significant and the data suggest that the increase in unconjugated bilirubin associated with atazanavir administration is rapidly reversible.

Ref: Gonzalez de Requena D et al. Bilirubin levels in HIV+ patients switching from atazanavir (ATV) 400 mg QD to ATV 200 mg BID. 11th PK Workshop, 2010. Abstract 42.

CONFERENCE REPORTS

17th Conference on Retroviruses and Opportunistic Infections (CROI)

16-19 February 2010, San Francisco

Introduction

The 17th Conference on Retroviruses and Opportunistic Infections (CROI), one of the most important annual HIV meetings, was held this year from 16-19 February. As with previous meetings, much of the conference is published online including all abstracts and webcasts of oral presentations including selected poster discussions.

Making this scientific content available without login or subscription is itself a significant achievement. It is a model for broadening access to medical research to a degree that is currently unmatched by any other meeting.

The webcasts this year include oral presentations, poster discussions, the opening lectures and the pre-meeting set of training workshops for young investigators.

The conference website also includes a searchable abstract database.

We encourage readers to view these lectures directly.

http://www.retroconference.org/2010/Abstracts/38289.htm

http://www.retroconference.org/2010/data/files/webcast_2010.htm

Lectures are also available as audio downloads and podcasts which include slides as audiobooks.

New articles continuing our coverage of this meeting are:

- HIV reinfection cases reported at CROI
- Hepatitis studies: IL28B genetics, HCV survival, FibroScan in acute HCV, MSM reinfection and responses to transplantation
- Poor bioequivalence with crushed and dissolved tablets

- Initial PK, safety and 12 week efficacy of raltegravir chewable tablets in children 6-11 years
- PK of efavirenz in children dosed according to WHO weight bands
- Virological and immunological responses in infants enrolled in the CHER trial
- Darunavir-associated mutations in PI-naive and PI-experienced children in the UK

HIV reinfection cases reported at CROI

Simon Collins, HIV i-Base

A poster discussion session included studies looking at different aspects of dual infection and reinfection and included two case studies that showed where this had a clinical outcome. Two other studies, one from London and one from San Francisco, reported on aspects of dual infections.

Erika Castro from University of Vaudois Hospital, Lausanne, and colleagues presented a useful case of reinfection between two men (M1 and M2) who had been sexual partners since 2006. [1]

M1 was initially diagnosed in 2000 during primary infection and had been suppressed on HAART through to 2007 with no history of drug resistance. M2 had been on HAART for five years with detectable viral load (range 3–4 log) and documented triple class resistance. In February 2008, viral load in M1 rebounded to 280 copies/mL and continued increasing. Resistance and phylogenetic tests were compared from 2000 and 2008 (86 sequences: whole-genome (n=28), env (n=28), and *gag* (n=25).

All sequences were sub-type B. The genotypic analysis from 2008 showed 25 new related drug resistance mutations in M1 (11 in RT and 14 in protease), of which 23 were also present in M2. Additionally, M1-2008 sequences clustered within the M2-2008 branches and distinct from M1-2000 sequence clusters in all trees. Recombination between the original M1 and M2 strains was not observed, with M1 being replaced with M2 sequences following superinfection.

The case is important for highlighting several aspects of HIV reinfection:

- That reinfection can occur in established infection.
- That it can occur between regular partners (that no immune protection develops to repeated exposure to one virus).
- That reinfection can occur after several years of exposure (as with initial infection, chance and probability are low).
- That there is a clinical risk from reinfection when partners have different resistance profiles (most reinfection cases are only discovered because of unexplained viraemia in stable patients).
- That ART did not offer protection against reinfection, probably because any PEP effect would be negligible if the new MDR virus was resistant to the ARVs in that combination.

Martine Braibant from University de Tours Hospital and colleagues presented another case of sub-type B being reinfected with subsequent sub-type B infection. [2]

This patient entered a long-term non-progressor (LTNP) cohort in 1995 aged 58, following a ten year history of HIV infection, with a CD4 count >600 cells/mm3 for the previous 5 years and viral load of 135 copies/mL on study entry. From 1995–1999, viral load slowly increased to around 10,000 copies/mL and CD4 count dropped steadily to <500 cells/mm3. The initial infection was found to have a 20 nucleotide deletion in nef (consistent in 28 sequences) and the loss of viral control and immunologic progression from 1995 was associated with detection of subsequent sequential reinfection with two fully competent phylogentically different strains. Both new strains were also sub-type B.

The patient responded well to HAART, achieving viral suppression and CD4 recovery >700 cells/mm3 within the first year of therapy, but potentially would have maintained the option to remain off-treatment for many years if reinfection hadn't occurred.

This case highlighted that:

- Progression rates may be determined by both virologic and immunologic factors
- Reinfection in the absence of resistance may have clinical implications on disease progression, requiring earlier treatment
- That long-term exposure to low level sub-type B virus did not promote an immune response that was protective of subsequent sub-type B infections,

The authors highlighted in their conclusion that this last point showed the inherent difficulties for development of a preventative vaccine.

Jane Deayton and colleagues from St Barts Hospital, London report three cases of inter-clade dual infection detected during routine genotype testing. The three cases were Caucasian UK-born MSM whose only risk factor was sexual exposure in the UK. Case 1 had been diagnosed in 2001 and received a genotype test in 2008 prior to starting therapy that indicated dual infection with sub-types B and G. Cases 2 and 3 were tested after their HIV diagnoses in 2007 and 2008 and showed dual infections with B and CRF02_AG, and B and A, respectively. Both these patients were reported to be stable off treatment.

None of the cases included significant drug resistance mutations.

The authors concluded that these were the reports of cross-clade dual infection from sexual transmission in MSM in the UK are rare (only one other was known). Additionally this indicated onward transmission of clades associated with African epidemics and an increasing cross-over of viruses between different demographic groups.

Finally, Larry Bragg and colleagues in San Francisco presented a poster looking at cases where majority viruses change in an individual though competitive expression following dual infection. Whilst difficult to distinguish from superinfection (ie reinfection after an initial infection) sequential expression of dual infections (SEDI) theoretically could come from dual initial infection or reinfection shortly after initial infection, especially prior to seroconversion. [4]

The group included 220 recently infected persons with at least two genotypes (560 person-years of follow-up). The mean age was 37 and median time from infection to first test was 107 days. Divergent viruses appeared in 7 cases, an overall incidence density of 1.24/100 person-years.

Their model estimated a risk of SEDI that was 16-fold higher in the first year post-infection compared to after one year. The estimated rate of SEDI was 4.1/100 person-years (95% CI, 1.8 to 9.2) in the first year following infection and was 0.2 per 100 person-years beyond 1 year post-infection (95% CI, 0.03 to 1.8).

This study highlighted that in the case of dual infection or early reinfection the predominant infection is determined within the first year.

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Hepatitis studies: IL28B genetics, HCV survival, FibroScan in acute HCV, MSM reinfection and responses to transplantation

Simon Collins, HIV i-Base

The following studies focused on aspects of hepatitis coinfection.

IL28 predict treatment response to IL28

Some of the most exciting coinfection studies included those elaborating on the recent association between genetic variations in the IL28B gene and both HCV pathogenesis and response rates to PEG-IFN and ribavirin treatment.

Andri Rauch from University Hospital Bern, introduced the HCV coinfection scientific session with an overview lecture of this research, most of which has become clearer within the last six months. [1]

Rauch detailed how several groups have independently screened the human genome for genetic variations associated with HCV immune response linked to spontaneous clearance or to explain the wide range of responses to HCV treatment: important as roughly 50% patients globally are unable to clear the virus. These studies consistently identified genetic variations in interleukin 28B (IL28B) as the strongest predictor of spontaneous clearance and treatment-related clearance, in both monoinfection and HIV/HCV coinfected individuals.

Rauch explained how IL28B on chromosome 19 encodes interferon-lambda, a type III interferon with antiviral activity mediated through the JAK-STAT pathway by inducing interferon-stimulated genes. Several single nucleotide polymorphisms (SNPs) might modulate function or expression of IL28B.

The correlation between allele frequency in different American ethnicities and treatment outcome was also detailed. The rs12979860 SNP is found in approximately 40%, 70% and 95% of those with African, European and Asian decent, which correlates with SVR rates of 25%, 55% ad 75%, respectively.

IFN-lambda is induced by IFN-alpha and encoded by IL28B, and is not known to play an important role though mechanism in yet to be determined. Phase 1b trials show a potential treatment, synergistic to IFN-alpha, but associated with fewer side effects including reduced fever, flu-like symptoms, neutropenia, bone marrow toxicity.

Together, these findings may enable greater understanding of individual response rates to current treatment, potentially developing management strategies based on genetic differences, and also, potential lead to new antiviral HCV treatments.

Julia di Iulio from University Hospital Lausanne and colleagues presented an analysis of the rs8099917 allele, linked to the Type II haplotype family, in a genome-wide association study involving 347 people with spontaneous HCV clearance and 1015 people with

chronic HCV. This in turn lead to identification 21 SNPs, and then four potential causal SNPs closer to IL28B, that are associated with chronic HCV and that may be more likely to influence IL28B function or expression. [2]

Norma Rallon and colleagues from Madrid reported on the role of rs12979860 on treatment responses of 198 HIV/HCV coinfected patients (106 with SVR and 92 non-responders). Due to sampling issues, 164 patients were included in final analysis.

The SVR rate was significantly higher in patients with the CC alleles than in those with CT/TT alleles across all HCV genotypes (75% vs 38%, p<0.0001) and by genotype (G1: 65% vs 30%, p=0.001; G-3/4 83% vs 57%, p=0.02). In the multivariate analysis, the rs12979860 CC genotype was a strong predictor of SVR (OR 3.4; 95%CI 1.4–7.9; p=0.006), independent of other well-known predictors such as HCV genotype 3, baseline serum HCV-RNA <600,000 IU/mL and fibrosis <F3-F4.

Jacob Nattermann from the University of Bonn, and colleagues, reported slightly different results to other coinfection cohorts when they looked at whether IL28B SNP rs12979860 affected treatment outcome in 192 co-infected patients (74 acute and 118 chronic). Rates of sustained virological responses (SVR) were compared in patients carrying different genotypes. As comparison, 136 uninfected and 156 HCV mono-infected patients were included as control groups. [4]

IL28B genotype distribution did not differ significantly between the HIV (acute and chronic) and uninfected groups but monoinfected patients had a low rate of the protective C/C genotype (30% vs 41-47%).

While coinfected patients with the C/C genotype had significantly higher SVR rates than patients with C/T and T/T (58.1% vs 40.6%; p=0.041). This effect reached statistical significance only in HIV-positive patients with chronic (50% vs 29%; p=0.04) but not in those with acute (73.3% vs 60%; p=NS) HCV.

C O M M E N T

In addition to the data in co-infected patients reviewed by Rauch, his group has also shown that, as in mono-infected patients, polymorphisms also determine spontaneous clearance rates. The potential for a genetic mechanism to explain differences in spontaneous clearance and HCV treatment response rates by ethnicity is clearly important given the social aspects of HCV care globally. This suggests perhaps a more accurate marker with, or instead of, early treatment response rates, in order to identify people who risk only toxicity without any likely clinical benefit if they use treatment with pegylated interferon and ribavirin.

Clearly, before these tests are utilised in clinical pathways, we need further studies. Positive- and negative-predictive values for genotype results need to be highly predictive to ensure this is not used as a way to exclude some patients from treatment. IL28 alayses are likely to be included in future treatment studies. Furthermore, there may be implications for the clinical utility of these tests to identify patients with a low likelihood of response to standard therapy who may be candidates for early treatment with specifically-targeted anti-HCV drugs.

Duration of infectious HCV survival in syringes

Elijah Paintsil and colleagues from Yale School of Medicine presented results of the impact that different gauge syringes and different temperatures has on the duration of HCV infectivity and therefore risk from residual blood. [5]

Syringes with low (2 uL) and high (32 uL) quantities of residual HCV-containing blood after full plunger depression, with 1-cc insulin syringe (permanently attached needle) and 1-cc tuberculin syringe (detachable needle), respectively. Syringes were either immediately tested for viable virus or stored at 4ºC, room temperature and 37ºC, for up to 56 days. Virus was recovered from stored syringes and tested for infectivity in cell culture using relative luciferase activity.

HCV infectivity was not detected in the small syringes beyond day one except for those stored at 4º where HCV remained viable in 5% of syringes up to day 7.

After 7 days of storage, 96% ± 7.5, 71%± 23.1, and 52% ± 20 of 32 uL syringes were HCV-positive at 4º, room temperature, and 37º, respectively. Viable virus was recovered from the 32 uL syringes up to day 56. In general, the infectivity of the recovered virus was inversely related to duration and temperature of storage.

Caution when interpreting FibroScan results from acute HCV infection

A study from the European NEAT coinfection group reported that liver stiffness was elevated during acute HCV infection, probably due to high levels of inflammation and short observation periods, and that early FibroScan results should therefore be interpreted with caution, rather than assume that greater stiffness are a marker of rapid progression. [6]

Fibrosis progression rate (FPR) was calculated dividing the difference in fibrosis units by the time of follow-up. The analysis included 28 HIV-positive men with acute HCV that become chronic (91% MSM sexual exposure risk), or if FibroScan prior to anti-HCV therapy was available. Plotting FPR over follow-up time revealed short observation times being strongly correlated with high fibrosis progression rates. No interaction of risk factors for cirrhosis or HAART exposure with follow-up time was observed.

The authors concluded: Calculated high fibrosis progression rates after acute HCV infection in HIV-positive individuals are probably influenced by short observation periods. Higher liver stiffness in the acute phase of HCV infection may be at least partially explained by higher inflammatory activity that has been shown to increase stiffness leading to overestimation of fibrosis. A linear model for fibrosis progression, as is currently applied in the setting of chronic HCV infection, should be used with caution in the setting of acute HCV infection.

HCV reinfection after spontaneous HCV clearance

A poster on acute HCV infection in HIV-positive MSM in Germany was interesting for two reasons. Firstly, 22% patients spontaneously cleared HCV, and secondly, a high rate of reinfection that was reported (5 patients: 17% of those with a spontaneous or treatment related SVR). [7]

Hans-Jürgen Stellbrink and colleagues reported on 46 cases of acute HCV in MSM since 2001, from an HIV cohort of >4,400 predominantly MSM. Incidence rates per 1000 PYFU increased steadily from 0.15 in 2001/02 to 2.48 in 2007/08. HCV was genotype 1, 2, 3 or 4 in 20 (43%), 1 (2%), 9 (20%) and 16 (35%) cases, respectively.

Of the 34 patients treated with peg-IFN/RBV, SVR was achieved in 20 (65% of the 31 subjects with follow-up after treatment), relapse occurred in 3 (10%), and primary non-response was observed in 8 (26%). Ten patients (22%/46) cleared HCV spontaneously, and 2 (4%) remain untreated with persistent infection.

Re-infection occurred in five individuals (17%) of those who cleared acute hepatitis C infection (three with different genotypes, 1 with the same, 1 with pending genotype). After primary infection with G3, one patient developed severe hepatitis upon second re-infection with G1; this patient cleared HCV all 3 times without therapy.

Of note, a 24% rate of spontaneous clearance was reported by Bradley Hare and colleagues in a group of 54 HIV-positive MSM in San Francisco and New York. This study also reported 100% response rates in patients who, having achieved undetectable HCV RNA at week 8 or 12, continued treatment with PEG-IFN only (dropping RBV) for the subsequent 12 weeks. [8]

People with haemophilia with HIV/HCV coinfection need earlier referral for liver transplant

Margaret Ragni and colleagues presented results of canditates for liver transplant from the US multicentre study in people coinfected with HIV/HCV, comparing outcomes in men with and without haemophilia. [9]

Of 100 HIV/HCV enrolled candidates, 33 (33%) underwent orthotopic liver transplantation (OLTX), including 8/16 (50.0%) with haemophilia and 25/84 (29.8%) without.

Men with haemophilia were less likely to still be alive, and more likely to have died before transplant (mainly related to sepsis or multi organ failure). Men with haemophilia reached transplant (OLTX) and MELD of 25 marginally faster than non-hemophilic subjects (p=0.09 and 0.06 respectively). Although younger (42 vs 48 years, p=0.004), there were no differences in BMI, CD4, detectable HIV RNA or detectable HCV VL, time to post-OLTX death, graft loss, and treated rejection or 3-year survival. See Table 1.

Table 1: Outcomes from liver transplant in men with and without haemophilia

	Haemophilia	Non-haemophilia	p
Candidates	16	84	
Transplant received	8 (50%)	25 (30%)	
Survival	3 (18.8%)	46 (54.8%)	
Died pre-OLTX	5 (31.3%)	13 (15.5%)	0.03
Rejection rates (95%CI)			
1 year	27% (7 to 72)	40% (23 to 64)	
3-year	51% (18 to 92)	48% (28 to 72)	
Post-OLTX survival (95%CI)			
1-year	75% (31 to 93)	62% (39 to 78)	
3-year	56% (15 to 84)	56% (33 to 74)	

The authors concluded that in HIV-positive men with hemophilia, "despite early acquisition of HCV, transplant outcomes appear to be similar to those in co-infected individuals without hemophilia. However, pre-transplant mortality appears higher among co-infected hemophilic men. Whether earlier intervention could reverse this finding is not known".

C O M M E N T

Although this was one of the few studies at CROI to mention management issues for people with haemophilia, these results should be interpreted cautiously. With only 16 haemophilia patients in the study who are, by definition, a highly selected group of long-term survivors, the researchers are unlikely to have been able to adjust for the likely differences between the two groups.

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All references are to the 17th Conference on Retroviruses and Opportunistic Infections, 16-19 February 2010, San Francisco. Oral presentations are included in the webcast: Oral Abstracts and Scientific Overview: Hepatitis C: Transmission, Outcomes, and Treatment. 17th CROI, 2010. Friday 09.30am.

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Poor bioequivalence with crushed and dissolved tablets

Polly Clayden, HIV i-Base

There are limited paediatric antiretroviral options. Despite manufacture labelling, crushing and/or dissolving tablets, against recommendations, has been reported. Two studies, presented as posters at CROI 2010, looked at bioequivalence of crushed and dissolved Atripla and crushed lopinavir/ritonavir (LPV/r) tablets, compared to whole tablets, in healthy volunteers and HIV-positive children respectively.

Neither strategy met FDA bioequivalence criteria (predefined as, 90%CI 0.8 to 1.25).

Atripla is a fixed dose combination (FDC) tablet combining efavirenz (EFV), emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF).

Use of this FDC is limited to patients who can swallow tablets, since there is no liquid formulation currently on the market.

Jennifer King and colleagues from the University of Alabama looked at the bioequivalence of the FDC tablet and a compounded liquid formulation made from the crushed tablet, dissolved in 5 mL of water and diluted with 20 mL of Ora-Sweet oral vehicle.

This was a randomised, single dose, open label, crossover study in 14 healthy volunteers.

Subjects received single doses of both formulations on an empty stomach separated by a 14-day washout period. Samples were taken pre-dose and 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours post dose.

The area under the concentration-time curve (AUC-inf) and maximum concentration (Cmax) of TDF, FTC and EFV were determined using noncompartmental methods. Geometric mean ratio (GMR) of liquid to tablet Cmax, AUC-inf, and 90% confidence intervals (CI) were calculated to determine bioequivalence

The mean ± standard deviation age and weight for the subjects were 33.3 ± 10.9 years and 85.7 ± 18.4 kg, respectively.

The bioequivalence geometric means (percent coefficient of variation) and 90% CI for each drug are shown in Table 1.

Table 1: Bioequivalence, geometric mean ratios for EFV, FTC and TDF liquid and tablet formulations (n=14)

Drug	Formulation	Cmax (mg/L)		AUC-inf	
		GM (%CV)	Ratio of GM: Liquid vs tablet (90% CI)	GM (%CV)	Ratio of GM: Liquid vs tablet (90% CI)
EFV	Liquid	1.3 (28.8)	0.86 (0.75-1.04)	56.7 (80.0)	0.97 (0.62-1.26)
	Tablet	1.5 (39.0)		58.7 (57.5)	
FTC	Liquid	2.1 (21.0)	1.15 (0.97-1.25)	10.8 (15.9)	0.99 (0.91-1.05)
	Tablet	1.8 (32.3)		10.9 (24.7)	
TDF	Liquid	0.3 (27.7)	1.38 (1.12-1.70)	2.2 (36.3)	1.21 (1.07-1.40)
	Tablet	0.2(47.8)		1.8 (29.2)	

The investigators found only the 90%CI for FTC Cmax and AUC fell within the range to meet bioequivalence in this study.

The 90% CI for EFV Cmax was below the range for bioequivalence and AUC above. TDF Cmax and AUC were approximately 40% and 20% higher with the liquid formulation.

The authors suggested careful consideration before crushing Atripla tablets to construct a compounded oral solution.

A related poster authored by Huy Diep and colleagues from the University of California and Children's National Medical Center, Washington DC,showed data from a PK study to determine the impact of crushing LPV/r on drug exposure in paediatric patients.

LPV/r is recommended for treating HIV-positive children. Although there is an oral formulation, it tastes unpleasant, contains 42% alcohol, needs to be refrigerated and must be taken with food.

The newer film coated tablet formulation of LPV/r does not require refrigeration and has no food restrictions. Although the manufacturer's instructions state that tablets should not be crushed or chewed, routine use of crushed tablets has been reported.

This was a randomised, open-label, cross over study of 12 patients (13 were enrolled but one child refused to take the crushed dose), age 10-16, already taking LPV/r for at least two weeks.

Two separate 12 hour PK sampling following observed doses of LPV/r 400/100mg either whole or crushed tablets were performed. Samples were taken at 0, 1, 2, 4, 6, 8 and 12 hours. Plasma concentrations of LPV and RTV were measured by HPLC and used to calculate non-compartmental area under the curve (AUC) and clearance (CL/F). Median PK values were compared, using the Wilcox signed rank test. Table 1 shows ratios of crushed to whole tablets.

Table 2: Ratios (90% CI) of crushed to whole tablets

	LPV	p-value	RTV	p-value
AUC (mg*hr/L)	0.60 (0.48-0.72)	0.003	0.61 (0.45-0.77)	0.005
CL/F (L/hr)	1.96 (1.52-2.41)	0.091	2.21 (1.56-2.86)	0.008
C12 (mg/L)	0.67 (0.48-0.86)	0.016	0.97 (0.75-1.19)	0.449
Cmax (mg/L)	0.81 (0.65-0.98)	0.021	0.86 (0.54-1.19)	0.075

The investigators reported significantly lower exposure after crushed than whole tablets; approximately 40% decreased oral absorption for LPV and RTV. They noted high interpatient variability, eg crushed/whole LPV AUC ratio range: 5-75%.

The extent and variability of reduced exposure after multiple crushed doses at steady state in HIV-positive children remains unpredictable. The investigators concluded that these data reinforce the need to discourage this dosing practice.

C O M M E N T

Besides emphasising the importance of following the manufacturer's instructions, these data once again highlight the need for appropriate paediatric formulations.

The development of a liquid formulation of efavirenz has been problematic, but the originator company are continuing with the programme and it is hoped that we will have one soon.

For lopinavir/r, as recommended, dividing tablets clearly is not a good option. Cipla are developing sprinkles using melt extrusion technology to make tiny beads. Bioequivalence studies are underway and this formulation will offer a very useful option to the lopinavir/r liquid.

References

1. King J et al. Assessment of Bioequivalence of Tenofovir, Emtricitabine, and Efavirenz Fixed-dose Combination Tablet Compared with a Compounded Oral Liquid Formulation Derived from the Tablet. 17th CROI, 16-19 February 2010, San Francisco. Poster abstract 605. http://www.retroconference.org/2010/Abstracts/37400.htm
2. Diep H et al. Pharmacokinetics of lopinavir/ritonavir crushed vs whole tablets in children. 17th CROI, 16-19 February 2010, San Francisco. Poster abstract 877. http://www.retroconference.org/2010/Abstracts/37445.htm

Initial PK, safety and 12 week efficacy of raltegravir chewable tablets in children 6-11 years

Polly Clayden, HIV i-Base

The raltegravir paediatric programme is ongoing in collaboration with IMPAACT (P1006). Children and adolescents age 2-18 who have failed at least one previous regimen, with viral load >1000 copies/mL are eligible. Age strata are accrued sequentially with the oldest group first.

Acceptable pharmacokinetics (PK), safety and short term efficacy has been reported for 6-11 and 12-18 year olds receiving the adult formulation. (poster 873)

In an oral presentation, Sharon Nachman presented initial PK, 12-week efficacy and safety data (as of January 4 2010) for children age 6-11 receiving a new chewable raltegravir tablet.

In this study, raltegravir was added to the children's existing antiretroviral regimen. Intensive PK sampling was performed between days 5-12 and then background therapy was optimised.

This was an AUC targeted design for the chewable formulation based on adult data. PK parameters and variability were compared to the adult formulation in children of the same age range.

There were 10 children in this cohort, of which 50% were male, 60% white and 30% black. They were a median of 8.5 years old and 33 kg in weight. Their median absolute CD4, CD4% and viral load were 456 cells/mm3, 22.5% and 4.2 log respectively. The median follow up was 19 weeks.

Initially the dose studied was 8 mg/kg (n = 4). This was reduced to 6 mg/kg because of the high AUC12 with maximum dose of 300 mg. All dosing was twice daily.

The actual geometric mean (GM) chewable formulation dose was 223 mg (vs 400 mg adult formulation).

At 6 mg/kg, GM AUC12 was 22.6 (range 12.8- 40.6) Mxh (n = 10). GM raltegravir trough (C12h) and peak (Cmax) concentrations were 128 (range 62-397) nM and 10.5 (4-23) uM, respectively.

Raltegravir oral clearance (CL/F) was 21 L/hr for chewable vs 49.6 L/hr for adult formulations. Overall PK variability (%CV) was less for chewable vs adult formulations (AUC12 34 vs 120%; Cmax, 53 vs 130%; C12h 84 vs 221%).

There was one grade 3 adverse event: possibly related (elevated fasting LDL). There were no grade 4 events and no treatment discontinuations. At Week 12, 7/10 children (70%, 95%CI 35% to 93%) had viral load <400 copies/mL (3/7 initially received 8 mg/kg).

The investigators concluded that the raltegravir chewable tablet had less PK variability and lower oral clearance compared to the adult tablet. The differences in clearance are likely to be due to greater relative bioavailability of the chewable tablet.

Study of raltegravir in children age 6-11 will continue with a dose of 6mg/kg (maximum 300mg) of the chewable tablet.

Ref: Nachman S et al. Interim results from IMPAACT P1066: raltegravir oral chewable tablet formulation in children 6 to 11 Years. 17th CROI, 16-19 February 2010, San Francisco. Oral abstract 161LB.

http://www.retroconference.org/2010/Abstracts/39677.htm

PK of efavirenz in children dosed according to WHO weight bands

Polly Clayden, HIV i-Base

Efavirenz (EFV) is used widely in children over 3 years old throughout the world. To date there is limited information about the steady state pharmacokinetics (PK) of EFV in African children.

A poster from Sabrina Bakeera-Kitaka and colleagues from the ARROW trial showed results from an investigation conducted to determine whether WHO recommended weight band dosing results in optimal EFV exposure in Ugandan children aged 3-12 years.

In this substudy, 41 HIV-positive children receiving generic EFV plus lamivudine (3TC) and abacavir (ABC) were enrolled in a crossover, PK study of twice vs once daily 3TC+ABC. This was conducted 36 weeks after the children started HAART in ARROW.

Children were dosed in accordance with WHO weight bands: 200/250/300*/350*mg for those weighing 10–15, 15–20, 20–25, and 25–30 kg respectively, using EFV capsules or *halved 600 mg tablets. Intensive sampling was performed at t=0, 1, 2, 4, 6, 8, and 12 hours post observed dose on twice-daily HAART at steady state and repeated 4 weeks later including a further 24 hour sample.

The investigators estimated EFV AUC0-24 and clearance (CL/kg) using WinNonlin, and predictors of log10AUC and CL were accessed using multivariate mixed models.

Of the children enrolled, 39 and 37 children had evaluable EFV profiles at the first and second PK sampling respectively.

The children were 41% (16/39) boys, 18 (46%) were aged 3–6 years and 21 (54%) 7–12 years. There were 5, 16, 15, and 3 children in the 10–15, 15–20, 20–25 and 25–30 kg weight-bands, respectively.

The investigators reported geometric mean (%CV) AUC0-24 of 50.4 (91.7%) and 54.0 (80.8%) h.mg/L at the first and second sampling respectively. They found no significant variation across weight-bands (p=0.51).

They noted a large inter- and intra-patient variability in EFV PK parameters (eg 81% and 28% for AUC0-24). They found 15% (6/39) children at the first sampling, and 7/37 at the second (7 children in total) had subtherapeutic C8hr and C12hr levels (≤1.0mg/L); 38% (14/37) had therapeutic C24hr levels at the second sampling. They also found 23% (9/39) and 27% (10/37) children in the first and second sampling respectably (11 children in total) with a toxic C8hr and/or C12hr level (>4.0mg/L).

The investigators identified three groups of children using normal mixture modeling: 40% with geometric mean AUC0-24 27.2 h.mg/L, 32% with 49.9 h.mg/L and 28% with 137 h.mg/L. They suggested that genetic polymorphisms might play a role.

Mean clearance overall was 6.8 (SD 3.9) and 6.2 (3.7) L/h at the first and second sampling respectively (p =0.04). C/F increased by

0.50L/h for every year older (p=0.05), but was independent of weight (p=0.85), weight-for-age (p=0.52) or height-for-age (p=0.80).

Overall they found lower exposure than that previously reported in the tablets.

The ARROW group, are conducting ongoing investigations into the relationship between efavirenz concentrations and toxicity. The children's viral loads will also be tested retrospectively. They wrote: "Increasing the EFV dose for children should be investigated, and has been proposed by WHO. However higher proportions of children with toxic levels might be expected."

Ref: Natukunda E et al. Pharmacokinetics of efavirenz dosed according to the WHO weight-bands in children in Uganda. 17th CROI, 16-19 February 2010, San Francisco. Poster abstract 878.
http://www.retroconference.org/2010/Abstracts/37642.htm

Virological and immunological responses in infants enrolled in the CHER trial

Polly Clayden, HIV i-Base

Avy Violari and colleagues from the CHER trial showed data describing response in young infants after early HAART initiation in South Africa.

Largely because of this trial, current guidelines recommend early treatment in HIV-infected infants and, where possible, infants exposed to nevirapine in prevention of mother to child transmission (PMTCT) should receive lopinavir/ritonavir (LPV/r) first line. There are few data describing virological outcomes in African infants.

In CHER, infants aged 6-12 weeks with CD4% ≥25% (n = 411) and CD4 <25% (n=40) started LPV/r, zidovudine (AZT), lamivudine (3TC) either immediately or when clinically or immunologically indicated.

In this analysis, the investigators defined virological response as viral load <400 copies/mL and immunological response as CD4% increase ≥10% from pre-treatment level, at 24 and 40 (or 48 if missing at 40) weeks after starting HAART. Using logistic regression, the investigators examined the association between age at baseline, CD4%, absolute CD4, viral load, weight for age z-score, TB and gender with virological and immunological response. By the end April 2009, 387/451 children had started HAART and had data for ≥1 outcome.

At baseline, the children were a median: age of 8.4 (IQR 7.1–11.4) weeks; weight-for-age z-score -0.8 (-1.6–0.0); CD4% 32% (24-38%). Over half (59%) had a viral load >750,000 copies/mL. The majority (79%) started HAART by 12 weeks.

At 24 weeks, 71% (95% CI, 65–75%, 246/349) of children had a viral load ≤400 copies/mL; 77% (245/320) at 40/48 weeks. Assuming loss to follow up as failure, these proportions were 65% and 68% at 24 and 40/48 weeks, respectively.

The investigators found no association between virological response and age at initiation (OR at 24 weeks 1.04 per 4 weeks increase, 95%CI 0.95–1.14, p=0.39), CD4%, weight-for-age z-score, viral load or gender.

Only 5/15 (33%) children with active TB (diagnosed before or within 1 month after initiation) receiving concurrent TB treatment were <400 copies/mL at 24 weeks vs 241/334 (72%) of the remaining children (RR 0.47, 95%CI 0.23–0.96, p=0.04).

Median change in CD4% from baseline was similar at 24 weeks (7%, IQR 1–13%) and 40/48 weeks (7%, 1% -13%). CD4% increase ≥10% occurred in 33% and 32% at 24 and 40/48 weeks respectively.

CD4% increase ≥10% was more likely with lower CD4% at initiation. The investigators noted this was the only predictor of immunological response at both time-points.

The investigators concluded: "Virological response was satisfactory in this large cohort of infants initiating lopinavir-based ART in South Africa, and similar to rates reported in infants from well-resourced settings"

They plan to look at suppression in relation to adherence in this trial and resistance in children with detectable viral load.

Ref: Violari A et al. Virological and Immunological Responses in Infants Receiving a LPV/r-based Regimen

17th CROI, 16-19 February 2010, San Francisco. Poster abstract 843.

http://www.retroconference.org/2010/Abstracts/39129.htm

Darunavir-associated mutations in PI-naive and PI-experienced children in the UK

Polly Clayden, HIV i-Base

Katherine Boyd and colleagues from the Collaborative HIV Paediatric Study (CHIPS) and the UK HIV Drug Resistance Database looked at the prevalence of duranavir associated mutations in children.

As duranavir boosted by ritonavir (DRV/r) has the potential for first or second line PI use in the UK, Identifying the prevalence of resistance associated mutations (RAM) in children is important for determining the clinical utility of this drug.

In this study, data from CHIPS (a cohort of approximately 95% of reported HIV-positive children in UK/Ireland since 1996) and the UK drug resistance database from 2000–2007 were combined.

The investigators identified DRV RAM from the 2008 IAS mutations list (V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V) and the Stanford database (I47A, G73S/T/C, I84A/C, V82F).

The prevalence of RAM was estimated in both PI and PI-naïve children. Using multivariate linear regression, the investigators examined the time on a PI, the area under the viraemia curve, and the type of PI. They used the Stanford database algorithm to assess the children's resistance to DRV/r.

Of 344 children tested when they were PI-naïve, 14 (3%) had a single RAM (2 V11I, 2 V32I, 1 I47A, 7 I50V, 1 G73S, 1 L89V). No child had more than one RAM. Of 156 PI-experienced children tested while receiving a PI, 21(13%) had one RAM, 5 (3%) had 2, and 3 (2%) had 3: 55 (35%) children received prior LPV/r only, median (IQR) 2.6 (1.2 to 5.0) years on PI.

In multivariate analysis, there were significant associations between greater number of DRV/r RAM and longer time on a PI (RR 1.14, p=0.04 +1 year), larger area under the viraemia curve since the start of PI (RR 1.78, p=0.01), and previous use of a PI other than LPV/r (RR 6.15, p=0.02 vs LPV/r only).

The investigators noted, only 3 (2%) PI-experienced children had intermediate level resistance to DRV/r using Stanford. They concluded that these results suggest that DRV/r is useful both a first PI and an alternative second PI as prevalence resistance is low.

Ref: Boyd K et al. Prevalence of Darunavir-associated Mutations in PI-naive and PI-experienced HIV-1-infected Children in the UK. 17th CROI, 16-19 February 2010, San Francisco. Poster abstract 851.
http://www.retroconference.org/2010/Abstracts/38696.htm

HIV persistence, raltegravir/maraviroc intensification and immunology

David Margolis MD, University of North Carolina, for NATAP

Persistent HIV infection despite successful ART

Ultimately, we must either acquiesce to treat HIV patients with ART forever, or find ways to definitively prevent infection and to decisively eradicate infection. Tony Fauci, director of the NIH's infectious diseases institute highlighted these priorities in his keynote address. [1]

Notable at CROI this year were several exhaustive and demanding studies of persistent infection. These were emblematic of the types of studies that are required to make progress in understanding the persistence of HIV infection despite ART, and required if the field is ever going to make progress towards eradication or drug-free control of HIV infection. Both the investigators, and most especially the patient volunteers, are to be applauded for their efforts and contributions.

Mary Kearney co-workers at the Frederick Drug Resistance Program presented very important observations on viral evolution during the initiation of ART. [2]

When a patient initiates ART, suppression of viremia to <50 copies/mL takes many weeks to achieve. It has been unknown to what extent drug resistant populations of virus could develop or expand during this period of time. To carefully characterise genetic diversity and divergence in patients before and during suppressive ART, Kearney and colleagues studied samples from 10 HIV-positive patients taken from the time of ART initiation and thereafter for as long as 5 years. A total of 1300 HIV-1 sequences (gag-pro-pol from p6 to RT) sequences were obtained by single-genome sequencing (SGS). Diversity was measured by average pair-wise difference (APD), genetic variation over time was assessed by phylogenetic analyses and a test for panmixia (the state of maximal mixing of all possible genetic sequences), and sequence changes were characterized using a comparison program called Highlighter.

Before ART, circulating HIV-1 sequences had differences of 0.2 to 2.5% per site. This is consistent with the work of this group and others, showing a relatively homogeneous pool of sequences at a moment in time, with episodic evolution of the circulating swarm in response to immunological pressure. In this group, ART reduced plasma viral RNA levels to undetectable (<75 copies/mL) in all patients within 5 months of initiation. In 8 of 10 patients, phylogenetic analyses and measurements of intra-patient APD revealed no change in viral diversity or population structure between pre- and post-ART samples despite up to 4-log10 decreases in HIV-1 RNA levels. That is to say, that after a 2 log, and a 3 log decline of viral load the residual viral swarm did not change significantly, and no novel viruses were selected or emerged from underneath the majority population. This was still the case when viral sequences were recovered and studied when HIV RNA was <75 copies/mL.

In two patients, divergence of HIV-1 was eventually evident after prolonged ART, resulting in a shift from pre-therapy virus populations containing occasional unique viral variants within a population of a dominant species, to a population with frequent G to A mutations, stop codons, and shifts in CTL escape mutation profiles. In one of these patients, a variant found one day after initiating ART became a predominant plasma clone after fours years on suppressive therapy, similar to that described by Bailey et al. (J Virology 2006). In this patient the predominant plasma clone was significantly different ($p<10^{-9}$) from the pre-therapy population by tests for panmixia and divergence (2.9%), resulting primarily from accumulation of G to A mutations.

These results suggest that both short- and long-lived cells are infected with diverse virus populations before therapy, but that viral replication is completely blocked by ART as no evolution of virus is observed during ART-induced decline of viremia. In some patients (as observed in the one patient described above) diverse replication-competent viral variants may decay with long-term suppressive therapy, leaving behind only defective proviruses produced by remaining clones of previously infected cells. This is an alternate or additional explanation for the predominant plasma virus clone described by Bailey, which is hypothesised by some to originate instead from an infected blood stem cell.

Steven Yukl exhaustively examined the HIV burden throughout the gut-associated lymphoid tissue (GALT). [3] He and his co-workers measured HIV DNA (cells that had been infected with HIV in the past) and HIV RNA (produced by infected cells that were potentially expressing HIV viral particles) in different area of the GI tract in patients on prolonged, suppressive ART. Eight HIV-positive patients on ART with CD4 counts >200 cells/mm3 (mean 480 cells/mm3) and plasma RNA viral load <40 copies/mL for 2.8 to 12 years were studied. Blood plasma, PBMC, and 7–10 endoscopic biopsies were taken from sites in the duodenum, terminal ileum, right colon, and rectum.

Using a sensitive research assay, plasma HIV RNA was detectable at very low levels in all patients (median 2.3 copies/mL). Unspliced HIV RNA was detectable in each gut site in the majority (63 to 88%) of patients using RT PCR, but levels were very low. So it is unclear if this HIV RNA represents tiny amounts of RNA produced by many cells, or large amounts of RNA produced by few cells. The latter would seem more likely, and consistent with the occasional ability to visualise HIV RNA by in situ hybridisation. Of course, the presence of HIV RNA does not guarantee that the cells involved are actually producing replication-competent viral particles, although for at least some of these cells that seems also likely to be the case.

Surprisingly, HIV DNA increased from the duodenum to the rectum, and the HIV DNA per CD4+ T cell was higher in all four anatomic regions relative to the PBMCs. Again, it is important to remember that the presence of HIV DNA means only that the virus has entered the involved cell at some time in the past, and does not prove that the cell is producing HIV RNA, or even competent viral particles. It does also not demonstrate that the involved cell was actually infected in the gut site from which the cell was recovered, as immune cells are frequently trafficking in tissues. Biopsies of the GALT, like any assay, are only snapshots in time. The terms persistence and reservoir are temporal and spatial ones, and these observations neither demonstrate that cells stably expressing virus persist in the GALT, or that the events that lead to persistent viral RNA production (and likely virion production) are occurring exclusively in the GALT. But we must measure what is possible to be measured.

Yukl and colleagues noted that the median unspliced HIV RNA was also higher in all gut sites compared to PBMCs, but oppositely was highest in the ileum and lowest in the rectum. Also surprising to the authors was the finding that cell activation markers were lower when HIV DNA levels in the gut tissue were higher. The authors concluded that “The inverse relationship between HIV DNA and T cell activation in the gut and the paradoxically low levels of HIV expression in the large bowel suggest that different processes drive HIV persistence in the blood and gut.”

This study is hopefully the first part of a longitudinal one, as such a study could tell us much of the processes that drive persistence. Persistence can be defined as:

- persistent infection without producer cell death,
- persistent rounds of infection with one cell passing new virus to another, or
- carriage of proviral DNA that can later express replication-competent HIV.

A conclusiuons from this study is only that cells that are expressing HIV RNA are found more frequently in the ileum. HIV DNA that predominates in the rectal tissue (also the tissue with the lowest levels of immune activation) could be, at least in part, a graveyard of proviral sequences that are incompetent for expression, in cells that were either infected there, or travelled there.

Ann Wiegand presented the results of an NIH intramural group study that found no reduction of persistent, low-level viremia as measured by the single-copy assay (SCA; Palmer J Clin. Micro. 2004) in treatment-experienced who intensified their ART with raltegravir (RAL). [4]

Eight participants had undergone an average of 4 suboptimal regimens with a prior history of virologic failure and genotypic resistance, but who had subsequently suppressed to <75 copies/mL were enrolled. Patients had baseline viral RNA levels determined during a 21-day period prior to RAL intensification, then weekly assays during a 30-day intensification period with raltegravir 400 mg twice daily, and then later additional sampling for 6 weeks after RAL was stopped. There was no significant change in viral RNA levels during intensification or afterwards. Some intensification studies have suggested a CD4 benefit in the absence of a change in viremia, but in this one mean CD4 cell numbers were not significantly different after 30 days of intensification.

Hatano reported the results of a similar study at UCSF in which 15 subjects with undetectable viral loads on ART for at least 1 year were randomised to add RAL 400mg twice daily, and 15 added placebo for 24 weeks. [5]

This was a group with a long disease history: the duration of HIV infection was 18 years, duration of HAART was 23 months, baseline CD4+ T cell count was 232 cells/mm3, and nadir CD4+ T cell count was 53 cells/mm3. Using a SCA with a lower limit of detection of <0.2 copies/mL, median baseline plasma HIV RNA level was 5.2 copies/mL; 9 subjects were below the limit of the assay. The proportion of subjects with undetectable plasma RNA levels at week 12 was not different across the 2 groups. Also, RAL intensification did not alter proviral DNA, cell associated HIV RNA, or CD8+ or CD4+ T cell activation in the blood. Further, 20 patients underwent GALT biopsies, and GALT CD8+ and CD4+ T cell activation was unaffected in the GALT by RAL. In addition, intensification did not significantly affect gag-specific responses in blood or GALT. However, higher levels of gag-specific IL2+INF-

gamma CD4+ T cells and CD8+ T cells in GALT were associated with lower levels of cell associated RNA (rho = -0.52, p=0.02 for CD4+ T cell responses; rho = -0.53, p=0.04 for CD8+ T cell responses). This association held regardless of receipt of RAL or placebo, and it is hard to be sure if the association is a marker for patients with better control of tissue viral replication, or whether the responses themselves actually contribute to control of replication.

In a companion piece to this study, Yukl and colleagues also presented a study of the effect raltegravir intensification on HIV RNA and T cell activation in the GALT in patients of suppressive ART. [6]

In this study, 7 HIV-positive men with viral load <40 copies/mL for 3 to 12 years and a CD4 count >200, underwent a variety of 12-week intensifications: raltegravir (n = 4), raltegravir and efavirenz (n = 2), or raltegravir and darunavir/ritonavir (n = 1). Again, GALT biopsies were done in 4 sites (duodenum, ileum, colon, and rectum) at entry and week 12.

As before, HIV RNA was detectable in plasma and PBMCs. HIV DNA was detectable in all GALT sites, and RNA detected in the GALT in most patients. Intensification resulted in no consistent change in HIV RNA in the plasma, peripheral blood mononuclear cells, or gut. There was a trend (in 5 of 7) towards decreased unspliced HIV RNA per 106 CD4+ T cells in the ileum, and similarly a trend towards decreased activation of CD4+ and CD8+ T cells in all GALT sites. The authors concluded that intensification reduced HIV RNA, reduced immune activation, and increased CD4+ T cells in the ileum, suggesting that the ileum may support ongoing productive infection in some patients on ART, even if the contribution to plasma RNA is not discernible. However, like their other study, this study should be followed-up with longitudinal evaluations. Most of the confidence intervals for the effects were wide, and not all the effects were concordant in each part of the GI tract.

Javier Martinez-Picado from Barcelona presented a third raltegravir intensification study actually initially presented last year at CROI and now published in Nature Medicine (March 2010). [7]

69 patients with <50 HIV RNA copies/mL for >1 year were randomised to intensify their ART with raltegravir (n = 45), or to continue their HAART (n = 24) for 48 weeks. As discussed last year, raltegravir intensification resulted in no change or difference in total HIV DNA. This year it was also shown that SCA viremia was unchanged. However raltegravir intensification of a 3-drug suppressive ART regimen resulted in a specific and transient increase in 2-LTR circle DNA in a significant percentage (29%) of ART-suppressed patients, primarily those on therapy that included a PI rather than an NNRTI. This was the same data as shown on a poster at CROI in 2009, but all the individual patient data points were shown. There was no doubt that in the subgroup of patients in the study who had an increase in circles, most followed a similar pattern of increase at week 2 and/or 4, then a decrease to baseline. It should be noted that the levels in most of the 69 patients in the study were <1 copy of DNA circle per million cells, and that in some of the few patients with LTR circles the values were very low and increased little (eg. increase from <1 copies to 6 copies, then decreased to 2 copies) and in others was more variable (eg. 40 copies at baseline, increased to 70 copies at week 2, then <1 copy at week 4).

Interestingly, patients who were 2-LTR+ showed higher levels of immune activation (HLA-DR+CD38+, CD38+CD45RO+, HLA DR+CD45RO+ in CD8 T-cells) at baseline and a decline after intensification. These immune changes appeared quite modest but real, but it was unclear what mechanism induced them. Remember, levels of viremia (by SCA) did not change with intensification, and so the effect of RAL did not reduce the amount of circulating viral antigen - the typical mechanism by which we believe that ART dampens immune activation. The group interpreted their findings as evidence of ongoing replication, but it is important to be picky about terminology here. Replication means full rounds of the HIV lifecycle, which on ART would generally be expected to induce drug resistance. Although this could be happening at a level that is somehow too low to select for drug resistance, there is no evidence for full rounds of replication here. There is evidence for expression of virus (as measured by SCA in some patients), and evidence that RAL had its effect by blocking integration and increasing 2-LTR circles. It would be interesting to know how the individual SCA levels related to the individual 2-LTR circle levels, but this was not shown.

de Laugerre reported on another RAL intensification study for the EASIER-ANRS 138 study team. [8]

There were not obvious technical differences in the implementation of the assays used, but the French group reported “No evolution of HIV-1 total DNA and 2-LTR circles after 48 weeks of raltegravir-containing therapy in patients with controlled viremia” a self-evident title and conclusion. However, the French group did not make measurements at the 2-4 week timepoint after intensification, the time when increased levels of circles were seen by the Spanish.

Several studies examined the effect of the CCR5 antagonist and HIV entry inhibitor maraviroc, as an alternate intensification agent in place of raltegravir. Wilkin reported the results of ACTG 5256 in which patients with suboptimal CD4 recovery after ART added MVC for 24 weeks. [9]

This was a single-arm pilot trial that enrolled patients with a CD4 count <250 celss/mm3, whose CD4 counts were stable despite continued ART such that their calculated CD4 slope was between -20 and +20 cells/mm3/year, despite at least 2 years of undetectable plasma HIV-1 RNA. 34 subjects enrolled in this study. The median baseline CD4 count was 153 cells/mm3 and despite maraviroc intensification a CD4 count increase of > 20 cells/mm3 was not seen. The mean increase in CD4 count to was 11 cells/mm3. Despite this lack of enhanced CD4 recovery, modest decreases in activation (%CD38+ cells, or % HLA-DR+/CD38+ cells) were seen.

Evering and colleagues enrolled patients infected with CCR5-tropic HIV-1 and treated with ART during acute, early infection. [10]

Subjects received ART for an average of 4 years prior to study entry. 4 patients intensified with maraviroc for 24 weeks; 2 patients intensified their NRTI for 12 weeks, followed by crossover to maraviroc for 12 weeks. Phlebotomy and flexible sigmoidoscopy with mucosal biopsies were performed at entry, weeks 12 and 24. HIV RNA was generally undetectable in tissue. In contrast to other studies, levels of immune activation and CD4+ T cell depletion in the GALT persist despite maraviroc intensification. And in the small sample thus far, no statistically significant effect of intensification of ART with MVC on a variety of immunologic and virologic parameters in the GALT is seen.

Carolina Gutiérrez presented a difficult study for the group from Ramón y Cajal in Madrid. [11]

Again, stably suppressed patients intensified ART with maraviroc, this time for 12 weeks. In this study latently infected resting CD4 T cells were quantified using a limiting dilution co-culture assay. Residual viremia was measured by quantitative real-time RT-PCR assay (Single Copy Assay, SCA, threshold: 0.3 copies/mL), episomal 2-LTRs DNA in peripheral blood mononuclear cells was measured, and activation measured (HLA-DR and CD38 on CD4 and CD8 cells).

In nine patients studied so far, at baseline, the reservoir could be quantified in 6 patients (mean 2.04 infectious units per million (IUPM)). After 12 weeks of maraviroc intensification, all patients maintained viral load <50 copies/mL and a decrease in the latent reservoir was observed in 5 patients, while no decrease was found in one (mean 0.08 IUPM, P =0.048 compared to baseline). SCA increased in several patients, but not >50 copies/mL, and episomal 2-LTRs DNA were undetectable in the 9 patients at baseline and became detectable in 4 of them at week 12. HLA-DR and CD38 decrease 2.9% on CD4s (p=0.003) and not significantly on CD8s.

So unexpectedly, there was an apparent depletion of the resting cell reservoir, with a paradoxical increase in SCA, 2-LTR circles, but a decrease in activation. These findings appear discordant, and are hard to reconcile. However, most of the effects seen are of marginal magnitude, and so if possible longer-term study might help to clear up these confusing results.

Is there a summary?

Overall, intensification of durable, suppressive ART appears to have no effect on low-level plasma viremia. In some but not all studies modest effects can be measured such as small reductions of HIV RNA in tissue, or HIV DNA species in cells, or of cellular activation markers in tissue or circulating cells, and in one study resting CD4 cell infection frequency. It does appear that drug intensification is perturbing some equilibrium in the virus-infected patient, but the mechanism is not clear. I would propose that RAL and MVC are exerting a subtle, uncharacterized, non-virological effect resulting in the cellular changes measured. Repeated measures, and interventions might help clarify the mechanism of these phenomenon.

Tired T cells

Michael Lederman and his Bad Boys of Cleveland looked for correlates to understand why a large minority (ca. 25%) of patients who are successfully treated with ART are not able to enjoy an increase of CD4+ T cells into the normal range. [12]

The “Cleveland failure project,” perhaps an accidental reference to place called by some “the mistake on the Lake” (sorry, couldn’t resist), studied local patients who has been on ART for more than 2 years, and had viremia suppressed to <50 copies/mL for at least 2 years. Patients within incomplete immune restoration were those that had CD4 <350 cells/mm3 and they were compared to those with >500 cells/mm3 (ignoring those in the middle, 350-500, for clarity of analysis).

Lederman’s group studied 61 patients who met the failure criteria, identified 168 who met the criteria for success, and studied 20 of these lucky patients. In multivariate analysis, only nadir CD4 was independently associated with immune failure (p <0.001). “Failures” were more predominantly male (82% vs. 70% for immune restoration patients), and slightly older (ca. 4 years older on average). Of note CD8 cells were 2-fold higher in those with immune restoration. Of the subpopulations of CD4+ cells–naive cells, central memory cells, and effector memory cells–all were lower in the patients without full CD4 cell restoration. So failure was not specific to a CD4 cell subpopulation.

The activation markers CD38 and HLA-DR on both CD4 cells and CD8 cells tended to be somewhat higher in “failure” patients. Ki67, a marker of recently proliferating/cycling cells was higher in CD4, especially central and effector memory cells, but not in CD8 cells. This was one of the sentinel findings of the study, which Lederman entitled: “Immune failure after suppressive ART: high level CD4 and CD8 T cell activation but only memory CD4 cells are cycling.” This finding suggested that failure to fully recover the CD4 cell count might be related to a greater need to expand the CD4 cell pool to replace cells, and an inability to completely accomplish that task, despite apparently equivalent viral suppression. This finding is consistent with the observation that nadir CD4 was most strongly associated with immunological failure, and adds another reason to consider ART sooner rather than later. An additional useful tidbit was the suggestion that a lower CD8 cell count might portend poorer CD4 recovery, and if validated might also be used as a trigger to initiate ART earlier, or implement an immunotherapy strategy to boost CD4 cells (if we can find one that really works).

This report is an edited version of a longer report on the NATAP website.

Source: NATAP.org
http://www.natap.org/2010/CROI/croi_181.htm

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ANTIRETROVIRALS

START study launched and endorsed by broad community support: over 140 community organisations sign letter to US guideline panel

Simon Collins, HIV i-Base

The long awaited START study is now open to enroll patients at 70 sites in over 30 countries. The study will randomise patients who have CD4 counts above 500 cells/mm3 to either immediate treatment or deferring treatment until the CD4 count reaches 350 cells/mm3, and follow-them for up to five years.

Choice of treatment is to be determined by treating doctors but antiretroviral drugs are provided free through a central drug depositary.

Enrollment this year is essential for the pilot phase to roll-over to the main study.

The following statement from a broad range of community organisations and advocates was released on 4 May 2010. It highlights the importance of the START trial to obtain the best quality evidence to inform treatment decisions.

It also highlights that this is a safe study for all participants, and that it will answer important questions that will benefit hundreds of thousands of other HIV-positive people, in both rich and poor countries.

i-Base is a signatory to this letter and is proud to be supporting this important research.

Community Statement On START study – PDF

Community statement on the START trial and the change in the US DHHS treatment guidelines

The following statement was produced in response to a change in the US treatment guidelines in December 2009 that stated that antiretroviral (ARV) treatment should be universally started at any CD4 count below 500 cells/mm3.

The START study is currently enrolling patients to look at whether there is evidence to support such a recommendation. Currently no randomised trial has provided data on the advantages and risks of earlier treatment. This statement affirms both the importance of the START trial and the safety for people who enrol.

We believe that the priority for HIV-positive people is to have accurate, reliable data on both the risks and benefits of earlier treatment in order to base any decision for when to start treatment.

We fully support this study and invite other individuals and community organisations to endorse the importance of this research.

Statement

When to start antiretroviral treatment is one of the most important outstanding questions for people with HIV and their clinicians. A large clinical trial, Strategic Timing of Antiretroviral Treatment (START), has begun and will hopefully help answer this and other important questions. [1]

The START trial includes antiretroviral-naive HIV-positive people with CD4 counts greater than 500 cells/mm3. It is taking place at about 90 sites in nearly 30 countries. Participants are randomised to either receive antiretroviral treatment immediately or to defer treatment until their first CD4 count less than 350 cells/mm3 or they have clinical signs of AIDS. Eventually, START will recruit 4,000 people.

The deferred arm is the current standard of care throughout the world, with guidelines recommending treatment at a CD4 count of 350 cells/mm3. Clinical trials have demonstrated that once the CD4 count drops to below 350 cells/mm3, antiretroviral treatment should begin. [2, 3] However, the recent US guideline change requires a community response for US patients who still want to take part in this study.

On 1 December 2009, the United States (US) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents were changed to recommend treatment for patients with CD4 counts between 350 and 500 cells/mm3. Of the more than two-thirds of Panel members who supported this recommendation, 55% recommended it strongly and 45% moderately. As explained in the guidelines, this recommendation is based solely on observational data primarily from two large cohorts known as ART CC and NA-ACCORD. As with all observational data the findings from these cohorts could be subject to confounding factors. [4]

Indeed, the ART CC investigators have stated, "We are concerned that some may interpret the new [US] recommendations as implying that the deferral group of this trial is no longer ethical. Such an interpretation would endanger the future of the trial in the [US]." [5]

They further state, "We … do not believe that there is convincing evidence to conclude that deferral of initiation of ART to a CD4 count of [350 cells/mm3] causes net harm, particularly in terms of mortality, compared with starting at any higher level. We strongly support continued enrolment into START. Large randomised studies represent the only means of eventually obtaining the definitive result we need to properly inform future patient care.

We agree with the ART CC investigators. The available evidence is insufficient to determine if the adherence challenges and long-term side-effects of early antiretroviral treatment are outweighed by reduced risk of illness conferred by these medicines. Only a randomised controlled trial, such as START, can determine this.

The NA-ACCORD data is also challenged by the researchers who orginally developed the new statistical methodology. They were not convinced that the application thereof was without problems. [6]

We too are concerned that the new US recommendation:

(1) raises theoretical concerns about continued enrolment of patients in the US, a substantial source of patients, and

(2) is based on poor evidence and therefore might not be in the best interests of patients.

We also have further concerns that:

(3) previous recommendations to use earlier treatment failed to recognise the negative impact of resistance and side effects, and

(4) a minority of individuals have normal CD4 counts between 350-500 and would therefore be using treatment prior to any significant immune damage.

We support research findings that the absolute risk of HIV-related complications remains very low at a CD4 count 350–500 and that individuals enrolled in START will be carefully monitored and access treatment if their health circumstances change.

We also support the unique importance of sub-studies in START.

These studies have the potential to answer important questions relating to the impact of HIV, treatment and ageing on neurology and mental health, bone health, heart disease, lung disease and behaviour risk.

We support the START investigators, community advocates and HIV-positive people interested in this dynamic research which will help close the essential gap in our current knowledge on the safety and risks of earlier treatment.

Signed:

(Members of the INSIGHT Community Advisory Board in surname alphabetical order)

Peer Aagaard, Denmark; Simon Collins, London; Nathan Geffen, South Africa; Joseph Hall, USA; David H. Haerry, Switzerland; Michael Meulbroek, Spain; David Munroe, USA; Dwight Peavy, USA; Claire Rappoport, USA; Siegfried Schwarze, Germany; Mirta Valdez, Argentina; Jo Watson, Australia.

The statement was also sent to the chairs of the United States Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents.

A list of the 140 organisations signing this letter and 120 individuals is available online:

http://i-base.info/home/community-statement-supporting-start-trial/

FDA safety updates to antiretroviral labels

The following summaries cover revisions to the US drug labels that were recently approved by the FDA in the US. Please check the full update for details.

Revised label are posted to the FDA website:

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory

Tenofovir for adolescent use

On 24 March 2010, the FDA approved revised labeling for tenofovir disproxil fumarate (Viread) to expand the indication to include patients aged 12–18 years of age and ≥35 kg, at the adult dose of 300mg once-daily.

This was based on 48-week clinical data from Study GS-321 which randomised 87 treatment-experienced adolescents 12 to <18 years of age were treated with tenofovir (n=45) or placebo (n=42) in combination with an optimised background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm3 and the mean baseline plasma viral load was 4.6 log copies/mL.

At baseline, 90% of patients had NRTI-associated mutations. Overall, the trial failed to show a difference in virologic response between the tenofovir and placebo treatment groups. Subgroup analyses suggest the lack of difference in virologic response may be attributable to imbalances between treatment arms in baseline viral susceptibility to tenofovir and OBR. Although changes in HIV-1 RNA in these highly treatment-experienced adolescent subjects were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of tenofovir in patients ≥12 years of age who weigh ≥35 kg and whose HIV-1 isolate is expected to be sensitive to tenofovir.

Assessment of bone mineral density (BMD) should be considered for adults and adolescents who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. In Study 321, bone effects were similar to adult subjects. Under normal circumstances BMD increases rapidly in adolescents. In this study, the mean rate of bone gain was less in the tenofovir-treated group compared to the placebo group. Six tenofovir-treated adolescents and one placebo-treated adolescent had significant (>4%) lumbar spine BMD loss at 48 weeks. Among 28 subjects receiving 96 weeks of tenofovir, Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir-treated adolescents suggest increased bone turnover, consistent with the effects observed in adults.

Tenofovir exposure achieved in eight adolescent subjects was similar to exposures achieved in adult studies. Pharmacokinetic studies have not been performed in pediatric subjects <12 years of age.

Efavirenz label changes on pregnancy, hepatotoxicty and drug interactions

On 14 April 2010, the Food and Drug Administration approved revisions to the package insert for efavirenz (Sustiva), for both capsules and tablets.

Under warnings and precautions during pregnancy, the update stated: 'As of July 2009, the Antiretroviral Pregnancy Registry has received prospective reports of 661 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first trimester exposures (606 pregnancies). Birth defects occurred in 14 of 501 live births (first trimester exposure) and 2 of 55 live births (second/third-trimester exposure). One of these prospectively reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported; however, this case included severe oblique facial clefts and amniotic banding, a known association with anophthalmia. There have been six retrospective reports of findings consistent with neural tube defects, including meningomyelocele.

Monitoring of liver enzymes before and during treatment is recommended for all patients with underlying hepatic disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with other medications associated with liver toxicity. Postmarketing reports of hepatic failure include patients with no pre-existing hepatic disease or other identifiable risk factors, and were characterised by a fulminant course, progressing in some cases to transplantation or death Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the unknown risks of significant liver toxicity.

Drug interactions included posaconazole (avoid concomitant use unless the benefit outweighs the risks) and maraviroc (refer to the full prescribing information for maraviroc for guidance on coadministration with efavirenz).

New dosing regimen for lopinavir/r (Kaletra)

On 27 April 2010, FDA approved a new dosing regimen for Kaletra (lopinavir/ritonavir) tablets and oral solution in the US.

Kaletra can be administered once daily (800/200 mg) in patients with less than three lopinavir resistance associated substitutions. Once daily administration of Kaletra is not recommended for adult patients with three or more of the following lopinavir resistance-associated substitutions: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. Of note, once daily administration of Kaletra is not recommended in pediatric patients.

The was based on similar virologic and immunologic response rates in study 802.

Class drug-interaction changes for all protease inhibitors

On 27 April 2010 an update was released for all protease inhibitors.

The approved protease inhibitors for the treatment of HIV-1 infection now all include the following drug-drug interaction information. Specific details of dose modifications are included in each new label.

- Sildenafil (Revatio) as a contraindicated medication when prescribed for the treatment of pulmonary arterial hypertension
- Alfuzosin (Uroxatral) as a contraindicated medication
- Recommendation that salmeterol (brand names are Advair and Serevent) should not be coadministered
- New dosing recommendation for bosentan (Tracleer) and tadalafil (Adcirca) when prescribed for the treatment of pulmonary arterial hypertension. Note, coadministration of bosentan and atazanavir (Reyataz) without ritonavir is not recommended.
- New dosing recommendations for colchicine when prescribed for the treatment of familial Mediterranean fever or gout
- New dosing recommendations for colchicine when prescribed for the prophylaxis of gout
- Recommendation that colchicine should not be coadministered with protease inhibitors in patients with hepatic or renal impairment

Development of apricitabine halted without finding backer for Phase 3

On 10 May 2010, the Australian biotechnology company Avexa, announced the closure of the development programme for the nucleoside apricitabine (AVX754).

According to an earlier statement in March, initial three-week results from the study suggest activity against HIV with M184V mutation, associated with high-level resistance to 3TC and FTC.

Apricitabine is a cytidine analogue similar to 3TC and 48-week results from Phase 2b studies were presented at the HIV Congress in Glasgoew in 2008. [2]

Avexa were developing apricitabine under license from Shire Pharmaceuticals.

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TREATMENT ACCESS

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
3TC/d4T 150/30mg tabs	Hetero, India	17 May 2010
abacavir, 300mg tablets	Strides Arcolab, India	12 May 2010
ddI delayed-release capsules, 125 mg, 200 mg, 250 mg, and 400 mg	Matrix, India	06 April 2010

"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.

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

C O M M E N T

This brings the total of FDA approved generic drugs and formulations to 112 since the programme started. 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

U.S. government leading backlash against AIDS funding

Shannon Kowalski, Open Society Institute

A few weeks ago, the Boston Globe published an article on the U.S. government's decision to flatline AIDS funding in countries that are currently receiving money through the President's Emergency Plan for AIDS Relief (PEPFAR). [1] This flagship program has put 2.4 million people on treatment, restoring life and hope for millions.

Globally, more than four million people are currently receiving treatment, with support of PEPFAR, the Global Fund to Fight AIDS, Tuberculosis and Malaria, UNITAID, national governments, and other donors. But there are at least six million people who need treatment now, who are still unable to get it.

Instead of scaling up, the Obama Administration is now saying enough is enough. It is telling the health providers it funds, that they can only put new people on AIDS treatment if some of the people they are already treating die.

The Boston Globe article quotes Eric Goosby, the U.S. Global AIDS Coordinator, as saying "People are struggling to find resources to honor the commitments we have made… We're not at a cap point yet. If it gets worse, we'll have another discussion."

Well, we just got our hands on a letter the U.S. government sent to treatment providers in Uganda in October, 2009. It says:

"In FY 2010 and 2011, each Partner should expect to have a set flat-lined budget for ARV procurement that should not be exceeded without discussion and written approval from their funding agencies. PEPFAR Implementing partners who directly provide antiretroviral treatment should only enroll new ART patients if they are sure that these new patients can continue to be supported without a future increase in funding...

"In filling treatment slots that are made empty through attrition – i.e. deaths and loss to follow-up estimated at 12-30% annually – priority should be given to the sickest patients, eligible pregnant women, children, TB/HIV patients, and family members of persons on ART. Partners should provide support as needed to ensure that patient information records are up to date and an equitable system of triage for total ART slots is worked out within their sites before enrolling any new patients."

If that's not a cap, then what is it?

Peter Mugyenyi, an AIDS specialist in Uganda, talked in that article about the anguish of turning people away: "Virtually every day, we have to turn away patients who need treatment, including breast-feeding women… We have to tell them 'There is a freeze.'"

And at an event in DC on Monday as reported in the Science Speaks blog, Dr. Lydia Mungherera, a Ugandan medical doctor, activist, and woman living with HIV, said, "The hopelessness we had in the 1980s, when we had no treatment, is what we are going back to now… The basic issue of right to life is being disrupted." [2]

Sources on the ground tell us that as many as 800 people are being turned away from clinics in Uganda a month, with no other option but to go home and hope that somebody else who is already on treatment dies before they do.

Treatment is one of the single most important HIV prevention tools that we have. Much, much more needs to be invested in better and more effective prevention programs. We know that treatment reduces infectivity and the availability of treatment encourages the uptake of voluntary HIV counseling and testing. According to an International AIDS Society briefing report *Will We End the HIV Epidemic?*, simply treating all of the people who need treatment now would decrease new infections by as much as a third. [3] When people know their HIV status, regardless of whether they are positive or negative, they are also more likely to take measures to protect themselves and others from HIV infection, whether that be by using condoms, reducing multiple partners, or not sharing needles.

Yet, the U.S. government's decision to cap treatment is undermining the overall HIV/AIDS response in Uganda. As Mungherera put it: "Seventy percent of Ugandans don't know their status. But what are we going to tell those people who come for testing? I'm sorry, there's no treatment?"

The Boston Globe article made clear that it's not just Uganda. The U.S. government has ordered a stop to building clinics in rural Mozambique and is starting to put limits on treatment in Zambia as well.

At the same time that the Obama Administration is flatlining PEPFAR funding, it is not doing anything more to make sure that it

can leverage funding from other donors to help fill the gap. For every $1 that the United States gives to the Global Fund to Fight AIDS, Tuberculosis and Malaria, other donors give $2. Yet in its FY2011 budget, the Administration proposed to not just flatline, but cut, funding to the Global Fund as well.

Other donor governments appear willing and ready to follow the U.S. government's lead.

Don't let it happen. The International AIDS Society website where you can send a personalised email to President Obama and other G20 leaders, asking them to fully fund the Global Fund and keep their promise to universal access to AIDS treatment and prevention now.

Source: Open Society Institute Blog, (23 April 2010).

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Evidence from six countries confirms fears of People Living With HIV/AIDS: treatment rationing is escalating

A new report from the International Treatment Preparedness Coalition (ITPC), a global community advocacy organisation, documents early warning signs of devastating impact to come from flatlining and cutting AIDS funding.

As evidence mounts that AIDS treatment is inexorably linked with other health issues, including maternal health and tuberculosis, ITPC argues that it will not be possible to build sustainable, credible health systems as the waiting lines for AIDS drugs grow.

The report 'Rationing Funds, Risking Lives: World backtracks on HIV treatment' is the 8th in the Missing the Target series, published by ITPC.

It analyses funding promises and changes in global approaches to treatment programmes and include community collected evidence from India, Kenya, Latvia, Malawi, Swaziland and Venezuela.

Download the report as a PDF file:

http://www.itpcglobal.org/

Launch of the 10th funding round and other outcomes from the Global Fund

Asia Russell, Health GAP

The Board of the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund), met in Geneva 28–30 April and on 20 May Round 10 was formally launched. Below is a brief summary of important decisions made by the Global Fund Board.

Round 10 launched

The Board decided to launch the Global Fund's 10th Funding Round—the Round 10 proposal form and guidelines was released on 20 May and the deadline for proposals is 20 August. Civil society helped to prevent the imposition of arbitrary restrictions to the size of Round 10, despite an effort by some donors to impose funding ceilings, in either a fixed dollar amount or a percentage of the total resources available for 2011-2013. However, the launch of Round 10 did include a decision to restrict spending on Round 10 grants only to the resources raised by the Global Fund by the end of 2011. This restriction applies only for Round 10.

Advocates must ensure that donors pledge the resources needed now to ensure that all applications considered by the Global Fund's Technical Review Panel (TRP) to be technically sound and recommended for approval, receive funding. Increased pressure on G20 countries is urgently needed, in order to expand funding available for Round 10—and beyond.

The next donor replenishment of the Global Fund—the main mechanism for Global Fund fundraising—will take place in October 2010 at a meeting at the UN, shortly after the UN Millennium Summit, which will attract heads of state from around the world. The Global Fund needs at least $20 billion over 2011-2013 to support scale up of programs to reach the Millennium Development Goals. $8.5 billion is needed to continue funding existing successful programs.

Round 10 and prioritisation criteria

When insufficient funding prevents immediate approval of all technically sound grant proposals recommended for funding by the

Technical Review Panel (TRP), the Global Fund uses the criteria of technical merit, disease burden, and poverty to rank the grants in a "queue."

The Global Fund Board decided to revise those criteria for prioritisation in Round 10. By giving technical merit weight that is comparable to disease burden and poverty, lower- and upper-middle income countries could be at a greater risk of being ranked lower in the queue, waiting longer for funding or risking not being funded at all if donors do not fully fund Round 10.

Round 10 and most-at-risk-populations

In order to ensure the needs of "most-at-risk-populations" (MARPs) are protected, particularly in lower- and upper-middle income countries, the Board decided that for Round 10 a pool of resources totaling $75 million (for the budget of the first 2 years of 5 year programs) will be set aside for HIV proposals focused on those populations. (Each proposal is subjected to an upper limit of $5 million—a figure derived based on assessment of the size of similar proposals in previous funding Rounds.)

Countries may either apply through the "normal" funding Round or through the special MARPs funding pool for HIV/AIDS only. Proposals to the MARPs funding pool that are recommended for funding by the TRP will not be subjected to the prioritisation criteria applied to the normal funding Round for as long as the resources allocated have not been exhausted.

National Strategy Applications: The Global Fund Board decided on its next steps in support of National Strategy Applications (NSAs). NSAs allow countries to request funding based on part or all of a national disease strategy, rather than through a Global Fund Rounds-based application. The Global Fund completed a "First Learning Wave" of NSAs in 2009 and based on lessons from that process, the Board decided to approve another NSA funding opportunity, which will not be funded until the fourth quarter of 2011—at the same time Round 11 is approved. Meaningful civil society involvement is needed at the global and country levels in shaping the second NSA funding opportunity, in order to ensure high-quality involvement of a range of civil society experts, advocates and implementers in developing evidence-based, ambitious strategies; preparation of NSA applications; and program implementation.

Joint health systems platform

The Global Fund Board decided to authorise the creation of a Joint Health Systems Funding Platform between the Global Fund, GAVI, and the World Bank.

There are many unanswered questions regarding how the Joint Platform will actually help make it easier for countries to receive funding based on ambitious, high quality, results-focused requests to address the major health systems bottlenecks undermining progress in the fight against AIDS, tuberculosis and malaria, such as increasing production and retention of health workers. This is particularly true given the substantial differences in core principles and governance between GAVI and the Global Fund on the one hand, and the World Bank on the other. As with the design of the second NSA funding opportunity, civil society should be closely engaged in monitoring and contributing to the development of the joint platform.

It is widely expected that the G8 summit in Canada in July will generate a new MCH initiative; the Board directed the Secretariat to "review...potential options...for enhancing the contributions of the Global fund to MCH, recognising the urgent need for additional and sufficient financing for MCH as well as for AIDS, tuberculosis and malaria."

These options will be reviewed by the Policy and Strategy Committee at its next meeting, with a decision by the Board at its final meeting of 2010.

This notes are edited from a longer report.

The Global Fund Board decisions are posted online:

http://www.theglobalfund.org/en/board/meetings/twentyfirst

PREGNANCY

Pregnancy outcomes with efavirenz

Polly Clayden, HIV i-Base

The low quality of evidence regarding the safety of efavirenz in pregnancy (associated with a potential increase in risk of central nervous system defects from preclinical studies), has led to much uncertainty when making recommendations. This is particularly problematic for guidance in resource-limited settings with fewer antiretroviral options and a public health approach.

Nathan Ford from Médecins Sans Frontières and colleagues conducted a systematic review of databases (to 2 February 2010) in order to identify observational cohorts reporting birth outcomes among infants exposed to maternal efavirenz during the first trimester of pregnancy. The findings from this analysis were published in AIDS ahead of print, May 24, 2010.

The primary endpoint of this study was birth defects of any kind. Secondary outcomes were spontaneous abortions, termination of pregnancy, stillbirths, and preterm delivery.

The investigators found 16 studies that met their inclusion criteria. These included 11 prospective and five retrospective cohorts.

Nine studies were conducted in resource-limited settings: South Africa, Botswana, Ivory Coast, Brazil and one multinational, MTCT-Plus. Six were European and one primarily in the US. Eight were reported in journal articles, six conference abstracts, one (MTCT-Plus) was an unpublished cohort and one the Antiretroviral Pregnancy Registry (APR) report.

Nine prospective studies reported rates for infants exposed to maternal efavirenz (35 defects out of 1132 live births) and non-efavirenz (289 defects out of 7163 live births) containing regimens during the first trimester. This gave a pooled non-significant relative risk of 0.87 (95% CI 0.61-1.24%, p= 0.45).

The investigators found low heterogeneity between studies (I2 = 0, 95% CI 0-56.3%, p= 0.85). There were no significant differences between studies conducted in industrialised counties compared with those in resource-limited settings, p=0.46.

There was an overall incidence of birth defects of 2.9% (95% CI 2.1-4.0%), range 0%-22.6% (95% CI 9.6-41%). Among all cohorts with birth defect data (1256 women with live births) they observed one infant with a neural tube defect (myelomeningocele), giving an incidence proportion of 0.08% (95% CI 0.002-0.44%).

Four prospective studies reported data for both first trimester (31 defects out of 920 live births) and second/third trimester exposure (19 defects out of 695 live births); the pooled relative risk between those groups did not differ (RR=0.91, 95% CI=0.46-1.79%, p=0.79).

Secondary outcomes were not reported consistently across studies. Seven studies reported spontaneous abortions in women with first trimester efavirenz exposure (39 abortuses out of 628 pregnancies); prevalence rates ranged from 2.6% (95% CI 0.1-13.5%) to 16.7% (95%CI 2.1-48.4%). Six studies and MTCT-Plus reported rates of stillbirths (24 out of 715 pregnancies); rates ranged from 0 (95% CI 0-9.3%) to 13% (95% CI 1.7-40.4%). Five studies reported preterm deliveries (55 out of 399 live births); rates ranged from 9.1%(95% CI 1.1-29.1%) to 18.2% (95% CI 7.0-35.5%).

Termination of pregnancy was reported by five prospective studies, three retrospective reviews and MTCT-Plus (81 out of 688 pregnancies); rates ranged from 2.5% (95% CI 0.8-5.7%) to 33.7% (95% CI 23.7-44.9%). The investigators noted that one study found a relative risk of termination 5.73 times higher (95%CI 1.45-22.75%, p=0.0017) among women receiving efavirenz compared to other antiretroviral drugs, indicating a need for careful counseling.

Overall the investigators found no increase in the incidence of birth defects among infants born to women receiving efavirenz in the first trimester. They note several limitations to the evidence base, including few studies reporting risk of bias or attempting to control for potential confounders, and most importantly the limited sample size.

They suggest that although these data should provide reassurance to providers, the low incidence of neural tube defects in the general population means a larger sample size is still needed to rule out the increased risk of this specific defect. They add that given an underlying incidence of neural tube defects in the general population of 0.1-0.4, even a five-fold increase would give an overall incidence of less than 1%.

They write: “The balance of risks and benefits of efavirenz in pregnancy merits some recalibration, particularly in resource-limited settings where drug formularies are limited, women of child bearing age represent the majority of those infected with HIV, coinfection with tuberculosis is frequent, and the risk of mortality for those who are eligible for ART is high.”

They suggest that better collection of birth outcome data should be performed in resource-limited settings where data are not always routinely captured. “It is critical that as efavirenz use increases among women in these countries that support is given to establish adequate pharmacovigilance systems to better define the risk.”

C O M M E N T

This useful analysis is reassuring for providers. As the authors emphasise, evidence with regards to the safety of efavirenz in pregnancy is weak. This uncertainty has led to conflicting recommendations. WHO have taken the view that the benefits outweigh the risks beyond the first trimester; national guidance in Zambia has done the same. In the new South African guidelines, the drug is contraindicated throughout pregnancy, which will make the scale up of treatment a bit more complicated.

It is worth noting that UKCHIC data, reported on page XX, shows that even in a well resourced setting with access to alternative antiretrovirals and awareness of the contraindication among providers, almost a fifth of women conceiving HAART were receiving efavirenz (and of these only about half switched).

Given that, whatever is recommended, it is inevitable that efavirenz use in pregnancy will increase with greater access to antiretrovirals, the authors correctly stress the need for pregnancy registries, particularly in African countries to capture these data in order to provide better guidance in the future.

Ref: Ford N et al. Safety of efavirenz in first trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. AIDS 2010, Published ahead of print May 24, 2010.

BHIVA GUIDELINES

Legal issues on HIV transmission and the law for healthcare workers: draft guidelines online for comment

A new joint guideline from BHIVA and BASHH on legal aspects of HIV transmission and work of the clinical team is now online for comment.

Prosecutions for reckless transmission of HIV have been brought in the UK since 2001 (Scotland) and 2003 (England & Wales).

This has raised complex questions among medical practitioners as to their ethical and legal responsibilities related to HIV transmission, particularly around disclosure of information on HIV status. Although established generic ethical and professional principles continue to apply, certain features of the HIV epidemic have required special consideration.

An underlying principle in the provision of clinical care for people with HIV is the need for a secure and confidential environment in which extremely sensitive matters can be frankly and fully discussed. The importance of ensuring that full trust is maintained by people with HIV in their clinical services in the light of the introduction of the criminal law into the HIV arena is fundamental, not only for the health of people living with HIV but also for people who may wish to seek information or testing and thus for the wider public health.

This guidance document sets out these responsibilities and how these relate to the roles and responsibilities of health care professionals when caring for individuals infected with HIV.

Comments can be made online and the draft document downloaded from the BHIVA website:

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

Infant feeding in the UK: draft guidelines online for comment

The joint BHIVA/CHIVA guidelines for infant feeding in the UK are currently online in draft and are available for comment.

Comments can be made online and the draft document downloaded from the BHIVA website:

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

BASIC SCIENCE

The antiviral impact of CD8 T cells: much ado about the mechanism

Richard Jefferys, TAG

The primary mechanism by which CD8 T cells contribute to controlling pathogens is by killing infected cells. The afflicted cells display pathogen epitopes on their surface via class I HLA molecules that constantly shuttle disused protein fragments to the cell surface in a manner akin to taking out the garbage. CD8 T cells that recognise the pathogen epitope in the context of an HLA molecule that matches the HLA molecule expressed by the CD8 T cell initiate a cascade of events that results in the infected cell being killed. Examples of the process have been captured on video (the Howard Hughes Medical Institute website has an excellent excerpt from a lecture by Bruce Walker showing such a video and explaining it [1]).

However, although this is the canonical mechanism of CD8 T cell activity (and the reason for their alternate moniker of cytotoxic T cell lymphocyte or CTL), CD8 T cells can also suppress pathogens by other means such as release of chemokines and cytokines and, in the case of HIV, an as-yet-unidentified antiviral factor that goes by the acronym of CAF.

While there is a vast amount of evidence demonstrating the importance of CD8 T cells in suppressing replication of HIV (and other similar viruses such as SIV), the relative contributions of direct killing and indirect suppression have not been clearly delineated. Attempting to do so is a complex task, as the contribution of these activities may vary based on factors such as the extent of immunologic control and disease stage.

Two new studies in PLoS Pathogens make a valiant first attempt to shed light on this issue by evaluating whether artificial depletion of CD8 T cells impacts the speed of SIV suppression by antiretroviral therapy (ART) in macaques. [2, 3]

The rationale of both studies is that the kinetics of ART-mediated viral suppression should be slower in the absence of CD8 T cells because infected cells will have a longer lifespan. In both experiments, no such effect is demonstrated, leading the researchers to argue that CD8 T cells do not impact the lifespan of productively infected cells and that therefore their primary mechanism of action in chronic SIV infection is indirect suppression as opposed to direct killing. In an accompanying commentary, Miles P. Davenport

and Janka Petravic invoke the tortured language of former US Secretary of Defense Donald Rumsfeld and suggest that CD8 T cell activity against HIV may qualify as a "known unknown." [4]

But there are a number of issues that make interpreting these data complicated. Both studies involve chronically SIV-infected macaques, and CD8 T cell dysfunction and exhaustion in the setting of chronic infection is well documented. It could be that in a milieu in which viral control is only partial and both functional and dysfunctional SIV-specific CD8 T cells co-exist, indirect suppression plays a larger role than in the setting of robust immunological control (e.g. elite controllers). The selection pressure imposed upon SIV and HIV by HLA-restricted CD8 T cell responses is also extremely well documented, and although the authors of these new papers argue that indirect suppression could also exert selective pressure this scenario is somewhat difficult to envision. It is straightforward to grasp how a virus with an immune escape mutation could survive as a result of CD8 T cells being unable to kill the cell it is occupying. But in the case of indirect suppression, the escape mutation would have to abrogate localized release of suppressive substances by virus-specific CD8 T cells; it seems unlikely that the epitope specificities of CD8 T cells in a localized environment would be so uniform that a single virus carrying an escape mutation would switch off the suppression to a sufficient degree to obtain a survival advantage (although this question may be amenable to study).

Both papers note the possibility that CD8 T cells might kill virus-infected cells prior to the release of new virions, therefore making their activity essentially invisible in this particularly experimental system. The data cited in support of this possibility comes from Jonah Sacha, who has shown that epitopes from incoming virions can be processed and presented to CD8 T cells prior to virus integration, leading to killing of infected cells before the establishment of productive infection. [5]

Another possibility is that CD8 T cell-mediated killing reduces the average number of virions produced by each infected cell while having only a minor impact on the average lifespan (I think the mathematical model used in these papers assumes the same average virion production – or "burst size" – for every infected cell). Due to considerable variation from animal to animal, relatively subtle differences in infected cell lifespan may not be easy to capture.

Despite all the complexity and caveats, the papers are provocative and highlight the need to better understand the mechanism of action of CD8 T cells in SIV, and by extension, HIV infection.

In a related development, a group of researchers headed by members of the Human Immunology Laboratory at the International AIDS Vaccine Initiative (IAVI) have just published details of an assay that measures HIV inhibition by CD8 T cells in vitro. [6]

Although the numbers of people studied is small, the paper reports that inhibition measured by the assay correlated with viral load control, i.e. CD8 T cell-mediated inhibition was strong among untreated individuals with viral loads <10,000 copies/mL but weak in those above that threshold. The researchers also use the assay to measure the inhibitory capacity of CD8 T cells from seven uninfected individuals immunised with a DNA/Ad5 HIV vaccine regimen, reporting that significant inhibition could be documented but only after receipt of the Ad5 boost. Importantly, there was no correlation between the degree of in vitro virus inhibition and the numbers of vaccine-induced CD8 T cell responses measured by ELISpot, which up until now has been the standard way to measure the immunogenicity of T cell-based vaccine candidates.

The new assay takes three weeks to run and involves less than 2 million cells, making it more practical than those developed previously. The study authors write: "We believe the viral inhibition assay will be a useful tool in the study of HIV-1 pathogenesis and vaccine development, complementing existing methods used to prioritise candidates for further trials."

Source: TAG Basics Science Blog. The antiviral impact of CD8 T cells: much ado about the mechanism. (9 February 2010).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2010/02/the-antiviral-impact-of-cd8-t-cells-much-ado-about-the-mechanism.html

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Bad to the bone marrow?

Richard Jefferys, TAG

The extent to which HIV may infect CD34+ hematopoietic progenitor cells (stem cells) in the bone marrow has been the subject of controversy for more than two decades. [1]

Early studies documented the presence of HIV in CD34+ cells in a subset of people with advanced disease, but a subsequent report offered little evidence of infection in asymptomatic individuals. [2]

In the new issue of Nature Medicine, a group of researchers from the University of Michigan revisit the issue in a paper that garnered substantial press coverage when it was released online a few weeks ago. [3]

The paper contains data indicating that CD34+ stem cells can be infected in vitro and also reports that HIV DNA could be detected in CD34+ cells sampled from the bone marrow of people with HIV infection, including four out of nine individuals on antiretroviral therapy (ART) with undetectable viral loads in peripheral blood. The researchers conclude that stem cells may be an important reservoir of latent HIV in people on ART.

There are some caveats, however, and it will be important for the findings to be confirmed (the researchers themselves acknowledge as much, stating: “further studies are needed to show that CD34+ stem cells are infected”). The in vitro work is primarily based on HIV isolates that are dual-tropic or target the X4 co-receptor, and the efficiency of infection by CCR5-using HIV appears lower (see the supplemental information panel “a” and compare the percentage of infected cells with the X4 and dual tropic viruses NL4-3 and 89.6 to the R5 viruses 94UG, MJ4 and YU2 [4]).

The numbers of individuals sampled for the in vivo results is also very small and analyses of larger cohorts are needed.

Source: TAG basic science blog. Bad to the bone marrow? (15 Apr 2010).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2010/04/bad-to-the-bone-marrow.html

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Cell-free vs cell-associated HIV transmission

Richard Jefferys, TAG

One of the most difficult questions to address regarding HIV transmission is whether virus floating free in plasma (cell-free virus) or contained inside cells (cell-associated virus) plays the primary role in causing infection. The issue has important ramifications for the design of biomedical prevention interventions, because cell-associated HIV may be less susceptible to some approaches than cell-free HIV.

Back in February a new journal called Science Translational Medicine published a paper that takes a detailed look at the question in six gay male transmission pairs. [1]

Although the sample is very small, the results show that virus found free in seminal plasma of the transmitting partner consistently bore the closest resemblance to the virus found in the newly infected individual. The authors acknowledge that larger studies are needed but also note that currently these results “provide the most compelling experimental confirmation for the hypothesis that that cell-free HIV RNA in seminal plasma, and not cell-associated HIV DNA in seminal cells, is the origin of sexually transmitted virus between MSM.”

Source: TAG basic science blog. Cell-free vs. cell-associated HIV transmission (15 Apr 2010).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2010/04/cellfree-vs-cellassociated-hiv-transmission.html

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Coagulation and inflammatory biomarkers in children and adolescents with HIV

Richard Jefferys, TAG

The Strategies for the Management of AntiRetroviral Therapy (SMART) trial has transformed HIV research by unambiguously demonstrating the link between viral replication, inflammation and clinical outcomes. A detailed sub-study in SMART found that, in adults, particular coagulation and inflammatory biomarkers (specifically D-dimer and IL-6) were very strongly associated with mortality risk, and levels of these biomarkers increased in association with HIV viral load when study participants interrupted ART. [1]

In the new issue of the journal AIDS, a group of Italian researchers describe results of a study designed to provide insight into whether the findings of SMART are relevant to children and adolescents with HIV. [2]

The researchers divided a cohort of 88 individuals (mean age 13.5 years) into high and low HIV viral load groups using a cut-off of 1,000 copies of HIV RNA/mL. Higher viral load levels were associated with significantly lower levels of protein S, a substance involved in blood coagulation; low levels of protein S are known to be associated with an increased risk of excessive blood clotting (thrombophilia). Levels of D-dimer were also significantly elevated in the high viral load group and showed a statistically significant correlation with HIV RNA levels (R2 0.37, P<0.001). D-dimer is a small protein fragment that is produced when blood clots are degraded in the body. Levels of C-reactive protein (CRP), which increased in SMART participants after ART interruption, showed no differences between the high and low viral load groups. IL-6 levels were not measured in this study.

In discussing their findings, the researchers state: “The study, given the low mean age of the cohort, highlights the direct role of HIV replication on coagulation disorders excluding the possible confounding role of major known risk factors for thrombosis and CVD, like hypertension, diabetes, and history of clinical thrombotic event. Furthermore, our analysis took into account the putative confounding action of other factors associated with an increased risk of thrombosis and CVD disease both in the general population (smoke, age, dyslipidaemia), and HIV-infected population (cumulative use of cART and protease inhibitor, actual use of ABC and ddI, dyslipidaemia). Nevertheless the study has some limitations since it is a cross-sectional study and the power for analysis of all variables considered has been limited by the relative small amount of observations. Prospective studies are needed to confirm and investigate the clinical implications of our observations.”

Source

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Pre-infection CD8 T cells targeting HIV linked to lower post-infection viral load

Richard Jefferys, TAG

The research group of Francis Plummer at the University of Manitoba was among the first to document evidence that some people can resist HIV infection despite multiple exposures. The evidence derives from a cohort of female sex workers in the Pumwani district of Nairobi; around 10% of the more than 1,000 women in the cohort have remained HIV negative despite ongoing exposures. A number of genetic and immunological factors have been described that associate with this apparent resistance to infection. [1] Among these factors are certain class I & II HLA genes and HIV-specific CD8 T cell responses (which have been detected in both the cervix and peripheral blood despite the absence of any detectable virus).

However, some of the women once thought to be resistant have seroconverted many years after first joining the cohort. In one published study, the most significant risk factor for this “late seroconversion” was taking a break from sex work, suggesting that at least in some women, ongoing exposure to HIV was involved in the maintenance of resistance (although the study also described some women who, after taking a break and returning to sex work, experienced an increase in their HIV-specific CD8 T cell responses and did not become infected). [2] One lingering question regarding these observations is whether women who have developed HIV-specific CD8 T cell responses prior to becoming infected are able to better control viral replication after infection occurs; in other words, does the presence of HIV-specific CD8 T cells give the immune system any kind of head start against the virus?

Although this is a difficult question to answer in a cohort study, Plummer’s group has now published data suggesting that pre-infection HIV-specific CD8 T cells may indeed be linked to better control of viral load post-infection. [3]

Because the numbers of people studied were small, the researchers conducted two analyses, one involving the Nairobi cohort and another with a different cohort in Kibera. In both cases, women who displayed HIV-specific CD8 T cell responses prior to infection had lower post-infection viral loads on average (by around 1 log) compared to women who lacked these responses. The researchers stress that all the pre-acquisition immunological assays were performed by investigators who were blinded to subsequent HIV acquisition status and viral load. In terms of the functionality of HIV-specific CD8 T cells between the two groups, the ability of the cells to proliferate in response to HIV antigens associated with better viral load control, while numbers of HIV-specific CD8 T cells

producing the cytokine interferon gamma showed the opposite trend.

In discussing the study results, the researchers point out that while it's possible that pre-infection HIV-specific CD8 T cells played a causal role in the observed outcomes, they could also represent a marker for other genetic and/or immune factors that are linked to better control of HIV replication. They nevertheless argue that their data support continued evaluation of T cell-based vaccines despite the disappointing results obtained with Merck's candidate.

Source: TAG basic science blog. Pre-infection CD8 T cells targeting HIV linked to lower post-infection viral load. (04 May 2010).

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TREATMENT ADVOCACY

The HIV Research Catalyst Forum: treatment, prevention, advocacy

Over 170 US treatment activists in the US met from 20–23 April in Baltimore for a community advocacy course organisied by the HIV Research Catalyst Forum (Formerly North American Treatment Action Forum—NATAF).

"From identifying research priorities to overcoming research barriers, HIV advocates have driven groundbreaking discoveries that have changed the course of this relentless epidemic. But with no cure or preventive vaccines in sight, rising new infection rates, and the continuing death toll, our work is far from over."

A wide range of workshops presented by many of the most experienced US advocates ensure that the only free access to all slides and related documents are available as a resource for other community networks.

http://www.hivresearchcatalystforum.org/

Experimental HCV drugs for HIV/HCV coinfected people: workshop on trial design

On 20 November 2009, the European AIDS Treatment Groups (EATG) organised the Brussels I / Sitges III third international workshop: "Clinical Trials Design: Experimental HCV Drugs for HIV/HCV Co-infected People" in Brussels, Belgium.

The 2009 meeting built on the success of two previous meetings held in Sitges in 2007 and 2008, that were instrumental in advancing HCV drug development in co-infected people. The European Medicines Agency (EMA) has now issued guidelines and recommendations, for HCV drug development including pre-approval studies in HIV co-infected people. Although FDA has not formally issued recommendations, they also support pre-approval studies in HIV/HCV coinfected people. Community members contributed to these guidelines.

Some companies also initiated clinical trials in co-infected people, while others began consulting with the community to discuss their HCV early drug development programs for HIV/HCV co-infected people.

The objectives of the 2009 meeting were to promote a multi-stakeholder discussion on how to move HCV research and clinical trial design forward for HIV/HCV coinfected people.

The meeting was attended by approximately 50 participants representing European and US Community Advocates, regulatory agencies (FDA and EMA), pharmaceutical companies, clinicians and researchers.

Presentations from the meeting are available to download form the EATG website:

http://www.eatg.org/eatg/ECAB/Conferences/Brussels-I-Sitges-III-Nov-20-Brussels

AIDS activists detained by Tanzanian authorities at World Economic Forum on Africa

Treatment Action Campaign, PR

On 5 May 2010, at the opening day of the World Economic Forum on Africa (WEF) in Dar Es Salaam, a group of nine AIDS activists from across the continent were detained for questioning by Tanzanian authorities after they handed over a memorandum entitled "Health is Wealth", which emphasised the need for increased investment in health and particularly HIV, TB and Malaria in Africa, to two prominent speakers at the WEF.

Yvonne Chaka Chaka, a popular South African musician and UN Goodwill Ambassador for the region, and Christoph Benn, the Director of External Relations for the Global Fund to fight AIDS, TB and Malaria, had arranged with the group to receive the memorandum from them outside the conference centre.

The small group had been delegated by 40 NGO representatives from more than ten African countries, who were gathered in Dar Es Salaam to discuss global and regional advocacy strategies to address the urgent need for resource mobilisation for universal access to HIV prevention, treatment and care (universal access), and for replenishment of the Global Fund in October 2010.

The group had chosen the WEF as a focal point for advocacy because of the inextricable links between health and socio-economic development.

In calling on global leaders to mobilise at least US$20 billion for the Global Fund replenishment in October 2010, the memorandum also pointed out that, as warned by the World Bank, "responding to immediate fiscal pressure by reducing spending on HIV treatment and prevention will reverse recent gains and require costly offsetting measures over the longer term".

The memorandum was originally intended to be handed over at a peaceful march with around 800 supporters, largely from Tanzanian community groups. However, the march was cancelled the night before, after the government revoked the permit to demonstrate.

Following the handing-over of the memorandum to Chaka Chaka and Benn outside the WEF, which lasted no longer than 15 minutes and caused no disruption to the conference activities, the group had boarded their bus and were preparing to return to their hotel when they were detained by police and taken to the police station for questioning. They were held for five hours, although ultimately no charges were issued or arrests made.

The group was then escorted under heavy security back to their hotel, where they were instructed to gather their luggage and proceed to the airport to wait through the night, under police supervision, until their flights departed from the country the following day. Although no formal "Prohibited Immigrant" notices were issued, members of the group were effectively treated as such and one member, who had planned to extend his stay by a few days, was compelled to accompany the group to the airport on standby for the next available flight.

Source: Treatment Action Campaign, Press Release (06 May 2010).

OTHER NEWS

China lifts travel ban on people with HIV

China, one of only a handful of countries who have tried to maintain an entry bar to HIV-positive visitors, announced that they have overturned a 20-year policy.

The change was made on 19 April, a few days before the opening of a large international trade fair called Shanghai Expo, and follows similar policy changes in January by the US and South Korea.

The State Council reportedly posted a statement on its website that the government had passed amendments on 19 April, revising the Border Quarantine Law as well as China's Law on Control of the Entry and Exit of Aliens. The changes were effective immediately. Restrictions for people with leprosy and sexually transmitted diseases were also removed.

Source: hivrestrictions.org

http://www.hivrestrictions.org

IAS statement in support of Chinese policy change:

http://www.iasociety.org/Default.aspx?pageId=408

Malawian court's 14-year sentence for gay men widely condemned

Nathan Geffen, TAC

A Malawian magistrate has sentenced Steven Monjeza and Tiwonge Chimbalanga to 14 years hard labour after convicting them of "indecent practices between males" and "unnatural offenses". This is the maximum sentence under Malawian law. Monjeza and Chimbalanga were arrested after holding an engagement ceremony for their civil partnership. They were denied bail and imprisoned throughout their trial. Monjeza is male and Chimbalanga is a transgender woman.

The conviction and sentence have been condemned by AIDS and human rights groups across the world, as well as the United States and United Kingdom governments and the South African Human Rights Commission. Demonstrations against the conviction have been held at Malawian embassies in the UK, the US and South Africa, with more planned.

The Southern Africa Law Centre, Centre for Human Rights and Rehabilitation, Centre for the Development of People and the AIDS and Rights Alliance for Southern Africa are assisting Monjeza and Chimbalanga with their legal defence. The magistrate's decision is being appealed.

The importance of this issue in the context of HIV prevention and treatment was highlighted by a press statement about the case, issued by the Global Fund for AIDS, TB and Malaria (GFATM). "The criminalisation of individuals based on their sexual orientation is not just a human rights issue - it also undermines investment in HIV and AIDS as it drives sexual behavior underground and creates an environment where HIV can more easily spread", says Prof. Michel Kazatchkine, Executive Director of the Global Fund. "This ultimately affects the broader population, in addition to the devastating impact it has on communities of men who have sex with men".

In southern Africa more than 50% of men who have sex with men also have sex with women. A recent study shows high levels of bisexual behavior in Malawi.

The linkage between proposed legislation in Uganda and actual judicial practice in Malawi - the links between MSM and HIV - are explained in an excellent article published last year in the Lancet by Adrian Smith and colleagues titled 'Men who have sex with men and HIV/AIDS in sub-Saharan Africa'.

S T O P P R E S S

As this issue went to press we learned that the President of Malawi overturned the convictions and issued a pardon for the two men.

This is an important outcome and achievement for these two people.

It needs to be followed with further progressive action, to enable similar abuses of human right to be tackled systematically in order to reduce the stigma faced by individuals highlighted by this case.

Magistrate Nyakwawa Usiwa-Usiwa's judgment can be downloaded from:

http://www.southernafricalawcenter.org/download/6/23

A petition for Monjeza and Chimbalanga to be freed can be signed here:

http://www.petitiononline.com/M100518R/petition.html

Community Media Trust have produced a video about this:

http://www.youtube.com/watch?v=51h7TYKtBeA

Youtube video from Malawi that protests the case results:

http://www.youtube.com/watch?v=eyIUg2VyHDs&feature=related

Press statement from the Global Fund (21 May 2010):

http://www.theglobalfund.org/en/announcements/?an=an_100521b

Smith A et al. Men who have sex with men and HIV/AIDS in sub-Saharan Africa. The Lancet, Volume 374, Issue 9687, Pages 416 - 422, 1 August 2009. doi:10.1016/S0140-6736(09)61118-1

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)61118-1/abstract

Uganda law proposes death penalty for homosexuality: can international reaction and vulnerability of treatment access programmes help?

Simon Collins, HIV i-Base

Growing publicity and concern over the proposals for Uganda to legislate even more severely against human rights on the grounds of sexuality have drawn widespread condemnation, but it currently remains unclear whether this will be sufficient to halt this shocking and depressing move. [1]

The proposed new laws, linking political opportunism, nationalism and religious extremism are particularly shocking for the devastating impact such discrimination has on the lives of gay men and women in Uganda and the impact this has on other African states.

It is also likely to contribute to reducing the effectiveness of HIV testing and treatment programmes on many levels. The discrimination faced by African men who have sex with men, and the link to HIV prevention was discussed in detail in an article last year in the Lancet which is available to view without subscription. [2] It is difficult to understand how this new legislation could help the currently fragile nature of international funding for treatment programmes. More depressingly, is the likely probability that the real impact on the lives of HIV-positive people is of no concern to those involved in the drive to impose the new legislation.

On the 14 October 2009, MP Bahati tabled the Anti-Homosexuality Bill in the Ugandan Parliament. The Bill is currently before the Legal and Parliamentary Affairs Committee. The stated objective of the Bill is to establish a comprehensive law to supposedly protect the traditional family by prohibiting any form of sexual relations between persons of the same sex; and to penalise homosexual behavior, including a death penalty for "aggravated homosexuality", to prohibit ratification of any international treaties, conventions, protocols, agreements and declarations which are contrary or inconsistent with the provisions of this Act, and to prohibit the licensing of organisations which promote homosexuality. The Bill makes it an offence not to report homosexual practices to the authorities and even seeks to criminalise Ugandans who commit homosexual acts outside of Uganda.

Uganda's Civil Society Coalition on Human Rights and Constitutional Law was established in October 2009 in response to the tabling of the notorious Anti-Homosexuality Bill in the Ugandan Parliament. The membership of the Coalition stands at 28 Ugandan civil society organisations. Its initial campaign is to see the Bill dropped from the Parliament's agenda. [4]

The Ugandans4Right.org website provides the most up-to-date information on the Bill, including the perspectives of the many Ugandans who are opposed to this draconian legislation. [4]

The story has been covered by mainstream media globally. In Uganda, BBC reporter John Simpson confronted the preacher Martin Ssempa saying "I have never heard so much hatred inside a church".

The US Senate passed a motion condemning the action [5] and numerous online petitions and letters had been sent in protest.

A letter from Southern African HIV Clinicians Society to Uganda Parliament included the following comment on the impact this would have on HIV. [7] An excerpt from this letter is reprinted below:

1. The measures proposed by the Bill will lead to the persecution of people who engage in same-sex relations. There is a large amount of international research which demonstrates that when specific groups are subject to victimisation, stigma and discrimination, they are less able to access health care services, which is particularly detrimental to public health measures in the context of the HIV pandemic.
2. By specifically targeting gay, lesbian and bisexual people who are living with HIV, the Bill will discourage such people from testing for HIV, knowing their status and accessing treatment. This will inevitably result in an increase in new HIV infections.
3. The Bill seeks to criminalise "the promotion of homosexuality", which includes funding organisations that work with lesbian, gay and bisexual issues, and the publication of material relating to these groups. In effect, this will mean that civil society organisations will not be able to provide outreach and health information to the gay, lesbian and bisexual community in Uganda. Preventing the dissemination of information on HIV prevention to a vulnerable group such as men who have sexual relations with other men will inevitably lead to a higher incidence of HIV in Ugandan society.
4. If the Bill is passed into law, Uganda will necessarily have to withdraw from international human rights conventions, including the Universal Declaration of Human Rights; the International Covenant on Civil and Political Rights; the International Covenant on Economic, Social and Cultural Rights; the Convention on the Elimination of all Forms of Discrimination Against Women; the Convention on the Rights of the Child; and the African Charter on Human and Peoples' Rights. Since the protection of human rights is an important aspect of reducing stigma regarding HIV, any deterioration in the human rights situation in Uganda will seriously undermine the work that has already been done in promoting openness and preventing new HIV infections.

We therefore strongly believe that the Bill will have profoundly negative impact on Uganda's efforts to combat HIV, and we call on all Members of Parliament who are committed to public health and human rights to ensure that this Bill is not passed into law in any form.

References:

1. Summary of Anti Homosexuality Bill, 2009.
   http://www.ugandans4rights.org/issues.php
2. Anti Homosexuality Bill, 2009. Proposed bill in full (PDF).
   http://www.ugandans4rights.org/downloads/09_10_14_Bill_No_2018_Anti_Homosexuality_Bill.pdf
3. Smith A et al. Men who have sex with men and HIV/AIDS in sub-Saharan Africa. The Lancet, Volume 374, Issue 9687, Pages 416 - 422, 1 August 2009. doi:10.1016/S0140-6736(09)61118-1
   http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)61118-1/abstract
4. http://www.ugandans4rights.org/
5. US sentate resolution.
6. Online petition and further information on Internation Gay and Lesbian Human Rights Commission
   http://www.iglhrc.org/cgi-bin/iowa/article/takeaction/resourcecenter/1088.html
7. Letter from SA HIV Clinicians Society to Uganda Parliament
   http://sahivsoc.org/index.php?option=com_docman&Itemid=59&task=doc_download&gid=65

FUTURE MEETINGS

2010 conference listing

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.

6th Intl Workshop on HIV and Hepatitis C Coinfection

31 May–2 June 2010, Tel Aviv

http://www.virology-education.com

5th International Workshop on Clinical Pharmacology of Hepatitis Therapy *and* 5th International Workshop on Hepatitis C - Resistance and New Compounds

23–24 June and 24–25 2010, Boston

http://www.virology-education.com

5th International Workshop on HIV Transmission - Principles of Intervention

15-16 July 2010, Vienna

http://www.virology-education.com

2nd International Workshop on HIV Pediatrics

16-17 July 2010, Vienna

http://www.virology-education.com

XVIII International AIDS Conference (AIDS 2010)

18-23 July 2010, Vienna

http://www.aids2010.org

50th ICAAC

12–15 September 2010, Boston

http://www.icaac.org

3rd Intl Workshop on Clinical PK of TB Drugs

11 September 2010, Boston

http://www.virology-education.com

BHIVA Autumn Conference

7–8 October 2010, London

http://www.bhiva.org

12th Lipodystophy Workshop 2010

4–6 November 2010, London

http://www.intmedpress.com/lipodystrophy

10th International Congress on Drug Therapy in HIV Infection

7-11 November 2010, Glasgow

http://www.hiv10.com

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

The i-Base website has been completely redesigned with new portals for healthcare professionals, HIV-positive people and community advocates.

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

http://www.i-Base.info

All i-Base publications are available online, including editions of the treatment guides. The site gives details about i-Base, the UK Community Advisory Board (UK-CAB), our phone service and meetings, as well as access to our archives and an extensive range of links. It can be used to order publications and regular subscriptions to be delivered by post or email (as PDF files).

The site also includes a web-based Q&A section for people to ask questions about their own treatment:

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

RSS news feed has been introduced for HIV Treatment Bulletin for web and PDA access - we welcome your feedback on this new way to provide treatment updates.

A section on Education, Advocacy and Training includes our training manual for advocates 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 6000 pages are served from the site each day.

Training manual – revised, updated and now fully online

This established training resource has been revised and updated and is now online in new format.

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

The Training Manual for Advocates provides entry-level curriculum relating to HIV and treatment.

It is made up of 8 modules for learning about aspects of HIV care has been updated and published online as an interactive resource. It provides entry-level curriculum relating to HIV and treatment.

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

Sections include:

1. Immune system and CD4 count
2. Virology, HIV and viral load
3. Introduction to antiretrovirals (ARVs)
4. Side effects of ARVs
5. Opportunistic infections and coinfections
6. HIV and pregnancy
7. Drug users and HIV
8. Clinical trial design and the role of advocates

Each module includes learning objectives, non-technical review material, test questions, an evaluation and a glossary.

We hope this will be useful for training advocates and other related healthcare workers as well as for HIV-positive people who want to know more about aspects of their healthcare.

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.

Generic clinic forms

We have also posted online 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

Please contact the i-Base office if you would like help adding your own hospital or Trust logo to these forms.

Report assessing the treatment information needs 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 six 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 earlier 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".

With text provided by activists from 25 countries and 50 full colour photographs by Wolfgang Tillmans, this limited edition 100-page publication is being sold by i-Base to raise funds to help support our international treatment literacy projects.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting since 2002. It now includes over 300 members from over 100 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 these meetings are posted. Membership is free,

http://www.ukcab.net

World CAB - reports on international drug pricing

Two reports from meetings between community advocates and pharmaceutical companies, that focused on pricing issues and global access to treatment, and that are now available online.

Both are available to download as a PDF file from the i-Base website.

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 (June 2009)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)
- Guide to changing treatment: what to do when your treatment fails (September 2008)
- Guide to HIV, pregnancy & women's health (January 2009)
- Guide to avoiding & managing side effects (May 2008)

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 currently include:

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

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.

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 10 times a year in a printed version, in a pdf file that we can email to you, and on our website.

The printed version is available at most HIV clinics in the UK and is available free by post.

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.

ARV4IDUs

An electronic publication, produced in English and Russian language editions, to provide an overview of research related to IV-drug use and antiretroviral treatment.

Treatment information request service - 0808 800 6013

i-Base offers specialised treatment information for individuals, based on the latest research.

We can provide information and advice over the phone, and we can mail or email copies of the latest research studies relevant to the caller.

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 900 questions online. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).

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

Recent questions include:

- How long will it take for my CD4 count to go back up?
- Is it possible for CD4 cells to decrease so quickly?
- What is the difference between the ELISA and ELFA test?
- Are there travel restrictions in France and Spain?
- I have been treated for hep B and hep C, now which HIV treatments should I take?
- I tested at 25 days, do I need another test?
- What is the window period for antigen-antibody tests?
- Will my CD4 count increase after I give birth?
- How do I treat or prevent skin problems?
- If I have unprotected sex with other HIV positive people will I get resistance?
- Why is my CD4 count not increasing?
- What are the best vitamins to take if I am HIV positive?
- Do people on HIV medication have to give up work?
- I am a male that is HIV positive and my partner is HIV negative, is there a way we can still have children?
- I am HIV positive, can I get a mortgage or life insurance?
- Are swollen lymph nodes early symptoms of HIV?
- How bad is to sniff the poppers for a people with HIV?
- What does 'an empty stomach' mean when taking Atripla?
- What resources are available for someone affected by HIV or Hepatitis B/C?

Find HTB on AEGiS

AEGiS.org - the longest established and largest global resource of online HIV information - includes HTB in the regular journals that it puts online. You can find us at:

http://www.aegis.org/pubs/i-base/2009

The AEGiS daily email news service also carries i-Base conference reports.

Order i-Base publications via the internet, post or fax

People with internet access can use our website to order and receive publications. You can access our publications online or subscribe to receive them by email or by post; and you can order single copies or bulk deliveries by using the forms at:

http://i-base.info/order

Copies of publications can also be ordered by post or fax using the form on the back page of HTB. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), HTB South, Treatment 'Passports' and all our guides to managing HIV and additional reports.

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:
http://www.i-Base.info; by fax or post using the form on the back page by sending an email to: subscriptions@i-Base.org.uk

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http://www.i-Base.info

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HIV i-Base

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

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

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REFUNDS FROM THE TAX MAN

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

Whichever of the above schemes you might chose to donate to i-Base we would like to thank you very much for your support.

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1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other _____ _____

Guide To HIV, Pregnancy and Women's Health *(January 2009)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

NEW: Introduction to Combination Therapy *(June 2008)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Changing Treatment - Guide to Second-line and Salvage Therapy *(September 2008)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Guide To Avoiding and Managing Side Effects *(May 2008)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Guide To HIV and hepatitis C coinfection *(May 2007)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Translations of earlier treatment guides into other languages are available as PDF files on our website

Phoneline support material *(pls specify required number of each)*

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

Adherence planners and side effect diary sheets - In pads of 50 sheets for adherence support

1 Sheet ☐ **1 pad** ☐ **5 pads** ☐ **10 pads** ☐ **Other** ☐ _____ _____

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