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EDITORIAL

Welcome to the January/February 2009 issue of HTB, the first issue in our tenth volume.

It is both somewhat sobering to find ourselves the most widely distributed HIV-specific print journal for healthcare professionals in the UK, and also something of an achievement for this to be provided free.

We now also distribute a southern African edition (HTB South) in association with the Southern African Clinicians Society, which is distributed to over 15,000 health workers in the region.

We lead this issues with conference coverage from two meetings from the end of last year: the 9th International Congress held in Glasgow and the 10th International Workshop on Adverse Drugs Reactions and Lipodystrophy (IWADRL).

Both these meetings continue to be a focus for important research and it is important that the results from the Antiretroviral Pregnancy Register were first presented here.

As we go to press, the annual Conference on Retroviruses and Opportunistic Infections is about to start, which is sure to provide plenty to report in the next issue.

Supplements with this issue

For electronic subscribers, we have included as a supplement to this issue of HTB, issue four of the English editions of ARV4IDUs.

We expect the Russian version of this electronic publication will be available online in the next week or so.

CONFERENCE REPORTS

9th International Congress on Drug Therapy in HIV Infection

9-13 November 2008, Glasgow

Introduction

The Glasgow conference, held every two years, has now produced webcasts from many of the lectures and these are online together with the conference abstracts.

Abstracts and webcasts can be accessed via the congress website at the following link:

<http://www.hiv9.com>

Abstracts are also online as a supplement to the Journal of the International AIDS Society 2008.

<http://www.jiasociety.org/supplements/11/S1>

The following reports from the conference are included in this issue of HTB:

- Summary of antiretroviral studies at Glasgow
- The Antiretroviral Pregnancy Registry: individual drug safety reports on health of infants exposed to ARVs during pregnancy
- Initial results from PENTA 11 trial of planned treatment interruptions
- Inflammation and coagulation markers askew in children with higher HIV RNA
- Dosing of lopinavir/ritonavir in the CHIPS cohort
- Number needed to treat to harm (NNTH) analysis of impact of underlying cardiovascular factors on risk of abacavir-related heart attack
- Bone disease and HIV
- Renal tubule damage with tenofovir despite normal glomerular function

Summary of antiretroviral studies at Glasgow

Simon Collins, HIV i-Base

The following short summaries cover some of the new research presented on current and pipeline antiretrovirals.

Please see abstract links for further details of each study.

Unboosted atazanavir as maintenance treatment in naïve patients

JF Delfraissy presented results from a 48-week study that randomised 252 treatment-naïve patients after a 26-30 week induction phase of boosted atazanavir/r 300/100mg plus 2 RTIs, to either continue or switch to once-daily unboosted atazanavir (400mg) plus continued RTIs. Only patients suppressed to <50 copies/mL were randomised to switch. Tenofovir was not allowed as an RTI because of the negative drug interaction with atazanavir.

Of 252 patients at baseline (median CD4 245 cells/mm³; median HIV-RNA 4.95 logs), 30 discontinued (nine for side effects) and 50 failed to reach undetectable viral load and continued on boosted ATV/r. This left 172 patients who were randomised 1:1 to either ATV or ATV/r.

At week 48, the ATV arm demonstrated similar (non-inferior, margin 15%) efficacy with 78% and 86% of patients suppressed to < 50 and <400 copies/mL respectively, compared to 75% and 81% of patients who remained on boosted ATV.

CD4 responses were similar. Although there were more discontinuations prior to week 48 with boosted atazanavir (14% vs 8%), fewer patients on ATV/r experienced virological rebound (7 vs 11). None had emergence of PI resistance.

As expected, side effects favoured unboosted ATV: grade 3–4 total bilirubin in 47% vs 14% and mean percent triglyceride change from the switch to week 48 was +9.8 vs. -27.0, both for ATV/r & ATV, respectively.

C O M M E N T

The balance between maintaining suppression and improved tolerability may make maintenance treatment without ritonavir an option for some naïve patients who have tolerability difficulties, but this will also reduce the safety buffer zone for adherence times.

Confirming individual drug levels using therapeutic drug monitoring (TDM) would be a safer approach.

Reference

Delfraissy JF et al. Efficacy and safety of 48-week maintenance with QD ATV vs ATV/r (both + 2NRTIs) in patients with VL <50 copies/mL after induction with ATV/r + 2NRTIs: study A1424136. 9th International Congress on Drug Therapy in HIV Infection. 9-13 November 2008, Glasgow. Abstract O415.

<http://www.jiasociety.org/content/11/S1/O42>

Darunavir/r vs lopinavir/r: 96 week resistance results from TITAN study

The Phase 3 TITAN study has previously reported superiority of darunavir/r (DRV/r) compared to lopinavir/r (LPV/r), with 67.5% vs. 59.5% patients achieving <400 copies/mL (difference 8%, 95% CI 0.1–15.8, p=0.03), in almost 600 treatment-naïve patients.

Virological failure was higher in the LPV/r arm (25.6%, n = 76) was higher than in the DRV/r arm (13.8%, n = 41).

Primary PI mutations were found in 25/72 of LPV/r and 7/39 for DRV/r patients with matched resistance results (with darunavir/r V32I occurred in three patients, I47V and L76V in two patients and M46I, I54L, I54M and L90M in one patient).

NRTI mutations occurred in 20/72 the LPV/r arm compared to 4/39 in the DRV/r, with similar proportions of patients losing phenotypic sensitivity to the study protease inhibitor. The majority of patients failing darunavir/r retained susceptibility to other PIs: amprenavir (31/31), atazanavir (29/30), indinavir (31/32), LPV (33/33), nelfinavir (24/26), saquinavir (31/31) and tipranavir (34/35). Susceptibility to the background NRTIs (20/55 vs. 4/35) or any NRTI (27/66 vs. 7/38) was also reduced in significantly more lopinavir/r patients.

C O M M E N T

The differences between darunavir/r and lopinavir/r suggest a greater role for darunavir/r in first-line therapy, and as we went to press once-daily darunavir/r was approved in Europe. The retained phenotypic sensitivity to second-line protease options is encouraging, but this will need confirmation with clinical results.

Reference

De Meyer S et al. Resistance development in virological failures with DRV/r or LPV/r: 96-week analysis of the Phase III TITAN trial in treatment-experienced patients. 9th International Congress on Drug Therapy in HIV Infection. 9-13 November 2008, Glasgow. Abstract O424.

<http://www.jiasociety.org/content/11/S1/O46>

Apricitabine 48 week results

Final 48 week results from a Phase 2b study of apricitabine (ATC), a new cytidine analogue similar to 3TC, in approximately 40 treatment-experienced patients with resistance to 3TC (at baseline, 52% of patients had ≥ 3 thymidine mutations and 76% had ≥ 1 non-NRTI mutation). At week 24 all patients switched to the higher dose 800mg ATC.

By week 48, around 90% patients achieved viral suppression < 50 copies/mL in all arms. CD4 increases were $\sim +260$ cells/mm³ in the ATC arms vs $+200$ cells/mm³ in the 3TC arm. No significant ATC-related SAEs were reported.

Reference

Cahn P et al. 48-week data from Study AVX-201 - A randomised phase IIb study of apricitabine in treatment-experienced patients with M184V and NRTI resistance. Abstract O414.

<http://www.jiasociety.org/content/11/S1/O41>

The Antiretroviral Pregnancy Registry: individual drug safety reports on health of infants exposed to ARVs during pregnancy

Polly Clayden, HIV i-Base

In an oral presentation Karen Beckerman described the role of the Antiretroviral Pregnancy Registry (APR) and presented the latest analysis of compiled data. [1, 3]

The APR is an international registry, started in 1989, to prospectively monitor potential birth defects in infants exposed to antiretrovirals in utero. It is one of the largest ongoing pregnancy registries in the world.

The objectives of the registry are to provide early warning of major teratogenicity; estimate risk of birth defects and collect supplementary data from animal, clinical and epidemiological studies. Data collection is through voluntary enrollment by healthcare providers of pregnant women exposed to antiretrovirals, and in turn infant follow up.

This analysis looked at the ability to detect, at 80% power with Type I error rate of 5%, potential increases in birth defect prevalence in infants following first trimester exposure (during which organogenesis occurs), vs. second and third trimester exposures.

The registry has sufficient numbers of reports to detect a 2-fold increase in overall anomalies following exposure to abacavir, atazanavir, efavirenz, FTC, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, d4T and tenofovir. For AZT and 3TC there are sufficient numbers of reports to detect a 1.5-fold increase in such anomalies.

Dr Beckerman presented data from 1989 to 31 July 2008. The majority of reports (88.2%) are from the US, with small numbers from elsewhere (eg UK 3.1%, SA 1%). One of the current goals of the registry is to increase non-US reporting.

During this period 11,950 pregnancies were enrolled. Of these 494 (4.1%) were awaiting outcome and 985 (8.2%) were lost to follow up. There were 10471 evaluable pregnancies; 47% were exposed to antiretrovirals during the first trimester.

9,948 (93%) live birth outcomes were available for analysis. Among this group Dr Beckerman reported an overall prevalence of defects of 2.7% (271/9,948) 2.9% (126/4329) from pregnancies with earliest antiretroviral exposure in the first trimester vs. 2.6% (145/5618) with second and third trimester exposures.

APR continues to monitor two drugs that in the past met criteria for evaluation and further monitoring: AZT was associated with an increased risk of hypospadias among infants in the Women and Infants Transmission Study (WITS), and the registry found a higher than expected, 4.4% (94/3068), defect prevalence following first trimester of ddl exposure that has no apparent pattern and is not statistically significant. Notably, defect prevalence for efavirenz exposures were, 3.2% (13/407) ie not elevated above background population risk, and were no different from first and second/third trimester exposure to any other antiretroviral.

C O M M E N T

A major recent change in the APR has been the inclusion of data from the Women and Infants Transmission Study (WITS). A higher than expected incidence of hypospadias in babies exposed in utero to AZT is reported in these data, and, when added to the individual prospective reports to the register, AZT is associated with an increased risk of hypospadias. However, this association is not found when the WITS data are excluded. It is difficult to explain this discrepancy. Data from the European Collaborative Study, which are summarised in the APR reports, but not included in the analysis, do not suggest any association between AZT and hypospadias.

The higher rate of congenital anomalies with ddl has been documented in the APR for a number of years without attracting much attention, in part due to the lack of association with a specific defect (as compared with efavirenz). However, the overall rate has steadily reduced over several years; there have been fewer reports of congenital malformations associated with ddl in recent years. It should be noted

that the APR has not examined rates of congenital malformations with specific combinations (which are legion) but one explanation of the trend is that ddI is no longer prescribed with other ARVs that increase the risk of congenital malformations.

As in all previous reports from the APR the overall risk of congenital malformation in babies exposed during the first trimester to efavirenz is not increased. One case of spina bifida has been reported in the prospective arm of the study but it is not possible to know whether this reflects an increased risk or is a chance observation.

Finally, it is important to note the paucity of data on all newly licensed antiretroviral therapies. These should be prescribed with caution in all women of child-bearing potential, regardless of stated family planning intent.

References

1. KP Beckerman, D Covington, K Dominguez et al. Antiretroviral Pregnancy Registry (APR) at 10,000 prospective reports. 9th International Congress on Drug Therapy in HIV Infection. 9-13 November 2008, Glasgow. Abstract 0223.
<http://www.jiasociety.org/content/11/S1/O22>
2. Watts DH, et al. Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. Journal of Acquired Immune Deficiency Syndromes: JAIDS 2007, 44(3):299-305.
3. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2008 Wilmington, NC: Registry Coordinating Center; 2008.
<http://www.APRegistry.com>

Initial results from PENTA 11 trial of planned treatment interruptions

Polly Clayden, HIV i-Base

Di Gibb presented findings from the PENTA 11 trial on behalf of the Paediatric European network for treatment of AIDS (PENTA).

PENTA 11 was a phase II randomised trial of antiretroviral treatment (ART) strategies, comparing CD4-guided planned treatment interruption (PTI) to continuous therapy (CT) in children with viral load <50 copies/mL, and CD4% \geq 30% (2-6 years) or CD4% \geq 25% and CD4 \geq 500 cells/mm³ (7-15 years). In the PTI arm, ART was stopped and restarted if a child had a confirmed CD4% <20% (<7 years) or CD4% <20% or CD4 <350 cells/mm³ (\geq 7 years).

After a DSMB review following the SMART results, the protocol was amended so that no interruption lasted longer than 48 weeks and further PTIs were only undertaken in children who spent >10 weeks off ART during their first PTI and had been back on ART for at least 24 weeks.

The trial was powered on equivalence; 2-sided with a 15% margin. The primary end-point was CD4% <15% (and/or CD4 <200 cells/mm³ \geq 7 years), new CDC C diagnosis or death. Minimum follow up was 72 weeks.

Professor Gibb reported that from 2004 to 2006, 109 children were randomised to CT (n=53) or PTI (n=56): 45% children were boys; their median age was 9.3 (range 2-16) years; 35% white, 31% black; 26% CDC stage C, median time on ART 5.7 (IQR: 3-9) years. Their median baseline CD4% was 37% (IQR: 33-41), CD4 966 (IQR: 793-1258) cells/mm³; prior to ART nadir (at age 3 years) CD4% 18% (IQR: 10-27) and CD4 627 (IQR: 320-1050) cells/mm³.

After a median of 130 (IQR: 80-144) weeks (one child lost to follow up), the investigators found that 4% of the study period was spent off ART by children in the CT arm vs 48% in the PTI arm.

During the first PTI, 9 children restarted treatment in <10 weeks; 21 (38%) children restarted ART <48 weeks (14 failing CD4, 7 non-protocol reasons); 32 (57%) restarted at or after 48 weeks and three remained off ART. 16 children had a 2nd PTI.

Professor Gibb reported no child died or had a CDC C event. CD4 primary end points occurred in 1 (2%) CT vs 4 (7%) PTI (difference 5% [95% CI -2%, 13%], p=0.2). 98.4% of total time in CT vs. 95.9% in PTI was spent with CD4 \geq 350 cells/mm³.

The mean change in CD4 count from baseline to 72 weeks was -106 vs. -240 cells/mm³ in CT vs. PTI (difference -134 cells/mm³, 95% CI -237, -31, p = 0.01). Differences between the two groups are difficult to interpret as some children in the PTI arm were off ART at 72 weeks. In an exploratory analysis, the mean CD4 change 0-72 weeks was -124 cells/mm³ in 27 PTI children who had all been back on ART for \geq 24 weeks; this is closer to the -106 value observed in CT children.

The CD4 fall of 106 cells in the CT arm is unlikely to be due to the natural fall in CD4 experienced by children throughout childhood, as children's CD4 counts normalise to those of adults by the age of 6 and the median age of the cohort was 9.3 years.

When the investigators looked at CD4 z-score change in the PTI arm from 0-24 weeks (1st PTI) after restarting, they reported that age adjusted CD4 recovery was significantly better in young children (mean, SE): -0.1 (0.3), -0.9, -1.3 for ages 2-6 (n=4), 7-10 (n=20) and 11+ (n=13) years, respectively, p = 0.02. Thus children <6 years almost fully recovered their CD4 values within 24 weeks, but older children did not.

At 72 weeks, 94%/85% vs. 81%/58% children had VL <400/<50 copies/mL in CT vs PTI ($p = 0.05/0.003$). Of the 28 PTI children back on ART for ≥ 24 weeks, 89%/68% had VL <400/<50 copies/mL, there was no evidence of more resistance in the PTI arm using standard genotype tests: 10 (5 CT and 5 PTI) of 13 children with 2 consecutive measurements >100 copies/mL on treatment had resistance; of these, 4 CT and 2 PTI had 4 or more mutations.

Although adverse events were more frequent in the PTI arm, these were mostly predictable (more lymphadenopathy, consistent with new onset viraemia).

With respect to both CD4 recovery and viral load suppression after PTI, Professor Gibb noted that because some children were off ART at 72 weeks, results so far are difficult to interpret and longer follow-up is essential, and is ongoing. The investigators concluded, "Longer-term assessment of all children after restarting ART will be required to fully assess risks and benefits of PTI in this population".

In the meantime, paediatricians have advised all children on PTI to be restarted on ART. These results do provide reassurance that ongoing interruption trials should continue in both chronically infected children (BANA trial in Botswana) and following primary infection (CHER trial in South Africa). Results of adherence/acceptability and immunology/virology studies alongside PENTA 11 are now being analysed.

C O M M E N T

The PENTA group does not currently support treatment interruptions in children outside of a research study and has recommended that children in this study now restart ART. The same questions raised by the SMART study that now need to be answered in children include:

- i) Whether children re-suppress viral load.**
- ii) Whether higher sensitivity resistance tests show development of resistance.**
- iii) Whether CD4 recovery similarly lags behind that of baseline levels, even 18 months after reintroduction of treatment, and**
- iv) What are the long-term implications of ongoing viral replication and importance of ongoing immune activation? (See the study from Pontrelli et al below).**

Reference

Gibb DM, Compagnucci A, Green H et al. Treatment interruption in children with chronic HIV-infection: the results of the paediatric European network for treatment of AIDS (PENTA) 11 trial. 9th International Congress on Drug Therapy in HIV Infection, 9-13 November 2008, Glasgow. Abstract O222.

<http://www.jiasociety.org/content/11/S1/O21>

Inflammation and coagulation markers askew in children with higher HIV RNA

Mark Mascolini, for NATAP.org

Levels of the thrombosis marker D-dimer were significantly higher in children and adolescents with an HIV viral load above 1000 copies/mL than in those with lower loads. [1] Protein C and S anticoagulant activity and antithrombin activity were lower in youngsters with high viral loads.

HIV researchers started pondering D-dimer when SMART trial investigators charted significantly rising levels of that marker in people randomised to intermittent antiretrovirals compared with steady therapy. [2] The SMART analysis also disclosed climbing concentrations of IL-6, an inflammation marker, in treatment interrupters. Higher SMART baseline levels of both D-dimer and IL-6 raised the risk of all-cause mortality.

A cross-sectional ("slice-of-time") study at Rome's Bambino Gesù Children's Hospital involved 88 children, adolescents, and young adults seen between December 2007 and June 2008. Their ages averaged 13.6 years and ranged from 3 to 25. Fifty-two cohort members (59%) were female, and 76 (86%) were taking antiretrovirals. The investigators measured the thrombosis marker D-dimer and several inflammation markers--antithrombin, protein C anticoagulant, protein S anticoagulant, and C-reactive protein.

Sixty-three youngsters (72%) had a viral load below 1000 copies, and 25 had a higher load. Sixty-eight people (77%) had a CD4% above 25% and 20 were under 25%. Sixty-one (70%) had CDC class B or C (symptomatic) HIV infection and 27 did not. Defining protein C and S activity deficiency as below 70% activity, the investigators found deficient C activity in 7 people (8%) and deficient S activity in 45 (51%). Antithrombin activity deficiency, defined as below 75% activity, affected only 1 person.

D-dimer levels were significantly higher in cohort members with a viral load above 1000 than in those with lower loads. In contrast, activity of protein C anticoagulant, protein S anticoagulant, and antithrombin was significantly lower in the group with a high viral load. C-reactive protein did not vary significantly by viral load, CD4%, or disease stage. None of the markers correlated with age or duration of HIV infection.

The SMART analysis of D-dimer and IL-6 factored in age, race, use of antiretrovirals, viral load, CD4 count, smoking status, body mass index (BMI), prior cardiovascular disease, diabetes, use of antihypertensives or lipid-lowering drugs, total-to-HDL cholesterol ratio, and coinfection with hepatitis B or C [2]. The Italian study excluded people with hepatitis but did not specify which variables they weighed in their analysis, other than those noted above.

The investigators speculated that the better protein C and anticoagulant activity in children and adolescents with symptomatic HIV infection could reflect antiretroviral treatment of these children compared with those who had less advanced infection. But none of the markers studied varied significantly by antiretroviral treatment status. The 1000-copy cutoff for good viral control may strike some as arbitrary.

Table 1: Inflammation and coagulation markers by viral load, CD4% and CDC class

Parameter	VL <1000 copies/mL	VL >1000 copies/mL	p-value
D-dimer, mean ng/mL (+/-SD)	206 (+/- 100)	341 (+/- 253)	0.024
Protein C activity, mean % (+/-SD)	101.9% (+/- 26.0%)	92.0% (+/- 14.7%)	0.007
CDC class N/A: 89.9% (+/- 20.4% SD)			0.02
CDC class B/C: 103.1% (+/- 24.1% SD)			
Protein S activity, mean % (+/-SD)	75.3% (+/- 18.2%)	57.6% (+/- 21.7%)	0.0003
CD4% >25: 74.1% (+/- 19.5% SD)			0.001
CD4% <25: 57.2% (+/- 20.0% SD)			
Antithrombin activity, mean % (+/-SD)	115.5% (+/- 13.6%)	107.5% (+/- 9.2% SD)	0.005
CDC class N/A 107.2% (+/- 9.2%)			0.002
CDC class B/C: 116.15% (+/- 13.6%)			
CD4% >25: 114.6% (+/- 13.2% SD)			0.024
CD4% <25: 108.9% (+/- 11.5% SD)			

The researchers acknowledged that “further studies are necessary to correlate such alterations with clinical events and to investigate the protective role of therapy in this particular population.” This line of research bears watching since treatment interruptions remain high on the research agenda for children, who otherwise face several decades of continuous antiretroviral therapy. But if coagulation and inflammation markers signal a higher risk of non-AIDS diseases in children with higher loads while interrupting therapy (as they do in adults [2]), treatment breaks may not be worth the risk, even in children.

References

1. Pontrelli G et al. D-dimer and anticoagulation activity markers in children and adolescents with HIV infection. 9th International Congress on Drug Therapy in HIV Infection, 9-13 November 2008, Glasgow. Abstract P213.
<http://www.iasociety.org/content/11/S1/P213>
2. Kuller LH et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008;5(10):e203.
<http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050203#top>

Dosing of lopinavir/ritonavir in the CHIPS cohort

Polly Clayden, HIV i-Base

Sarah Walker from the Medical Research Council presented data from the UK/Irish Collaborative HIV Paediatric Study (CHIPS) cohort looking at paediatric dosing of lopinavir/ritonavir (LPV/r). [1]

Dr Walker explained that the licensed LPV/r paediatric daily dose is 460 mg/m² without, and 600 mg/m² with concomitant NNRTI therapy. The 460 mg/m² dose without NNRTIs was chosen in preference to 600 mg/m² in a post-hoc drug-interaction analysis [2]. Following the completion of the phase II trial, this post-hoc analysis revealed a significant interaction between NNRTI and LPV/r, leading to the lower dose being licensed for use without NNRTI. The phase II trial showed very good viral load data overall, with 79% of children <400 copies/mL at 48 weeks, but this was based on the higher 600 mg/m² dose. Because of this uncertainty some paediatricians prefer to prescribe the higher dose of LPV/r irrespective of concomitant NNRTI therapy.

In the CHIPS study the investigators evaluated the LPV/r doses prescribed without NNRTIs in the cohort from 2000–2007.

They looked at predictors of current dose, including sex, VL and CD4, age, CDC stage, height/weight-for-age, calendar year, formulation, frequency and previous PI use, using mixed models allowing child and hospital effects.

They also evaluated the impact of the LPV/r dose on viral load suppression 6 months after starting it using logistic models and over longer follow up using binomial mixed models.

Dr Walker reported, 311/1,336 (25%) children in the cohort had received LPV/r without an NNRTI; for a total of 654 child-years. Of these children, 238 (77%) were still on LPV/r when they were seen last.

The median age of the children at initiation of LPV/r was 9 (IQR 5–12) years. The investigators recorded 684 doses in 299/311 children of which 52% were syrup, 38% capsules and 10% tablets. 662 (97%) doses were taken twice daily.

Overall the dose/m2 could be estimated 2,748 times in 278 children (the remaining children did not have height/weight recorded). They found few (7%) doses were >10% below the 460 mg/m2 target, and few (9%) >10% above the 600 mg/m2 target, with the majority >410–<530 mg/m2 (46%) or >530–<660 mg/m2 (39%).

In a multivariate analysis, the investigators found doses were: 17 mg/m2 [95%CI 0–34], higher in children who had prior CDC C event, $p=0.05$; 2 mg/m2 [0–3] higher for every log10 higher VL, $p=0.02$; 48 mg/m2 [38–58] higher with capsules/tablets vs syrups, $p<0.001$; 22 mg/m2 [4–40] higher with twice- vs once-daily dosing, $p=0.02$; 19 mg/m2 [15–24], $p=0.001$, and 10 mg/m2 [6–14], $p<0.001$ higher for every one unit lower current weight- and height-for-age, respectively; and 9 mg/m2 [5–14] higher for every year younger over 10, $p<0.05$.

Dr Walker noted that the mean dose for a 10 year old, without prior CDC event, average weight and age for height receiving capsules or tablets was 546mg/m2. She also noted that dosing varied greatly by centre with some using higher and some lower doses.

The investigators found no evidence that the initial LPV/r dose was associated with significantly improved viral load suppression at 6 months and reported: <400 copies/mL, AOR=1.06 per 50 mg/m2 (95%CI 0.87-1.28), $p=0.58$; <50 copies/mL, AOR=0.81 per 50mg/m2 (95%CI 0.65-1.01), $p=0.06$.

The investigators concluded: “Doses were higher with capsules/tablets, likely reflecting over- rather than under-dosing when solid formulations cannot achieve exact doses. However, we found no clear evidence that higher doses improved VL suppression.”

Dr Walker added: “Opinion seems to be split as to the most appropriate LPV/r dose in children.”

References

1. Walker AS et al. To overdose or underdose? The question of Kaletra in children in the UK/Irish Collaborative HIV Paediatric Study (CHIPS). 9th International Congress on Drug Therapy in HIV Infection, Glasgow. November 2008. Abstract O123. <http://www.ijasociety.org/content/11/S1/O8>
2. Saez-Llorens X, et al.: Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 2003, 22:216-224.

Number needed to treat to harm (NNT_H) analysis of impact of underlying cardiovascular factors on risk of abacavir-related heart attack

Simon Collins, HIV i-Base

JD Kowalska from the D:A:D study presented a model looking at the ‘number needed to treat to harm’ (NNT_H) in order to help interpret the clinical importance of the 90% increased relative risk (RR=1.90), previously reported between abacavir use and the risk of heart attack. [1, 2]

This estimate changed depending on an individuals underlying cardiovascular risk. The underlying risk was calculated based on 5-year Framingham score [3] and the relative rate was assumed to remain constant across the range of underlying risk of MI.

NNT_H was calculated as:

$$\frac{1}{(\text{underlying risk of MI} \times 1.90) - \text{underlying risk of MI}}$$

The lowest NNT_H values were observed in the high risk group, while the most dynamic changes in NNT_H is in the low risk group, showing an exponential relationship between NNT_H and underlying risk of MI. The NNT_H dropped steeply from 185 with an underlying risk of MI of 0.6% to only 5 when underlying MI risk is 20%.

The importance of additional risk factors was illustrated by starting with a low risk patient (0.1% risk of MI); in this case, 1111 patients would need to be treated before seeing an abacavir-related MI. When two unfavourable risk components are present the NNT_H drops to around 100 for most pairs, except smoking and low HDL, for which NNT_H drops to 69. When all risk factors are unfavourable, in patients with 15% underlying CVD risk, only 7 people would need to be treated with abacavir to see a treatment associated MI. (See Table 1).

Table 1: Change in factors contributing to underlying risk

Underlying risk of MI in 5 years	5-year risk of MI (%)	NNTH
Low risk profile (40 year old man with none of risk factors listed below)	0.1	1111
Impact of additional single risks:		
If total cholesterol 240 mg/dL (6.2 mmol/L)	0.2	555
If diabetes	0.2	555
If ECG-LVH	0.2	555
If sBP 160 mmHg	0.3	370
If HDL 35 mg/dL (0.9 mmol/L)	0.3	370
If smoking	0.4	277
Impact of multiple risks:		
If HDL and total cholesterol unfavourable	0.8	138
If smoking and diabetes	1.1	101
If smoking and total cholesterol unfavourable	1.0	111
If smoking and sBP 160 mmHg	1.3	85
If smoking and HDL unfavourable	1.6	69
If smoking and lipids unfavourable	3.1	35
If all unfavourable combined (excluding ECG-LVH)	10.1	11
If all unfavourable combined (including ECG-LVH)	15.0	7

C O M M E N T

This model supports the conclusions from both D:A:D and SMART studies to caution against using abacavir in patients with high underlying cardiovascular risk.

It also demonstrates the potential clinical impact from reducing other risk factors where alternative treatment options are not available.

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Bone disease and HIV

Simon Collins, HIV i-Base

Many studies have highlighted the significantly increased rates of osteopenia and osteoporosis in HIV-positive individuals compared to the general population, but, although this is one of the foremost concerns in an aging patient group, very few clinics actively incorporate either screening or monitoring of bone disease into routine HIV care.

The following summary covers an overview of osteoporosis and HIV presented at the conference by Dr Paddy Mallon from University College Dublin. [1]

The WHO defines osteopenia and osteoporosis as individual bone mineral density (BMD) scores that are between -1.0 and -2.5 (for osteopenia) and > -2.5 (for osteoporosis) standard deviations from the norm. T-scores relate to levels for a 30 year-old Caucasian woman and Z-scores relate to norms adjusted for age and gender.

In the setting of HIV, where the main outcome is to reduce the risk of fracture, T-score is the best validated surrogate marker, because the main management goal is to reduce fractures and each reduction of 1.0 in the T-score indicates an approximately doubled risk of fracture.

Cross-sectional studies have shown remarkably high incidence rates of reduced bone mineral density of between 40-80% in HIV-positive people, and a prevalence of 10-15% for osteoporosis. HIV-positive people are 6.4 times more likely to have osteopenia and 3.7 times more likely to have osteoporosis. [2]

As with the general population, risk factors include patient factors (female gender, Caucasian race, family history and falls risk) and lifestyle factors (smoking, exercise and alcohol use). However, HIV-related factors (which have included duration

of infection, use of PI and NRTIs, hypogonadism, steroid use, and vitamin deficiency and low BMI) are less consistently clear, perhaps because HIV-specific studies have involved lower numbers of patients to have the statistical power to find significant associations.

In the HIV-negative people, BMD increases until around age 30 where it remains stable for perhaps 5-10 years before starting to decline (at a rate of 0.5-1% per year), especially, in women during menopause (during which it declines at -2% bone volume a year). [3] Women generally have lower BMD than men.

The importance of the bone health in the context of HIV is that many people will be diagnosed and treated for HIV before they are 30, prior to reaching their natural peak bone health.

This is a particular concern for children, and recent data from the paediatric ACTG studies have shown statistically lower BMD in HIV-positive compared to HIV-negative children, and also that this increases with Tanner development stage, particularly in males. [4]

Several prospective studies suggest that BMD in HIV-positive patients on stable therapy declines at similar rates to HIV-negative individuals, perhaps with an additional decrease associated with starting treatment. In the Gilead 903 study patients using tenofovir/FTC had a greater loss in hip BMD compared to the d4T/3TC arm but this difference became non significant at year three with both groups losing 2.4-2.8% from baseline levels. [5]

Importantly, similar reductions have been reported for combinations using AZT/3TC (with efavirenz or lopinavir/r), and these reductions continued in patients after discontinuing nucleoside analogues. [6] Some studies have continued to report a potentially greater effect with protease inhibitors. [7]

Results from a sub-study of the SMART trial (see report from the Lipodystrophy Workshop later in this issue of HTB) reported a similar rate of reduction in hip and spine BMD in patients who used continuous treatment to the studies above, but less of a reduction in patients who used CD4 guided treatment interruptions. [8]

Finally, a large US database, that included over 8,000 HIV-positive patients and over 2 million HIV-negative patients, provided convincing results that lower HIV-related BMD does result in a clinically significant increase in the risk of fractures (even though the study didn't measure BMD directly). In this study, HIV was significantly associated with increased rates of vertebral, wrist and hip fractures (overall 2.87 vs 1.77 per 100 patient years, $p=0.0001$) with a slightly higher impact for men compared to women. [9]

Pathogenic mechanisms in HIV are relatively complicated. The principal hormonal control of bone disease revolves around parathyroid hormone (PTH). In the kidney this affects tubular calcium re-absorption by upregulating 1-alpha hydroxylase, which is involved with the production of active vitamin D (1.25vitD), which in turn acts upon calcium absorption in the gut to maintain serum calcium levels. In bone, PTH acts at the osteoblast level to induce production of RANKL factor. This increases osteoclast activity to shift the balance of bone turnover in favour of bone resorption, increasing calcium levels which itself feeds back to reduce levels of PTH.

Several studies have also highlighted vitamin-D deficiency in HIV-positive patients, related both to low dietary intake (40-60% patients estimated at less than 10ug daily) and access to sunlight. A US study in disadvantaged youths, in both southern and northern states, found that almost 90% had low vitamin D levels (less than 37.5nmol/L) and that these were predicted by latitude, dietary intake and alcohol use. [10]

A possible complication from HAART, presented at ICAAC this year, included preliminary findings from a small New York study of 34 men on tenofovir-containing HAART and 17 men on non-tenofovir HAART and highlighted the potential complexity of the PTH mechanism. While over 80% of the whole study group were vitamin D deficient (unrelated to use of tenofovir), significantly higher PTH levels were found in the tenofovir group (median 80 vs 55 pg/mL, $p=0.03$; and 39% vs 7% with levels >65 pg/mL, $p=0.02$) and within the subgroup of patients with lowest vitamin D levels. [11]

Most interestingly, recent research has also suggested an interaction between bone metabolism and metabolic changes, through the production in adipose tissue of an adipokine called leptin that acts on the hypothalamus to induce the sympathetic nervous system to increase osteoclast activity. A less well-described feedback mechanism may be mediated back to adipose tissue by the bone-derived factor osteocalcin. The increase in adipose tissue generally seen in the first 6 months of HAART may therefore be directly related to the higher rates of bone loss reported in the same period.

Other pathogenic mechanisms have looked at the effect of individual ARVs on osteoblasts and osteoclasts function and vitamin D metabolism in vitro, although interpreting the clinical implications of these findings is less clear.

In terms of management, there are currently no consistent evidence-based guidelines relating to osteoporosis in HIV-positive patients and a few studies from treating men in general. Both treatment and management however should focus on reducing the risk of fractures.

Modifiable risk factors include stopping smoking, reducing alcohol intake, increasing exercise, and monitoring use of steroids. Treatment with bisphosphonates, calcitonin, parathyroid hormone and oestrogen are supported by studies in the general

population. [12] Alendronate increased lumbar BMD in HIV-positive patients by an additional 4% from baseline at week 48, compared to the approximate +1.5% from vitamin D and calcium supplementation alone. [13] Vitamin D and calcium replacement, while widely used to correct low serum levels, and known to increase BMD, are less supported by data relating to their impact on reducing fractures. [14]

C O M M E N T

The link between bone and metabolic changes may be particularly important. This presentation rightly concluded with a call for more research and for the productions guidelines for management and treatment in HIV.

A useful overview article on this issue was posted online on Medscape in December. [15]

Several London clinics have already reported low vitamin D levels in HIV-patients. In Glasgow, a poster from the Chelsea and Westminster reported that 20% of 74 patients (17 women, 57 men) admitted to their hospital in a two month period were vitamin D deficient (<15nmol/L) and 45% had insufficient levels (15-50nmol/L). [16]

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Renal tubule damage with tenofovir despite normal glomerular function

Mark Mascolini, for NATP.org

Asymptomatic renal tubule damage may affect people taking tenofovir even if they have a normal glomerular filtration rate, according to findings in a prospective Spanish study. [1] Older age and treatment with tenofovir both independently predicted renal tubule dysfunction in these patients.

Madrid clinicians measured 24-hour urine in three unmatched groups: 81 antiretroviral-naïve people with HIV, 49 antiretroviral-treated people who never took tenofovir, and 154 tenofovir-treated individuals. The naïve people were significantly younger than both antiretroviral-experienced groups, but median age was similar in the non-tenofovir-experienced group and the tenofovir group (46 and 44 years). CD4 counts were statistically equivalent in the two experienced groups (572 and 487, $p=0.2$). Similar proportions in all three groups had hypertension or took nephrotoxic drugs (other than tenofovir), and about 25% of people in the two experienced groups had diabetes.

Creatinine clearance was lower in tenofovir takers (109 mL/min) than in the other groups (119 mL/min in the nontenofovir treated group and 123 mL/min in the untreated group), but not significantly so. Fractional tubular resorption of phosphorus was significantly lower in the tenofovir group than in either of the other groups: 82% versus 87% in naïve patients ($p<0.001$) and 85% in non-tenofovir-treated people ($p=0.002$).

The investigators defined altered tubular function as having two of the three following conditions: nondiabetic glucosuria, reduced tubular resorption of phosphorus, or pathologic aminoaciduria. By that definition, 22% taking tenofovir had tubular damage versus 6% taking a nontenofovir regimen ($P = 0.01$) and 12% taking no antiretrovirals ($P = 0.06$). Among people taking tenofovir, 51.4% had fractional tubular resorption of phosphorus (versus 27.1% taking a nontenofovir regimen, $P = 0.003$); 11.4% had fractional excretion of uric acid (versus 0 taking a nontenofovir regimen, $P = 0.01$); and 19.5% had beta2 microglobulinuria (versus 4.3% taking a nontenofovir regimen, $P = 0.01$).

Multivariate analysis determined that a tenofovir-containing regimen independently raised the risk of renal tubule damage more than 20 times (odds ratio 21.6, 95% confidence interval 4.1 to 13, $P < 0.001$). Every extra year of age raised the risk 6% (odds ratio 1.06, 95% confidence interval 1.0 to 1.1, $P = 0.01$). Variables that did not affect the risk of tubule damage in this analysis were gender, body weight, history of hypertension or diabetes, viral load, CD4 count, length of antiretroviral therapy, protease inhibitor therapy, concomitant nephrotoxic drugs, or hepatitis B or C virus coinfection. Kaplan-Meier survival analysis confirmed a significantly higher risk of tubule dysfunction with tenofovir than with a nontenofovir combination ($P < 0.001$).

The investigators concluded that tenofovir, though “relatively safe,” may be linked to functional damage of the proximal renal tubule. And that damage may be asymptomatic when studied prospectively. They proposed that “the long-term consequences of abnormal tubular dysfunction in patients on tenofovir warrant close examination.”

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CONFERENCE REPORTS

10th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV (IWADRLH)

6-8 November 2008, London, UK

Introduction

This annual workshop continues to retain its importance as an important focus for research and discussions between scientists, researchers, clinicians and patient advocates, and expert in a wide range of comorbidities from outside the HIV field.

The research covered by this annual workshop has gradually expanded beyond lipodystrophy to include complications relating to other metabolic changes, cardiovascular, renal and bone disease, hepatitis coinfection and cancer.

We include two overviews from this years conference, both from long-standing researchers involved in the meeting - Jacqueline Capeau (from CDR Saint-Antoine, Inserm, Paris) and Michael Dubé (from University of Southern California). Both reports are based on articles from natap.org. We also include a summary of a community research project that highlights why the original focus of the meeting remains as important as ever.

- Report from the 10th IWADRLH by Jacqueline Capeau
- Report from the 10th IWADRLH by Michael Dubé
- Impact of body changes on the quality of life of HIV-positive treatment experienced patients: an online community-based survey

Webcasts from the 10th Workshop are available online including two short video webcasts from the Organising Committee discussing the 10th Workshop and reviewing the history of the meeting.

<http://www.intmedpress.com/lipodystrophy>

Abstracts are published in a supplement of Antiviral Therapy 2008, 13, suppl 4. The indication close to the name of the first author refers to the page in this supplement.

Report from the 10th IWADRLH by Jacqueline Capeau for natap.org

Insulin resistance: effect of new ART

Three studies from London looked at the impact of ARVs on insulin resistance.

A study performed in 19 healthy volunteers searched for the effect of tenofovir (300 mg QD) versus placebo on muscle insulin sensitivity evaluated by an euglycemic hyperinsulinemic clamp and revealed that tenofovir neither modified insulin sensitivity nor adipokine or endothelial markers level. [1]

Similarly when comparing the effect of raltegravir (400mg BID) versus lopinavir boosted with ritonavir (400/100 mg BID) for 2 weeks, P Randell et al did not find any effect of raltegravir on muscle insulin sensitivity while LPV/r induced a 16% decrease, as previously reported. [2]

In treatment-experienced patients on a double PI, the authors (A30) evaluated the effect of the switch towards boosted darunavir (600 mg BID) on insulin sensitivity. They did not observe a modification in insulin sensitivity and in the more insulin resistant patients, insulin sensitivity tended to improve. [3]

Alterations in body fat distribution

Two groups studied human fat samples from visceral and subcutaneous area to try to understand the different phenotypes observed during lipodystrophy with loss of subcutaneous fat while the visceral depot is expanded.

M Giralt and colleagues studied 10 subcutaneous fat biopsies from lipodystrophic patients and 7 biopsies from visceral fat (4 from the same patients). The expression of a number of genes was evaluated: mitochondrial dysfunction was present in both types of samples. A phenotype of poor differentiation was observed only in samples issued from the subcutaneous depot. Markers of inflammation and macrophages were observed in the two depots but were not equivalent. Therefore, in HIV-infected patients the profile of gene expression is different in the two fat depots. [4]

C Vatter presented data from subcutaneous and visceral fat from HIV-negative lean women. The samples were incubated ex vivo with different antiretroviral molecules. Protease inhibitors (nelfinavir, lopinavir and ritonavir) but not stavudine were able to induce an inflammatory profile with increased IL-6 production in subcutaneous fat samples but were devoid of an effect in visceral samples. This resulted in increased free fatty acid release from subcutaneous but not visceral fat. These results help to understand how some antiretroviral can have opposite effects of each fat depot. [5]

Several in vitro studies evaluated the effect of efavirenz on adipocyte differentiation and function and reported that efavirenz was highly deleterious in the setting.

F Villarroja and colleagues compared the effects of efavirenz and nevirapine on murine and human adipocyte differentiation and observed that efavirenz strongly inhibited differentiation and exhibited toxicity while nevirapine did not impair and even enhance differentiation. [6]

E Hammond presented further data on sequential adipose tissue biopsies from patients under thymidine analogue NRTI before and after switch to other NRTIs. Fat samples from patients under tNRTI exhibit an inflammatory phenotype with invading macrophages expressing a number of pro-inflammatory cytokines while the expression of adiponectin is decreased. When patients are switched from thymidine analogues, the level of mtDNA was partly restored but the inflammatory phenotype poorly reversed in patients with the more severe lipoatrophic phenotype. Evaluation of these markers in the serum was generally not correlated with their expression in fat tissue. [7]

E Martinez showed data on limb fat obtained comparing patients with intermittent relative to continuous thymidine sparing antiretroviral therapy in patients with lipoatrophy. 147 patients were randomised to continuous (n=44) viral-guided group

(maintained at HIV-1 RNA < 30 000 copies/ml, n=50) or immune-guided group (maintained at CD4 > 350/mm³, n=53). Compared to the continuous treatment group, patients with immune and viral-guided interruptions gained more limb fat (+700-900 g at 24 months). Bone mineral density in femur and lumbar spine remained stable or increased on the two interruption groups whereas it decreased in the continuous treatment group. [8]

Metabolic alterations

M Boffito studied the effect of boosting dosages of ritonavir on metabolic parameters in healthy volunteers. She previously presented at the 2008 CROI meeting that RTV 100 mg BID but not RTV 100 mg QD increased triglycerides concentrations after 2 weeks and that reduced HDL and CD36 expression in blood leucocytes were observed for both RTV doses. In 20 individuals randomized to RTV 100 then 200 for 2 weeks with a washout period of 2 weeks in between or the reverse scheme, they found that CD40 plasma levels were increased with the two doses while the inflammation marker us-CRP (C reactive protein) and the endothelial marker sICAM remained unmodified. RTV 200 but not 100 increased adipophilin gene expression, a marker of lipid-laden macrophages. Thus boosting doses of RTV can modify some parameters and the effect is generally related to the RTV dose. [9]

Switching NRTIs to TDF/FTC

G Ionescu and colleagues evaluated the effects on fat, liver and muscles of substituting TDF for ZDV versus continuing ZDV in patients treated for an average of 5 years by a ZDV-containing regimen. Five controls and 7 switching patients completed the study. At week 24, whole body, lower limb and visceral fat increased in the switch group and decreased in the ZDV continuation group as expected. Hepatic fat content and lactate clearance by the liver tended to improve in the switch group. Skeletal and cardiac muscle mitochondrial function tended to improve while muscle insulin sensitivity remained unmodified. [10]

In the TOTEM study presented by MA Valantin, dyslipidemic patients under NRTI were switched to tenofovir/FTC. Lipid levels, TG and LDL-c, decreased early at week 4 and remained lower at week 12. The proportion of patients with a LDL-c level higher than 4,1 mmol/l decreased from 48% at baseline to 26% at week 12. Therefore, switching the NRTI backbone to TDF/FTC was beneficial for the lipids in dyslipidemic patients. [11]

The RECOMB study performed in Spain and presented by E Martinez (A35) evaluated the limb fat change 48 weeks after switching from ZDV/3TC to FTC/TDF (n=39) versus continuing on ZDV/3TC (n=41). Median change from basal level in total limb fat measured by DEXA-scan was +392 g in the FTC/TDF group vs -257 g in the ZDV/3TC group. The recovery in limb fat was observed in particular in patients with lower limb fat level (< 7,2 kg), prolonged exposure to ZDV (more than 5 years) and BMI < 25 kg/m². Therefore, switching from ZDV allowed a good recovery in limb fat even if lipotrophy was severe and if exposure to ZDV was prolonged. [12]

In the prospective, open-label, single arm SETTLE study presented by JC Gathe, 24 HIV-infected suppressed patients were switched from abacavir/3TC to tenofovir/FTC for 48 weeks. At week 4, total cholesterol and triglycerides were decreased but the effect was not maintained at week 48. However, the proportion of patients with total cholesterol over 240 mg/dl decreased from 43% at baseline to 33 % at week 48 and the proportion of patients with TG over 200 mg/dl decreased from 54% at baseline to 29% at week 48. [13]

Metabolic results from the BICOMBO substudy BICOMBOMET were presented by M Saumoy. BICOMBOMET is a multicentre trial comparing TDF/FTC (n=55) versus ABC/3TC (n=48) in virologically suppressed patients. At week 48, a significant increase in total cholesterol, LDL-c and Apo B but also of HDL-c and Apo-A1 was observed in ABC/3TC compared to TDF/FTC. LDL to HDL and Apo A1 to Apo B ratios remained stable in both arms. An increase in small, dense LDL-c subfractions was observed in both arms but only ABC/3TC use was associated with an increase in the more atherogenic B phenotype and a decrease in LDL particles size. Therefore, ABC/3TC led to a more atherogenic profile. However, no change was observed in the estimated CV risk. [14]

Cardiovascular alterations

To investigate whether increased CRP levels and HIV infection are independently associated with acute myocardial infarction (AMI), V Triant and colleagues performed a study in the a large US healthcare system in Boston. Among patients between 1997 and 2006 with a recent CRP determination and AMI (CRP determination between 3 years and 1 week prior to AMI), 487 were HIV-infected and 69870 were not. Multivariable logistic regression analysis was used to test the association of increased CRP and HIV with AMI after adjustment for demographic and other cardiovascular covariates: increased CRP (OR : 2.13) and HIV (OR: 1.93) were independently associated with AMI. HIV patients with increased CRP have a fourfold increased risk of AMI compared to those with neither risk factor. Measurement of CRP may be useful in the cardiovascular assessment and prediction of AMI in HIV-infected patients. [15]

The involvement of the renin-angiotensin system (RAS) in ARV-induced adverse effects was evaluated in cultured adipocytes by F Boccara and colleagues. The association of ATV and LPV with boosting concentrations of RTV was able to up-regulate the RAS system on adipocytes and to induce an increased oxidative stress. Two angiotensin II type 1 receptors blockers (ARB), irbesartan and telmisartan used as antihypertensive drugs, were able to revert the effect of the boosted PI. Therefore,

the adipocyte RAS system might be activated by some ART and ARBs could be beneficial in that setting. [16]

Bone toxicity

A subgroup of the BICOMBO study evaluated bone toxicity, the BICOMBO body composition substudy, and was presented by A Curran. The authors compared the long-term effect on body fat and bone mineral density after switching from NRTI to either TDF/FTC (n=25) or ABC/3TC (n=20). The two groups were similar at baseline with 5 kg limb fat. After 96 weeks, there was an absolute gain of limb fat in the two groups of about 300g in the TDF/FTC group and 750g in the ABC/3TC group. Total fat was decreased by 130g in the TDF/FTC group but increased by 1.8 kg in the ABC/3TC group. Bone mineral density was significantly increased in both groups. Patients on thymidine analogues at baseline experienced higher increments in limb fat than those not using AZT or d4T. Therefore, after 96 weeks of follow-up, switching from NRTI to either TDF/FTC or ABC/3TC similarly improved bone mass density, the gain in limb fat was not different in the two groups but the increase in total fat mass was more marked with the ABC/3TC combination. [17]

DL Jacobson presented data from the multicentre PACTG1045 study on total body and spine bone mineral density across Tanner stages in 236 vertically HIV-infected compared to 143 uninfected children and youth (7-24 years). Among females, there was no significant differences between HIV- and HIV+ subjects for total body bone mineral density and bone mineral content at any Tanner stage. In contrast among males, HIV+ subjects presented lower BMD and BMC than HIV- at Tanner stages 3 to 5 while at stages 1-2 these parameters were not different. These data suggest that perinatally infected males might be at increased risk for bone mineral disease during adulthood. [18]

B Grund presented data on the bone mineral density obtained in the body composition substudy of the SMART study. Bone parameters were compared in 98 patients randomised to the viral suppression (VS) group and 116 in the drug conservation group (DC) and followed for a mean duration of 2.4 years. At baseline 73% of patients were on ART, 12% had osteoporosis, median T-scores were -0.5 (femur) -0.9 (spine by quantitative computed tomography qCT) and -0.7 (spine by DEXA). In the VS group participants received ART for 93% of the follow-up compared to 37% in the DC group. BMD declined by 0.9% per year (femur) 2.9% (spine qCT) and 0.4% (spine DEXA) in the VS group and significantly less in the DC group. The differences were significant at the two levels and with the two types of measurements. No consistent drug-specific association with BMD decline was found. In the parent study, with the entire cohort, the number of reported fractures as grade 4 adverse events was significantly higher in the VS group. Therefore, continuous ART is associated with progressive decline in BMD and possibly more fractures relative to intermittent CD4-guided ART. [19]

Renal toxicity

SME Vrouenraets compared glomerular filtration rate (GFR) measured directly or estimated by different methods in the PREPARE study including in 19 patients with suppressive ART under AZT/3TC switched or not to tenofovir/FTC for 24 weeks. The mean measured GFR by using radioactive iothalamate decreased by 11 ml/min-1.73m² in the tenofovir/FTC group as compared to a 7 ml/min-1.73 m² increase in the AZT/3TC group after 24 weeks. Among the estimated methods, a significantly greater reduction was observed in the tenofovir compared to the continued AZT arm for all estimated GFR methods except the creatinine clearance and cystatin derived GFR. The mean (accuracy) and SD (precision) of the deviations from the measured GFR were reasonably good for the Cockcroft-Gault and the creatinine clearance methods but MDRD with 4 or 6 parameters and cystatin C underestimated real GFR and performed poorly. [20]

Therefore, mean GFR decreased by almost 10% at 6 months after switch to tenofovir and routine monitoring of renal function is warranted. In this small group, Cockcroft calculation best reflected measured GFR than the other estimated measures.

Cancer

The distribution of AIDS and non-AIDS defining malignancies was studied in the French 2006 ONCOVIH study by E Lanoy. This was a national cross-sectional study with a prospective reporting of all new cases of malignancies diagnosed in HIV-infected patients in 2006 in over 300 care centers. Overall, 694 new malignancies were reported: the most common were non-Hodgkin lymphomas (21.5%) Kaposi's sarcoma (15.9%) anal cancers (8.2%) Hodgkin's lymphoma (7.6%) cutaneous non-melanoma (6.8%) and hepatocarcinomas (5.6%). Almost two thirds were non-AIDS defining. However, both AIDS-defining and non AIDS-defining were diagnosed in patients with lower CD4 T-cells count than the whole French population of HIV-infected patients. This suggests that a better control of HIV and its associated immunodeficiency could prevent malignancies in HIV-infected patients. [21]

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Report from the 10th IWADRLH by Michael Dubé for natap.org

Does C-reactive protein (CRP) predict whether HIV-positive patients will have heart attacks?

Perhaps the most intriguing presentation was from Dr. Virginia Triant from Harvard, who reported on blood C-reactive protein (CRP) levels and myocardial infarction (heart attack) risk. [1]

CRP is in the news with the publication of the JUPITER trial. [2] In JUPITER, patients in the general population who had high CRP levels but relatively normal cholesterol levels had about a 50% reduction in the risk of myocardial infarction (MI) or stroke when they received the cholesterol-reducing statin drug rosuvastatin. In the general population, statin class drugs reduce CRP levels in addition to their well-known beneficial effects on cholesterol levels.

Generally speaking, levels of CRP in the blood reflect the amount of inflammation going on in the body. CRP itself is involved in some of the atherosclerosis-producing processes in the blood vessel wall. Increased CRP levels have been proven to be associated with increased MI risk in the general population for many years, but the blood test still is not generally used in managing cardiovascular risk or considered to as a routinely modifiable risk factor for MI. What has not been known is whether higher CRP levels predict greater MI risk in patients with HIV. Patients with HIV may have increased CRP levels due to HIV infection itself, other infections, and more cigarette smoking than in the general population.

Prior reports from this group showed an approximately 75% increase in the rate of MI among HIV-positive patients compared to non-HIV patients. In this large database study, increased CRP was associated with significantly increased MI risk in both the HIV-positive and HIV-negative patients. Among the minority of patients that had CRP levels measured, 59% of HIV-positive subjects had high CRP while 39% of those without HIV were elevated. The investigators were able to control for a variety of conditions that contribute to MI risk, but not all. In adjusted analyses, both HIV infection and a high CRP level were independently associated with about a doubling of the risk of MI. Unfortunately, the nature of the database that they researched retrospectively did not contain reliable smoking data - so they went back and looked at a subset of around 400 patient charts and found similar smoking rates among the groups with high CRP and low CRP, suggesting that the differences they observed were not due to smoking alone being more prevalent in the HIV group.

Although this was a huge database, only a small minority of subjects actually had CRP drawn. A variety of CRP assays were used with different normal ranges, so they were unable to say precisely what level of CRP indicates a significantly increased risk among the HIV patients. It is also likely that CRP levels were done for reasons other than evaluating CVD

risk, so it raises the question of whether HIV-positive patients were tested because of another illness?

This study is important because it reports that increased CRP is associated with increased MI risk in HIV-positive patients. However, the level of CRP that should cause concern is unclear, and what, if anything, we should do if we find elevated levels in our HIV-positive patients. It may not be appropriate to extend the findings of a study like JUPITER to HIV, because statin drugs may not have a similar effect in HIV. Conversely, giving statins to patients with HIV may have an even more profoundly beneficial effect than the drugs had in the general population. Until there are controlled studies large enough to answer these questions, we are left with only speculation as to what level of CRP justifies intervention and then what sort of intervention should be used and when. This writer believes that it is likely that statins will ultimately prove to be effective at reducing CRP levels in HIV.

Are children on ART at particular risk for CVD complications?

The implications of increased lipids, insulin resistance, and lipodystrophy on children and their long-term CVD risks are unknown. Ross from Rainbow Babies and Children in Cleveland reported that carotid IMT, a marker for cardiovascular disease risk in adults, actually decreased in HIV-infected children over a year. [3]

However, it is not known what a normal carotid IMT is in children, or what happens to the measure over time as healthy children grow normally. Nonetheless, it was encouraging that these ART-treated kids did not appear to be experiencing serious early signs of subclinical CVD.

Why does abacavir use cause more CVD?

The reasons behind why abacavir use is associated with increased risk of MI remains unclear and was a topic of considerable discussion. Jens Lundgren from Denmark reviewed the results from the D:A:D study and the recently published results from the SMART study which appear to confirm an approximately 90% increased risk of MI when patients are currently using abacavir in their antiretroviral regimens. [4]

Importantly, he emphasised again that the bulk of this increased risk is primarily borne by those individuals who are already at high risk for cardiovascular disease. There is, therefore, general agreement that it is those with multiple pre-existing risk factors such as family history of MI, high cholesterol, cigarette smoking, hypertension, and diabetes for whom we must be most cautious with the use of abacavir.

Podzamczar and colleagues reported results of a trial comparing tenofovir/FTC (Truvada) with abacavir/3TC (Kivexa, Epzicom) with regards to careful lipid testing. [5]

Total and LDL cholesterol were modestly higher and triglycerides were slightly higher with abacavir and the composition of LDL particles was somewhat more atherogenic with abacavir. However the magnitude of the differences was small and unlikely to translate into a significant increase in MI risk. Furthermore, HDL cholesterol actually increased significantly only with abacavir, and the ratio of apolipoprotein A1/apolipoprotein B (one of the most reliable lipid-related measures of CVD risk) were similar in both treatments. This study only suggests minor lipid disturbances from abacavir that do not appear to translate into clear-cut increases in cardiovascular risk. We need to be looking elsewhere for exactly what it is about abacavir that increases MI incidence.

In an excellent plenary presentation, Georg Behrens of Hannover, Germany suggested that the likely culprit is some form of increased tendency of the blood to clot, increased inflammation, or other dysfunction of the lining of the blood vessels (endothelium) related to use of the drug. Notably, earlier this year at the XVII International AIDS Conference, the SMART investigators reported that abacavir use increased CRP and IL-6 levels (interleukin-6, an inflammatory cytokine associated with insulin resistance and vascular dysfunction). Whether these increases are the true cause of the approximately 90% increase in the risk of MI or cardiovascular disease with abacavir use, or whether they merely are associated with some other undefined underlying problem that is leading to the increased risk, remains a matter of speculation. [6]

Is visceral (intra-abdominal) fat different in patients with lipodystrophy?

Giralt from University of Barcelona in Spain presented interesting data regarding the nature of visceral fat (fat inside the abdomen and around the abdominal organs) in 7 patients with HIV who had lipodystrophy (facial lipoatrophy and some increase in visceral fat) and compared their results with visceral fat from 10 non-HIV infected controls. [7]

In addition, comparison was made with subcutaneous fat (i.e. beneath the skin) in both groups. Prior studies have focused on subcutaneous fat, because that is more accessible to biopsy compared to visceral fat. It has been hypothesised in the past that ART makes subcutaneous fat dysfunctional while the more metabolically-active visceral fat remains more functional, predisposing to visceral fat accumulation (at least in certain susceptible individuals) while subcutaneous fat fails to be able to accumulate fat when excess calories are taken in. However, these investigators reported that mitochondrial function and mitochondrial DNA was reduced in both subcutaneous and visceral fat, suggesting no clear differential effect from ART in the 2 fat depots.

Markers of inflammation tended to be increased in both fat depots, but interestingly markers of adipogenesis (formation of new fat) appeared to remain adequate only in the visceral fat - suggesting that visceral fat may be able to better retain/

accumulate new fat stores once lipodystrophy is established. This might explain why losing visceral fat may become more difficult in those with established lipodystrophy, at least in those individuals who have lost subcutaneous fat. However, no particular insight into treatment or prevention of lipodystrophy was suggested by this work.

Does treatment with IGF-1 improve visceral obesity?

Morrie Schambelan from UCSF reported results from a small pilot trial of trial of IGF-1/IGFBP-3. [8]

IGF-1 (insulin-like growth factor 1) is the hormone that goes up when growth hormone is administered and is thought to be responsible for all the good and few of the bad effects of hGH. IGFBP-3 is the "binding protein" for IGF-1, and so the formulation they used gives both of them together to make the IGF-1 last longer in the bloodstream than giving IGF-1 by itself.

Ten stable ART-treated subjects with big bellies got a full course of treatment: 7 got a low dose and when it was recognised that this was having no effect on visceral fat, twice the dose was given to the next 3.

Unfortunately, no decrease in visceral fat was seen. However, overall trunk fat decreased, which could be an advantage even if visceral fat did not. Oddly, although muscle mass and overall insulin sensitivity improved, glucose production by the liver (gluconeogenesis) increased, which was not expected. This increased gluconeogenesis is what happens when the liver tissue becomes more insulin resistant. Lipids also did not improve in this study, like they do with other therapies. The treatment appeared to be well tolerated.

While these are very preliminary findings, and higher doses may need to be studied to find a beneficial effect, these studied doses of IGF-1/IGFBP-3 do not appear to have the beneficial effects on visceral fat and lipids that giving growth hormone or tesamorelin (which stimulates growth hormone production) have.

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Impact of body changes on the quality of life of HIV-positive treatment-experienced patients: an online community-based survey

Nelson Vergel, PozHealth@yahoo.com

Eleven years have passed since the first report of lipodystrophy at an HIV conference. The excitement and hope for a longer life that accompanied the arrival of Highly Active Anti-Retroviral Therapy (HAART) was then tempered by accounts of humps, bellies, and facial wasting. A decade on, many unanswered questions and misconceptions about HIV associated lipodystrophy persist with only a limited number of treatment options available.

Frustrated while waiting for answers, many people living with lipodystrophy have turned to the internet for advice, treatment and support in the hope of reversing some of the effects of this stigmatising syndrome that decreases their self image, mental health, quality of life, and the possibility to re-enter the work force. Most approved interventions for lipodystrophy are perceived as purely cosmetic and have a very low probability of reimbursement. Therefore, it is important that more data are generated from patients to enable advocacy for policy change in third party reimbursement guidelines for HIV-associated body changes. This is the first large online survey of its kind that attempts at determining lipodystrophy-related issues affecting patients in the field.

This study aimed to collect data on the impact of HIV-related lipodystrophy and its management on quality of life of HIV-positive members of pozhealth at yahoo.com, a 6-year listserv with close to 3000 members.

A link to a survey with 23 multiple-choice and open ended questions was posted in pozhealth asking people to share information about demographics, time since diagnosis, HIV medication and thymidine analogue exposure, perceived body changes, incidence of depression/anxiety, suicidal thoughts, medication interruptions, social interaction, self-image, therapeutic interventions and their cost coverage, use of lipoatrophy-related products, incidence of lipid and glucose abnormalities,

perceptions on the role that HIV medications play on body changes, and community input for lipodystrophy researchers. The survey was publicised for 9 months in 2007-2008 with the help of volunteer help of TheBody.com and other online venues. It is a work-in-progress with more people participating as time progresses.

As of October 2008, a total of 1011 people had participated, with a majority being white males over 40 years old, with over 10 years since HIV diagnosis, on HAART for over 5 years, and with prior exposure to d4T and AZT.

- 90% self reported body changes including facial lipoatrophy (78%), buttock wasting (71.3 %), venomegaly in extremities (68%), abdominal fat (62.4 %), and wasting syndrome (44%.)
- Due to body changes, past or current depression or anxiety was present in 87% of survey responders and 25% had suicidal thoughts in the past.
- 41% had interrupted HAART due to body changes in the past.
- Over 50% of survey responders stopped socialising and dating, decreased sexual activity, had decreased self-image, stopped looking at themselves in the mirror, and changed clothing style.
- The most popular therapeutic interventions used were exercise and nutritional changes, followed by facial fillers, supplements and testosterone.
- Most used own funds to pay for therapies. 40% have done nothing about their facial lipoatrophy, 30% used poly lactic acid, and 32% have switched from d4T to tenofovir or abacavir.
- 70% had high lipids and 29% had high glucose in the past. Most participants perceived that HIV medications caused their body changes. 505 participants posted suggestions to guide further research (available upon request).

Author conclusions

Despite the inherent limitations and possible biases of self-selection and the limited survey population, body changes appear to take a major toll in patients' quality of life. The majority of patients in this sample reported eroding self-image, increased isolation, and depression/anxiety; and most associate these with drugs used in the treatment of HIV disease. Disturbingly, 25% of participants had suicidal thoughts in the past due to body changes. The patients' belief that there is an association with the treatment drugs they use may have a negative effect on patient adherence to prescribed regimens.

We suggest that more information is obtained from other patient populations via targeted outreach venues. More data on the impact of lipodystrophy on quality of life are essential in justifying federal, estate, and foundation funding for exercise, nutritional, and wellness programs and to improve the current low rate of third-party reimbursement of therapies to manage body changes in HIV disease.

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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
Paediatric abacavir/3TC 60mg/30mg tablets	Aurobindo, India	19 December 2008
FTC (emtricitabine) 200mg tablets	Matrix, India	23 December 2008
d4T (stavudine) 15 mg, 20 mg, 30 mg and 40 mg	Aurobindo, India	29 December 2008
d4T (stavudine) oral solution 1mg/mL	Aurobindo, India	29 December 2008
d4T (stavudine) 15 mg, 20 mg, 30 mg and 40 mg	Hetero, India	29 December 2008

“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/docs/obdetail.cfm?Appl_No=3D021360&TABLE1=3DOB_Rx

C O M M E N T

The approval FDC of low dose (60/30mg) abacavir/3TC tablets is particularly important as this allows children with body weight down to 5kg. The GSK formulation, although approved for children, are the same dose as adult tablets (ie are ten-fold higher at 600/300mg).

They are scored, which is important for splitting half-doses, and are also dispersable in water. Both are intended for paediatric patients 3 months - 16 years of age.

The new formulations of d4T have more limited interest given the widespread shift away from d4T, even in WHO guidelines for ARV use in resource-limited countries. As d4T is now off-patent in the US, these generic formulations can also be used there.

This brings the total of FDA approved generic drugs and formulations to 78 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/oashi/aids/listserve/archive.html>

Lost benefit of ARVs in South Africa

Nathan Geffen, Treatment Action Campaign

Two studies have calculated the number of excess AIDS deaths due to the South African government’s delayed rollout of highly active ARV treatment (HAART) and prevention of mother-to-child transmission (PMTCT).

Nicoli Natrass analysed what would have happened if PMTCT had been rolled out from 1998 instead of 2001 and HAART was rolled out at the same rate as the Western Cape Province (from 10% in 2000 to 65% in 2007), the province credited with the most expeditious implementation. [1]

She compared these scenarios using the Actuarial Society of South Africa’s ASSA2003 model [2] and estimated that 343,000 deaths could have been averted.

Pride Chigwedere and colleagues at Harvard School of Public Health used a slightly different method. [3]

They argued that reduced drug prices and the availability of resources from programmes like the Global Fund and PEPFAR enabled the South African government to implement PMTCT and HAART earlier. South Africa’s public sector HAART programme only moved beyond pilot sites in 2004. According to the WHO and UNAIDS 3x5 records, South Africa scaled up HAART from less than 3% in 2000 to 23% in 2005. The authors considered the number of life-years that could have been saved had the state initiated its ARV programme at 5% coverage in 2000, scaling up to 50% by end of 2005, which is lower than the 85% achieved by Botswana or 71% by Namibia. They used UNAIDS estimate of AIDS deaths to determine the number of people who were eligible for HAART but did not receive it.

For PMTCT, they used data from the Department of Health’s PMTCT Task Team showing that coverage rose from less than 3% in 2000 to 30% in 2005 and compared this to a programme that started with 5% coverage in 2000 and scaled up to 55% in 2005.

Their model calculated that the delayed HAART rollout resulted in 2.2 million lost person-years and over 330,000 deaths. Delayed PMTCT resulted in over 35,000 excess infections and 1.6 million lost person-years. This is a total of 3.8 million lost person-years.

Both studies were intentionally conservative. For example, Chigwedere *et al.* assumed low estimates for additional life-expectancy on HAART (6.7 years) and paediatric infections. Both studies assumed low peak coverage rates in the alternative scenarios and that only the sub-optimal single-dose nevirapine PMTCT regimen was feasible. Neither took into account less tangible parameters such as deaths due to the promotion of quackery and infections due to poor state condom messaging and equivocation on the cause of AIDS.

Chigwedere *et al.* also performed several sensitivity tests. They found, for example, that by varying HAART peak coverage from 40% to the Namibian rate of 71%, excess deaths varied from about 226,000 to 503,000. They concluded: "Access to appropriate public health practice is often determined by a small number of political leaders. In the case of South Africa, many lives were lost because of a failure to accept the use of available ARVs to prevent and treat HIV/AIDS in a timely manner."

C O M M E N T

These studies both calculated very similar estimates for the number of lives lost due to the delayed rollout of HAART and PMTCT, even though they use different methodologies. Communication between Nattrass and Chigwedere after the latter's paper was published shows that they were unaware of each other's work. This increases confidence in their findings.

Their calculations confirm that the policies of President Thabo Mbeki and Minister of Health Manto Tshabalala-Msimang resulted in hundreds of thousands of avoidable deaths. Mbeki and Tshabalala-Msimang also created long-term problems, such as the proliferation of quackery and loss of public confidence in scientific medicine.

The Rome Statute of the International Criminal Court, to which South Africa is a signatory, defines the "intentional infliction of conditions of life, inter alia the deprivation of access to food and medicine, calculated to bring about the destruction of part of a population" as a crime against humanity.

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ANTIRETROVIRALS

Increased atazanavir dose recommended when used in combination with efavirenz or Atripla in naïve patients

In December 2008, BMS changed their package insert to indicate that treatment-naïve patients taking efavirenz (Sustiva or Atripla) with atazanavir (Reyataz) in their first combination, should increase the atazanavir dose from 300mg to 400mg and take this with 100mg of ritonavir (Norvir) and food.

The insert now states:

"If atazanavir is combined with efavirenz, atazanavir 400 mg (two x 200mg capsules) with ritonavir 100 mg should be administered once daily all as a single dose with food, and efavirenz should be administered on an empty stomach, preferably at bedtime."

This combination remains limited to treatment-naïve patients and is still contraindicated for treatment-experienced patients.

Link to package insert:

http://packageinserts.bms.com/pi/pi_reyataz.pdf

EMA approves once-daily darunavir/ritonavir (800mg/100mg) for treatment-naïve patients in Europe

On 3 February 2009, the European Commission approved once-daily dosing of 800 mg darunavir (Prezista), with low-dose ritonavir as part of combination therapy in treatment-naïve adults.

The approval is based on 48-week analyses from the Artemis Study, an open label phase III trial in antiretroviral treatment-naïve HIV-1-infected adults which compared darunavir/r vs. lopinavir/r in combination with other antiretrovirals. The results showed that darunavir was non-inferior to the lopinavir/r, (84% vs. 78% achieved viral load <50 copies/mL compared to

lopinavir/r). The common adverse drug reactions reported of at least moderate intensity (\geq Grade 2) in the darunavir/r arm were hypertriglyceridaemia, hypercholesterolaemia, headache, diarrhoea, nausea, and increased alanine aminotransferase.

Darunavir was given conditional marketing authorisation by the European Commission in February 2007, and received full marketing authorisation in December 2008.

The recommended dosing for treatment-naïve adult patients is 800 mg (two 400 mg tablets) taken with 100 mg ritonavir once daily.

For treatment-experienced adult patients, the dosing for darunavir remains 600 mg taken with 100 mg ritonavir twice daily. Darunavir must be taken with food and in combination with other ARVs. Darunavir is not recommended for use in patients with severe hepatic impairment.

Source: Tibotec Press Release 'Once-daily darunavir/r for treatment-naive adults with HIV-1 receives approval in the European Union as part of combination therapy'. (3 February 2009)

<http://www.tibotec.com>

Maraviroc safety label changes included with US traditional approval

On 25 November 2008, the FDA granted full, traditional approval for the use of maraviroc in treatment-experienced patients infected with CCR5-tropic HIV-1 and approved new information to be included in the label.

Some of the major changes associated with the approval are shown below.

Under the "**Indications and Usage**" section of the label the first bullet now reads "Tropism testing is required for the appropriate use of maraviroc."

Under the "**Warnings and Precautions**" section of the label the second sentence under subsection 5.2 Cardiovascular Events now reads "Eleven subjects (1.3%) who received maraviroc had cardiovascular events including myocardial ischemia and/or infarction during the Phase 3 studies [total exposure 609 patientyears, (300 on once daily + 309 on twice daily maraviroc)], while no subjects who received placebo had such events (total exposure 111 patient-years).

Under the "**Use in Specific Population**" section of the label, subsection 8.7 Hepatic Impairment, now reads "Maraviroc is principally metabolised by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because maraviroc concentrations may be increased. Maraviroc has not been studied in subjects with severe hepatic impairment. [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

Under the "**Clinical Pharmacology**" section of the label, **Hepatic Impairment** section was added following the **Excretion** section and reads, "Maraviroc is primarily metabolised and eliminated by the liver. A study compared the pharmacokinetics of a single 300 mg dose of maraviroc in patients with mild (Child-Pugh Class A, n=8), and moderate (Child-Pugh class B, n=8) hepatic impairment to pharmacokinetics in healthy subjects (n=8). The mean C_{max} and AUC were 11% and 25% higher, respectively, for subjects with mild hepatic impairment, and 32% and 46% higher, respectively, for subjects with moderate hepatic impairment compared to subjects with normal hepatic function. These changes do not warrant a dose adjustment. Maraviroc concentrations are higher when maraviroc 150mg is administered with a strong CYP3A inhibitor compared to following administration of 300mg without a CYP3A inhibitor, so patients with moderate hepatic impairment who receive maraviroc 150mg with a strong CYP3A inhibitor should be monitored closely for maraviroc associated adverse events. The pharmacokinetics of maraviroc have not been studied in subjects with severe hepatic impairment. [see Warnings and Precautions (5.1)]

Under the "**Clinical Pharmacology**" section of the label, subsection **Effects of Maraviroc on the Pharmacokinetics of Concomitant Drugs**, the following was added after the first paragraph: "Maraviroc does not induce CYP1A2 in vitro. In vitro results indicate that maraviroc could inhibit P-glycoprotein in the gut and may thus affect bioavailability of certain drugs.

The fourth sentence in the second paragraph of this section now reads, "Maraviroc had no effect on the debrisoquine metabolic ratio (MR) at 300 mg twice daily or less in vivo and did not cause inhibition of CYP2D6 in vitro until concentrations > 100uM."

Under the "**Microbiology**" section of the label, the **Clinical Resistance** subsection now reads, "Virologic failure on maraviroc can result from genotypic and phenotypic resistance to maraviroc or through outgrowth of undetected CXCR4-using virus present before maraviroc treatment (see Tropism below). Week 48 data from treatment-experienced subjects failing maraviroc-containing regimens with CCR5-tropic virus (n=58) have identified 22 viruses that had decreased susceptibility to maraviroc characterised in phenotypic drug assays by concentration response curves that did not reach 100% inhibition. Additionally, CCR5-tropic virus from 2 of these treatment failure subjects had \geq 3-fold shifts in EC₅₀ values for maraviroc at the time of failure. Fifteen of these viruses were sequenced in the gp 120 encoding region and multiple amino acid substitutions with unique patterns in the heterogeneous V3 loop region were detected. Changes at either amino acid position 308 or

323 (HXB2 numbering) were seen in the V3 loop in 7 of the subjects with decreased maraviroc susceptibility. Substitutions outside the V3 loop of gp 120 may also contribute to reduced susceptibility to maraviroc.”

Maraviroc is manufactured by Pfizer under the tradename Celsentry in Europe and Selzentry in the US.

Other minor changes made to the product label, are posted online at:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Source: Food and Drug Administration list serve

US approval of paediatric abacavir

On 19 December 2008, FDA approved abacavir (Ziagen) 300 mg scored tablets with corresponding dosing information for paediatric patients weighing 14 kg or more using the scored tablet.

The recommended oral dose of abacavir Oral Solution in HIV-1-infected paediatric patients ≥ 3 months of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.

Abacavir is also available as a scored tablet for HIV-1-infected paediatric patients weighing ≥ 14 kg for whom a solid dosage form is appropriate. Before prescribing abacavir Tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow abacavir Tablets, the oral solution formulation should be prescribed. The recommended oral dosage of abacavir Tablets for HIV-1-infected pediatric patients is presented in Table 1.

Table 1. Dosing Recommendations for abacavir Tablets in Pediatric Patients

Weight (kg)	Dosage Regimen Using Scored Tablet		Total Daily Dose
	AM Dose	PM Dose	
14 to 21	1/2 tablet (150 mg)	1/2 tablet (150 mg)	300 mg
>21 to <30	1/2 tablet (150 mg)	1 tablet (300 mg)	450 mg
≥ 30	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

The pharmacokinetics of abacavir have been studied after either single or repeat doses of abacavir in 68 paediatric patients. Following multiple-dose administration of abacavir 8 mg/kg twice daily, steady-state AUC (0-12 hr) and C_{max} were 9.8 ± 4.56 mcg·hr/mL and 3.71 ± 1.36 mcg/mL (mean \pm SD), respectively [see Use in Specific Populations (8.4)]. In addition, to support dosing of abacavir scored tablet (300 mg) for paediatric patients 14 – > 30 kg, analysis of actual and simulated pharmacokinetic data indicated comparable exposures are expected following administration of 300 mg scored tablet and the 8 mg/kg dosing regimen using oral solution.

Abacavir is manufactured by GlaxoSmithKline under the trade name Ziagen.

EMA supports extension of D:A:D study until at least 2012 and the new remit to include non-AIDS cancers and kidney disease

The EMA released the following press release on the D:A:D Study on 3 February 2009.

European Medicines Agency welcomes the continuation of D:A:D study

The European Medicines Agency (EMA) has welcomed the commitment of the sponsors to continue the D:A:D study at least until 2012. This ensures that the study, which was started on the initiative of the EMA in 1999, will remain one of the most powerful pharmacovigilance tools to monitor the long-term safety of antiretroviral medicines.

D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) is a prospective study based on multinational cohort collaboration, which includes data from 33,308 patients in 11 ongoing HIV cohorts in Europe, Australia and the United States of America.

The D:A:D study was started in response to a request from the EMA to all marketing authorisation holders of antiretroviral medicines. It set out to conduct a collaborative review of the cardiovascular safety and metabolic and body composition changes possibly associated with HIV treatment. The scope of the study was extended in 2005 to also investigate liver-related safety.

Although marketing authorisation holders of antiretroviral medicines contribute to the funding of the study, it is run in scientific independence. This is ensured by an independent scientific steering committee, which takes all scientific and procedural decisions, and by the so-called HAART Oversight Committee, which administers funds for studies, follows their progress and ensures their completion and reports regularly to the EMA. The Oversight Committee includes representatives of

academia, patient organisations, the EMEA and the US Food and Drug Administration (FDA).

Due to its large size and long follow-up, the D:A:D study has had a pioneering role in drug safety, helping to address existing and new emerging safety concerns, as well as to learn more about HIV infection itself. This is likely to serve as a model for future collaborative observational studies that will analyse the safety of whole therapeutic classes of medicines.

During the January 2009 meeting of the EMEA's Committee for Medicinal Products for Human Use (CHMP) representatives of the HAART Oversight Committee and the steering committee presented the achievements made over the last ten years and the plans for the study's continuation.

The study now monitors all authorised antiretroviral medicines. In addition, the marketing authorisation holders for any new antiretroviral medicines authorised in the future will be required to take part in the study.

D:A:D will continue to explore cardiovascular and liver-related safety. An association between antiretroviral combination therapy and myocardial infarction was identified in 2003. Further follow-up established that this is mainly explained by cumulative exposure to protease inhibitors. More recently an association with the recent use of abacavir and didanosine is being investigated.

The study will also be expanded to consider whether antiretroviral medicines affect the risk of contracting non-AIDS defining cancers and endstage kidney disease, as well as to examine patterns of causes of death over time and laboratory markers of liver and kidney function.

The results from the first ten years of the study have shown that the benefit-risk balance of antiretroviral medicines remains strongly positive and that the overall mortality of HIV-infected patients has dramatically declined since the introduction of highly active antiretroviral therapy (HAART).

Source:

EMEA Press Release: European Medicines Agency welcomes continuation of D:A:D study (3 February 2009). Doc. Ref. EMEA/44937/2009.
<http://www.emea.europa.eu>

Applications to approve non-refrigerated ritonavir submitted to EMEA and FDA

On 21 January 2009, Abbott announced that it has submitted applications seeking registration for a new tablet formulation of the protease inhibitor ritonavir (Norvir) with the European and US regulatory authorities. This new formulation will not require refrigeration.

Data from a pivotal bioavailability study, which compared the new formulation to the current ritonavir soft gel capsule was presented at the XVII International AIDS conference in Mexico City (AIDS 2008) in August 2008.

The expected timelines for decisions on the applications were not included in the announcement, nor whether they have been accepted for accelerated approval.

Source: Abbott press release (21 January 2009)

DRUG INTERACTIONS

Recent reports on new drug interactions

A selection of the latest news and reviews from the Liverpool University pharmacology team at hiv-druginteractions.org are included below.

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

Drug interactions with integrase inhibitors

This is an outstanding review on the pharmacology of integrase inhibitors with a substantial section on raltegravir drug-drug interactions and elvitegravir drug-drug interactions. There are four tables summarising all known interactions to date. The authors conclude that overall raltegravir has a low propensity for clinically meaningful drug interactions, whereas elvitegravir (with the presence of ritonavir) has modest potential for interactions.

The review is highly recommended and will appear in 2009. An advance version is available online, but minor changes may still occur before final publication.

Ref: Hazuda DJ et al. Emerging pharmacology: Inhibitors of Human Immunodeficiency Virus integration. *Rev Pharmacol Toxicol*, [Epub ahead of print]
<http://www.ncbi.nlm.nih.gov/pubmed/18928385>

Serum bilirubin increases when PEG-interferon and ribavirin are used with atazanavir

This was a retrospective study of 72 HCV/HIV co-infected patients who initiated HCV therapy (peg-IFN weekly and ribavirin 1000-1200 mg/day) and were on either an atazanavir-containing regimen (n=36) or other antiretrovirals (not including indinavir, n=36). Fourteen subjects in the atazanavir group and six in the control group were then excluded from analysis due to poor drug adherence.

The major finding was that on average serum bilirubin increases following initiation of peg-IFN and ribavirin were 1.9-fold higher in patients on atazanavir than in controls. In the atazanavir group, the proportion of patients with grade 3-4 hyperbilirubinaemia increased from 2/22 to 10/22 after beginning hepatitis therapy. No controls developed hyperbilirubinaemia.

The elevation in serum bilirubin levels is directly related to the haemoglobin decline as a result of ribavirin use and haemolysis. The clearance of the increased bilirubin is compromised by atazanavir.

Ref: Rodriguez-Novoa S et al. Increase in serum bilirubin in HIV/hepatitis-C virus co-infected patients on atazanavir therapy following initiation of pegylated-interferon and ribavirin. *AIDS*, 2008, 22(18): 2535-2548.

<http://www.ncbi.nlm.nih.gov/pubmed/19005277>

Drug interactions between efavirenz and itraconazole

This is a case report of the interaction between itraconazole and efavirenz in a woman with disseminated histoplasmosis and HIV-1 infection. Previous data in healthy volunteers have shown a decrease of about 40% in exposure of itraconazole and its active metabolite (hydroxyitraconazole) and a recommendation to consider alternative antifungal treatment. Here the authors recommend that by the use of therapeutic drug monitoring of both efavirenz and itraconazole individual optimization of dosage can be made so that a change in therapy is not necessary. In this case the patient had a good clinical response and obtained therapeutic concentrations with a regimen including efavirenz 400 mg once daily and itraconazole 800 mg once daily.

Ref: Huet E et al. Therapeutic monitoring is necessary for the association itraconazole and efavirenz in a patient with AIDS and disseminated histoplasmosis. *AIDS*, 2008, 22(14): 1885-1886.

<http://www.hiv-druginteractions.org/frames.asp?new/Content.asp?ID=403>

Effect on tacrolimus when switching from nelfinavir to fosamprenavir

This case report outlines the change in tacrolimus trough blood concentrations when 4 HIV-infected orthotopic liver transplant patients were switched from nelfinavir (1250 mg twice daily) to fosamprenavir (1400 mg twice daily without ritonavir) due to the EMEA ruling on nelfinavir in June 2007. After the switch, tacrolimus trough concentrations dropped significantly (>50%) and a marked dosage increase was required to attain the desired target concentration. The cases highlight the need for caution in immunosuppressed patients when switching or starting a protease inhibitor.

Ref: Pea Fet al. Drop in trough blood concentrations of tacrolimus after switching from nelfinavir to fosamprenavir in four HIV-infected liver transplant patients. *Antivir Ther*, 2008, 739-742.

<http://www.hiv-druginteractions.org/frames.asp?new/Content.asp?ID=404>

Elvitegravir with tipranavir/ritonavir or darunavir/ritonavir

Two studies are described evaluating potential pharmacokinetic interactions among elvitegravir and ritonavir-boosted tipranavir or darunavir.

In the tipranavir study healthy volunteers received elvitegravir/ritonavir (200/100 mg once daily) alone, or tipranavir/ritonavir (500/200 mg twice daily) alone, or elvitegravir (200 mg once daily) in combination with tipranavir/ritonavir (500/200 mg twice daily). For the darunavir study subjects received elvitegravir/ritonavir (125/100 mg once daily) alone, or darunavir /ritonavir (600/100 mg twice daily) alone, or elvitegravir (125 mg once daily) in combination with darunavir /ritonavir (600/100 mg twice daily). Steady state pharmacokinetics for elvitegravir, tipranavir, darunavir and ritonavir were determined.

No subjects discontinued for adverse events during treatment with elvitegravir/ritonavir alone. On coadministration, AUC and C_{max} of elvitegravir/tipranavir and elvitegravir/darunavir were within prespecified no-effect boundaries versus treatment alone; trough concentrations were also not substantially altered. The authors concluded that elvitegravir can be added to tipranavir/ritonavir or darunavir/ritonavir regimens without dose adjustment.

Ref: Mathias AA et al. Effect of ritonavir-boosted tipranavir or darunavir on the steady-state pharmacokinetics of elvitegravir. *J Acquir Immune Defic Syndr*, 2008, 49(2): 156-162.

<http://www.hiv-druginteractions.org/frames.asp?new/Content.asp?ID=405>

BASIC SCIENCE

Recent basic science updates from Richard Jeffery's excellent web log.

Cause for caution on HIV cure report

Richard Jefferys, TAG

An avalanche of media coverage has been loosed by the recently announced case of an individual who may have been "functionally cured" of HIV infection.

The term functional cure has entered the lexicon due to the impossibility of formally proving that HIV has been entirely eradicated from the body; due to that limitation, long-term absence of detectable virus without therapy has been adopted as a reasonable definition of a cure, prefixed with the "functional" caveat.

The individual in this case is a 40 year old, HIV-infected American living in Berlin who had been on successful antiretroviral therapy prior to developing acute leukemia. The treatment for this condition involves bone marrow transplantation, which carries a 30% risk of mortality and is frequently associated with post-procedure complications. Due to the individual's HIV infection, his doctors found a donor who was homozygous for the delta32 mutation, which completely abrogates expression of CCR5 (the major HIV co-receptor) on cells. Preparation for transplantation involves chemotherapy and radiation to essentially wipe out the immune system in order to prevent transplant rejection (with the salutary side effect of also depleting HIV-infected immune cells). The donor cells successfully engrafted but leukemia initially returned, requiring a second transplantation. Since that time – now close to two years ago – the individual has been free of leukemia, and HIV has remained undetectable without further antiretroviral treatment.

As can be gleaned from the press articles, opinions are divided on the significance of what has occurred. Some researchers have suggested it is a "proof of principle" that gene therapies with the capacity to block CCR5 expression could be curative.

However, a 1999 review of bone marrow transplants in people with HIV [1] identified two similar instances in which virus did not reappear after the procedure, so the contribution of the delta32 status of the donor in this current case is uncertain (although it is also possible that the prior examples also involved delta32 donors, unbeknownst to the doctors).

The 1999 review also offers a grim perspective on the mortality associated with the procedure: the longest documented survival was around 300 days. While cynics might question whether AIDS professionals (including this writer) have their own self-serving reasons to express skepticism about cure claims, the complexity and danger of bone marrow transplantation clearly severely limits its use. It also must be stressed that while the individual is said to be "recovering," there are no details available regarding his current health.

Despite the many caveats, the case may be able to inform the pursuit of a safer curative strategies. The Foundation for AIDS Research (amfAR) has already sponsored a small meeting of experts to discuss the subject, attended by Mark Schoofs who wrote the first mainstream media article in the Wall Street Journal in November. [2]

One lesson may be that depleting HIV reservoirs to very low levels – if it can be done safely – will be beneficial, perhaps tipping the balance in favor of the host such that any residual virus can be controlled. If the individual remains well enough and is willing to undergo further evaluation, additional analyses to look for HIV in tissues will be important, along with evaluations of HIV-specific immunity. The presence of HIV-specific T cells carrying the donor delta32 mutation would suggest that sufficient viral activity has occurred after the transplantation procedure to induce new immune responses while, conversely, the absence of such responses might add to the evidence that HIV has been rendered completely inactive. Given that the case is now under the spotlight, the doctors involved will hopefully be forthcoming with updates as more information becomes available.

Source: TAG basic science blog (14 November 2008)

<http://www.treatmentactiongroup.org/basicsciblog.aspx>

References

1. Huzicka I. Could bone marrow transplantation cure AIDS?: review. *Med Hypotheses*. 1999 Mar;52(3):247-57. PMID: 10362285. <http://www.ncbi.nlm.nih.gov/pubmed/10362285>
2. Schoofs M. A Doctor, a Mutation and a Potential Cure for AIDS. *Wall Street Journal*. (7 November 2008). <http://online.wsj.com/article/SB122602394113507555.html>

Low-level HIV replication versus latency: identifying the source of viral rebounds during treatment interruption

Richard Jefferys, TAG

In HIV research, there is a persistent and vigorous debate around the question of whether or not viral replication persists in the face of successful antiretroviral therapy. During a plenary session at the International AIDS Conference in Mexico City back in August, Bob Siliciano made a compelling argument that, in most cases, antiretroviral therapy completely shuts down virus production. [1]

Now, a new paper in PNAS provides additional support for this view. [2]

Beda Joos and colleagues evaluated a staggering 1,753 genetic sequences from the envelope region of HIV, sampled over the course of a treatment interruption trial known as SSITT (Swiss-Spanish Intermittent Treatment Trial). The study design involved a series of two-week treatment breaks followed by a prolonged interruption (therapy was subsequently reinitiated according to the CD4 and viral load thresholds used in current treatment guidelines).

The researchers used the sequence data to plot the relationships between the different viruses, using a technique called phylogenetic analyses. For each study participant analyzed, the sequences were used to define "the most recent common ancestor" (MRCA), which is the virus sequence from which all the others derived. Viruses that appeared during treatment interruptions (TIs) were then compared to the MRCA, to see if the sequences suggested that there had been ongoing replication and evolution while the study participants were on ART. The results showed that the rebounding viruses during TI were actually more distant from the MRCA than the viruses detected when the participants first entered the study. The researchers conclude: "the striking lack of a temporal relationship between rebounding virus and pretreatment viruses strongly suggests that rebounding virus originates from reactivated, latently infected cells rather than from a cellular pool or compartment engaged in low-level replication."

Source: TAG basic science blog (20 November 2008)
<http://www.treatmentactiongroup.org/basicsciblog.aspx>

References

1. Siliciano R. HIV persistence on patients on HAART: re-evaluating prospects for eradication. XVII Intl AIDS Conference, 3-8 August 2008, Mexico City.
http://www.kaisernetwork.org/health_cast/hcast_index.cfm?display=detail&hc=2909
2. Joosa B et al. HIV rebounds from latently infected cells, rather than from continuing low-level replication. PNAS October 28, 2008 vol. 105 no. 43 16725-16730
<http://www.pnas.org/content/105/43/16725>

OTHER NEWS

Martin Delaney, leading treatment activist and founder of Project Inform, dies at 63

It is with great sadness that we report that Marty Delaney, one of the most outspoken and respected American treatment activists, died on 23 January 2009.

The numerous articles and obituaries linked below hint at the impact from over 20 years work to extend and improve lives of HIV-positive people. He was as concerned with individual empowerment and care as he was changing policy on a national level.

He played a major role in changing the FDA drug approval process: shortening approval time for life-saving drugs and establishing the right for patients to choose to access treatment prior to approval through expanded access programmes.

His experience from the earliest pre-treatment years, first drug trials and later understanding of HAART, through to recent focus on drug costs and pricing, ensured he was one of the most informed and intelligent people working in HIV and he will be greatly missed.

Related links:

Project Inform

<http://www.projectinform.org/martindelaney.shtml>

NIAID

http://www3.niaid.nih.gov/about/directors/news/Martin_Delaney.htm

NIAID Honors AIDS Activist Martin Delaney

<http://www3.niaid.nih.gov/news/newsreleases/2009/mdelaney.htm>

<http://www.youtube.com/watch?v=Ud51h76u3cc>

Treatment Action Group

<http://www.treatmentactiongroup.org/base.aspx?id=2802>

POZ magazine

http://www.poz.com/articles/hiv_martin_delaney_401_16017.shtml

New York Times

http://www.nytimes.com/2009/01/27/us/27delaney.html?_r=1&partner=rss&emc=rss

Community memorial site

<http://www.martydelaney.com>

Report refutes HIV denialist claims on childrens HIV trials

Simon Collins, HIV i-Base

Several years ago, allegations from a fringe group of HIV denialists who claiming that foster children in New York were used as guinea pigs for adult HIV drug trials, gained media publicity when used as a basis for a BBC documentary. It is important that these have been quashed following a lengthy investigation, detailed in a recent article in the New York Times. [1]

Complaints to the BBC after the documentary was aired in 2004, also resulted in a lengthy apology and retraction recognising the inappropriate balance used in their programme. [2]

An independently commissioned investigation determined that city officials had acted in good faith and in the interests of the children, many of whom were seriously ill.

The report, from the Vera Institute of Justice, an independent nonprofit group, is now available online [3]. It also found that foster children were not removed from their families because a parent had refused to consent to a child's treatment, and that researchers did not specifically select foster children for enrollment in the trials. While the foster children were overwhelmingly black and Hispanic, as some critics, this mirrored the demographics of children with HIV infection in the city at the time.

C O M M E N T

This was probably one of the most inappropriate and inflammatory HIV-related stories to be picked up by mainstream media who themselves failed to appropriately research the real issues: that children are generally denied access to potentially life-saving pipeline compounds until after they have been approved for adult care.

References

1. Foderaro L. Study refutes claims on AIDS drug trials, New York Times (27 January 2009).
http://www.nytimes.com/2009/01/28/nyregion/28foster.html?_r=1
2. BBC Admits that "Guinea Pig Kids" is Misleading, Erroneous: Apologises for HIV Denialist Bias and False Allegations about NYC AIDS Drug Trials
<http://www.aidstruth.org/BBC-Apologizes-for-HIV-Denialist-Bias.php>
Link to BBC letter
<http://www.aidstruth.org/Complete-BBC-complaint.pdf>
3. Ross T et al. The Experiences of New York City Foster Children in HIV/AIDS Clinical Trials. Available online:
<http://www.vera.org/cyj/hivtrials-pubs.html>

ON THE WEB

Conferences:

39th Union World Conference on Lung Health

October 16-20, Paris

Online coverage includes:

- Session webcasts, audio podcasts and transcripts with slide presentations of all plenary sessions and selected other sessions including the October 16th Stop TB Symposium: Working with the Whole Health System.
- Interviews with newsmakers providing analysis of current issues in the fight against TB.

<http://www.Kaisernetwork.org/paris2008>

Guidelines:

Management of hepatitis B: consensus statement and data review

National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis B

Sorrell MF et al. Ann Intern Med 2009;150 104-110.

<http://www.annals.org/cgi/content/full/150/2/104?etoc>

Antiviral Therapy for Adults With Chronic Hepatitis B: A Systematic Review for a National Institutes of Health Consensus Development Conference

Shamliyan et al. Ann Intern Med 2009;150 111-124

<http://www.annals.org/cgi/content/abstract/150/2/111?etoc>

Free access peer review papers

PLoS medicine and PLoS clinical trials

Inflammatory and coagulation biomarkers and mortality in patients with HIV Infection

Kuller LH et al.

<http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050203#top>

“IL-6 and D-dimer were strongly related to all-cause mortality. Interrupting ART may further increase the risk of death by raising IL-6 and D-dimer levels. Therapies that reduce the inflammatory response to HIV and decrease IL-6 and D-dimer levels may warrant investigation.”

Effectiveness of cellulose sulfate vaginal gel for the prevention of HIV infection: results of a Phase III trial in Nigeria

Vera Halpern et al.

<http://clinicaltrials.plosjournals.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0003784>

“Cellulose sulfate gel appeared to be safe in the evaluated study population but we found insufficient evidence that it prevented male-to-female vaginal transmission of HIV, gonorrhea or chlamydial infection. The early closure of the trial compromised the ability to draw definitive conclusions about the effectiveness of cellulose sulfate against HIV.”

Reporting bias in drug trials submitted to the Food and Drug Administration: review of publication and presentation

Rising K et al.

<http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050217>

This study concluded “Many trials were still not published 5 years after FDA approval. Discrepancies between the trial information reviewed by the FDA and information found in published trials tended to lead to more favorable presentations of the NDA drugs in the publications. Thus, the information that is readily available in the scientific literature to health care professionals is incomplete and potentially biased.

Conducting unlinked anonymous HIV surveillance in developing countries: ethical, epidemiological, and public health concerns

Rennie et al.

<http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.1000004>

A comparison of international ethical guidelines on UAT with ethical and public health challenges encountered with HIV sentinel surveillance in sub-Saharan Africa, among populations usually targeted by UAT efforts, and proposals for practical approaches, informed by field research in southern Africa, to improve the quality of HIV surveillance data, strengthen the ethics of surveillance activities, and enhance the capacity of public health systems.

FUTURE MEETINGS

2009 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.

8-11 February 2009: 15th Conference on Retroviruses and Opportunistic Infections, Montreal

<http://www.retroconference.org>

25-27 March 2009: 7th European HIV Drug Resistance workshop, Stockholm

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

1-3 April 2009: 15th Annual Conference of the British HIV Association (BHIVA), Liverpool

<http://www.bhiva.org>

15-17 April 2009: 10th Intl Workshop on Clinical Pharmacology of HIV therapy, Amsterdam

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

4-6 June 2009: 5th Intl HIV and Hepatitis Co-infection workshop, Lisbon

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

9-13 June 2009: XVIII International HIV Drug Resistance Workshop, Fort Myers, Florida

<http://www.informedhorizons.com/resistance2009>

25 - 26 June 2009: 4th Intl Workshop on Hepatitis C Resistance & New Compounds, Boston

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

26-27 June 2009: 4th Intl Workshop on Clinical Pharmacology of Hepatitis Therapy, Boston

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

16-18 July 2009: 1st Intl Workshop on HIV Paediatrics, Cape Town

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

16-18 July 2009: 4th Intl Workshop on HIV Transmission, Cape Town

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

19-22 July 2009: 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2009), Cape Town

<http://www.ias2009.org>

12-15 September 2009: 49th ICAAC, San Francisco

<http://www.asm.org>

29 October-1 November 2009: 47th IDSA, Philadelphia.

<http://www.idsociety.org>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

The fully searchable website is designed to be fast to access, easy to use, and simple to 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/questions>

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.

NEW publications

- A guide to HIV, pregnancy & women's health (January 2009)

This guide aims to help you get the most out of your own HIV treatment and care if you are considering pregnancy or during your pregnancy.

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

- Spanish online edition of the Guide to HIV and Hepatitis C (all web pages are now simultaneously available in both English and Spanish)

<http://www.i-base.info/guides/hepc/es/index.html>

i-Base announcements list

A free email News and Announcements list. By subscribing you can be kept up-to-date on new and revised publications from i-Base. This is an announcement only list with low traffic, mainly to announce new and updated publications and services. Messages will contain a link to a PDF file of the publication and/or a link to the web version.

To subscribe please fill out the form at this link:

<http://www.i-base.info/forms/newssub.html>

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 are 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://www.i-base.info/clinicforms>

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://www.i-base.info/pdf/africantreatmentneeds.pdf>

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 recent meeting, held in Cape Town earlier this year, 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 for three years. 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.

<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.

<http://www.i-base.info/wcab/index.html>

Introduction to combination therapy

June 2008 edition

This non-technical patient guide to treatment explains combination therapy, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and how to avoid drug resistance.

Printed and/or PDF versions of earlier versions of this booklet are available in other languages.

Guide to hepatitis C for people living with HIV: May 2007 edition

This is a new i-Base guide. It is a non-technical patient guide to Hepatitis C and coinfection with HIV.

This booklet mainly covers treatment related aspects of coinfection including transmission, natural history, tests and monitoring, HCV treatment and side effects, research into new drugs and living with coinfection. It also includes contributions from a wide range of people with direct experience of coinfection. The online version of this guide includes additional text.

Guide to changing treatment: what to do when your treatment fails

September 2008 edition

This is a non-technical patient guide to changing treatment, drug resistance and what to do if treatment fails. It is updated to include recent advances in new treatments and strategies, especially in relation to use of new and expanded access treatments.

This booklet helps patients in discussions with doctors, and covers what can be done if viral load starts to rise, and the importance of considering or finding out why the current combination failed, treatment strategies and new pipeline treatments.

Guide to HIV, pregnancy & women's health

January 2009 edition

Updated and revised, this patient guide helps women get the most out of HIV treatment and care before, during and after pregnancy. It should help whether on therapy or not and includes information for the mothers health and for the health of the baby.

The guide gives information on medication, Caesarean section and breastfeeding, as well as details of other sources of help. It is aimed at people in a wide range of circumstances including positive women thinking about having children and pregnant women who have recently been diagnosed HIV-positive.

Guide to avoiding & managing side effects

May 2008 edition

This is a comprehensive 72-page A5 guide that is aimed at helping anyone using HIV drugs to get the most out of their treatment, the most out of their relationships with their doctor and other health professionals, to get better medical care to improve their health and, most importantly, to enjoy a better quality of life.

Translations of i-Base guides

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://www.i-base.info/about/downloads.html>

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.

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

Our 'question and answer' service now has over 750 questions posted online in over 25 categories. 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/questions>

Recent questions include:

- What makes someone a fast progressor?
- What does the word 'analogue' mean in HIV treatment?
- What does genotype stand for and other questions
- What can I do for my CD4 to rise?
- What is your life expectancy if treatment is not an option?
- Timing for starting Sustiva + Truvada combination?
- Can I take omega-3 and multivitamins with ARVs?
- What does the rise of CD8 mean?
- Will augmentin help with my pneumonia?
- Does finasteride (Propecia) interact with HIV drugs?
- What does a CD4% of 8 mean for starting treatment?
- Are there interactions between scabies lotions and ARVs?
- Would you recommend K-Pax supplements with ARVs?
- What tests are used when somebody is HIV-positive?
- Can I get HIV-related illnesses with a CD4 over 200?
- Can I still have AIDS even if my test is negative?
- What do these lab results mean?
- How many combinations are there before salvage?
- Could I have lipoatrophy if I am not on meds?
- Are aches in my fingers and knees a side effect?
- Should my partner take Sustiva and Truvada separately?
- Can we have an HIV-negative baby?
- Should my friend change Sustiva because of side effects?
- Would a sunbed session be bad about my status?
- Is my life expectancy reduced if I'm a rapid progressor?

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/2008>

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://www.i-base.info/forms/index.html>

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

Some articles are reproduced from other respected sources and copyright for these articles remains with the original authors and sources, as indicated at the end of each article.

We thank those organisations for recognising the importance of providing widely distributed free access to information both to people living with HIV and to the healthcare professionals involved in their care. We also thank them for permission to distribute their excellent work and we encourage HTB readers to visit the source websites for further access to their coverage of HIV treatment.

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

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HIV i-Base is a registered charity no 1081905 and company reg in England no 3962064. HTB is also known as DrFax

i-Base appeal

This appeal has been launched because both the London Commissioners and the Department of Health have decided not to fund ANY HIV i-Base project in 2008/9.

We would like to thank everyone who helped with letters of support, which came from doctors, nurses, pharmacists, HIV-positive patients and other service users.

We would now like to collect a fax from every clinic that uses our services.

Since April, there has been no drop in the level of our services. We have answered more phonenumber calls, email information requests and distributed more treatment guides than the same period last year. We are just doing this without statutory support.

Some clinics with a budget for patient or healthcare educational material have already agreed to donate an annual amount (£500 - £1000, or £1-2 per patient) towards unlimited use of all our resources. We need to raise £50,000 to cover the withdrawal of Commissioner support.

If your clinic or Trust is able to help, please fax your details using this form so we can contact you. We understand that this will not always be possible, and we still commit to continue providing all publications and services free. But if you can help, then many clinics contributing to our shortfall will make a huge difference.

Name: _____

Hospital/clinic/organisation: _____

Contact phone number: _____

Contact email: _____

Our hospital/clinic/organisation (delete as appropriate) use the following i-Base services. to improve patient care.

- HIV i-Base treatment guides
- HIV i-Base phonenumber and information service
- HIV Treatment Bulletin

Comment: _____

Please tick one of the following boxes:

We ARE able to contribute financially towards these services. Please contact us to arrange details.

Unfortunately we ARE NOT able to contribute financially towards these these services but we would be worried if they did not continue. We are happy for you to use this confirmation and the above comment for future fundraising and sponsorship.

Please fax to: 020 7407 8489



HIV i-Base

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

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

STANDING ORDER DONATION

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

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

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

Please complete the above and return to: HIV I-Base, 44-46 Southwark Street, London SE1 1UN

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

ONE-OFF DONATION

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

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

GIVE AS YOU EARN

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

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

REFUNDS FROM THE TAX MAN

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

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

HIV i-Base

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HIV Treatment Bulletin (HTB) monthly by Email (PDF format) by Post

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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

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

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

Office use: