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EDITORIAL

Welcome to the first issue of HTB for 2010 which includes reports from the EACS Conference and updates of three important guidelines.

At EACS, we start with a review that focused on the lack of screening programmes for anal cancer for HIV-positive people. Many studies have already highlighted that the increased risks, especially for gay men, are comparable to rates of cervical cancer in women prior to those screening programmes. Focussing on the benefits of newer treatment options to successfully reverse this disease, the review suggests that there is now compelling evidence supporting more active monitoring.

An ongoing UK review due in April 2010 will hopefully reverse the decision made at the previous review (in 2003), though this will also be related to whether HIV-positive gay men are seen as a group that deserves further interventions. The study reported later in this issue of HTB, by Bini and colleagues, adds to the growing evidence to at least support a UK pilot screening programme in the highest risk groups.

Our coverage of guidelines includes new communications from the US DHHS panel, WHO, and PENTA.

Each document includes valuable guidance for clinical management of HIV-positive patients and is essential reading. However, as the remit for each guideline ranges between defining a minimum standard of care and a more aspirational summary of best possible care, they also highlight controversial issues for which evidence is still lacking.

In the US DHHS panel review, the recommendation to universally start treatment at any CD4 count lower than 500 cells/mm³ is problematic given the confounding issues from cohort studies on which the recommendation is based.

As the large randomised START study addressing the risks and benefits of earlier treatment is just enrolling, the decision to guess these results is premature.

START, and its related sub-studies, is likely to provide the most important dataset to inform not only the question of when to start treatment, but also about the pathogenesis of essential aspects of HIV, treatment and aging including neurological and bone health.

It is welcomed that the WHO guidelines also recommend earlier treatment (at CD4 <350) and that they place a stronger emphasis on using alternative nucleosides to d4T. However, arguably earlier treatment should only be recommended in settings where non-d4T-based regimens are freely accessible, and in this aspect of management is not discussed.

We also include latest reviews of drug interactions from HIV-druginteractions.org and basic science reviews from Richard Jefferys excellent weblog.

CONFERENCE REPORTS

12th European AIDS Society Conference (EACS)

11-14 November 2009, Cologne

Introduction

In this issue we continue reports from this European conference that is held every two years.

This year a comprehensive programme of lectures and sessions available as webcasts and podcasts and include many of the slide sets:

<http://www.europeanaidscinicalsociety.org>

<http://www.multiwebcast.com/eacs/2009/12th>

Access requires a free one-time registration using the invitation code: EACS2009

It is disappointing that the abstracts from the meeting were not available online (as we went to press), and are only available as a subscription issue of HIV Medicine (2009, volume 10, issue S2).

The following reports are included in this issue.

- Screening for anal cancer recommended for HIV-positive men
- Once-daily darunavir/r monotherapy is suboptimal as initial regimen in treatment-naïve people
- Central fat accumulation remains a significant problem in patients starting HAART after 2005 with higher incidence in women compared to men
- Alendronate improves bone mineral density in HIV-positive people with osteoporosis at 96 weeks
- Pilot PK study of two generic paediatric formulations of lopinavir/ritonavir vs originator products

- TMC278 does not show teratogenic potential in animal models
- No clinically relevant interactions between TMC278 and oral contraceptives (norethindrone plus ethinylestradiol)
- Etravirine pregnancy data from five cases: no dose adjustment required
- Selected PK and drug interaction summaries at EACS

Screening for anal cancer recommended for HIV-positive men

Simon Collins, HIV i-Base

A plenary session at EACS reported that new evidence supports screening for anal cancer in HIV-positive men. [1]

This is important, because the increased risk of anal cancer in gay men, and particularly in HIV-positive gay men, has been highlighted for many years. Screening is safe and treatment is effective, especially when diagnosed early and the importance of establishing a screening programme has been repeatedly raised by community-based advocates for many years. Controversially, NHS guidelines do not recommend screening for anal cancer in the two largest risk groups: HIV-positive people and gay men.

The presentation, by Professor Mark Bower from the Chelsea and Westminster Hospital, London, who also chaired the panel for the BHIVA malignancy guidelines [2], clearly supported a review of the NICE decision. He also highlighted that current healthcare resources could not cope adequately with any significant increase in demand for screening.

The lecture started by highlighting the difficulties that are inherent in proving the clinical benefit for any screening programme, including for those that are now an integrated part of NHS care (such as cervical and breast cancer). Interpreting data is dependent on the choice of endpoints, control groups and inherent biases that generally will always support the benefits from screening, even if reduced mortality cannot be inferred.

For example, the incidence of a cancer, or advanced cancer, or even using reductions in cancer specific mortality as an endpoint, does not necessarily provide the data to prove the benefit of screening due to three important inherent biases in evaluating any screening programme are just as relevant in the context of anal cancer and HIV.

Firstly, lead time bias refers to greater survival time after diagnosis. This may be driven by the earlier diagnosis commonly resulting from any availability of broader screening and so survival time since diagnosis does not necessarily have any impact on final mortality. Awareness of a diagnosis for longer is dependent on effective treatment to translate into better prognosis and longer survival.

Secondly, lag time bias refers to the tendency for a greater proportion of cancers picked up in a screening programme to be more slowly progressing and less aggressive compared to symptomatic cancers picked up in any control group. In this case, slow growing cancers have a longer screening time in which to be detected and this will translate to an apparent improvement in survival.

Finally, over-diagnosis bias relates to picking up cancers in screening programmes which are never going to progress, or in patients who will die from unrelated or natural causes. This translates to a higher incidence of diagnosis in a screening population but a lower incidence of cancer-related mortality.

Despite the scientific difficulties associated with proving the effectiveness of a screening programme, the presentation outlined why anal cancers screening is now appropriate, based on proven incidence in this population and the effectiveness of treatment.

Although anal cancer was not included as an AIDS-defining malignancy in the US CDC 1993 definitions, unlike cervical cancer that has a similar incidence and etiology, a meta-analysis of major cohort studies has suggested that anal cancer is 20-50 times more common in HIV-positive people than age and gender matched general population. [3] This is an enormous relative risk: by comparison, tobacco smoking is associated with an approximate 17-fold increased risk for lung cancer.

The HIV effect is also more than a direct result of a weakened immune system: transplant patients who have artificially reduced immunosuppression, only have a 4-5 fold increased risk of anal cancer.

Part, or much, of this increased incidence in HIV-positive gay men, may be related to the increased risk that was reported in MSM in pre-HIV data. [4]

Results from 11 linked HIV and cancer registries estimated a relative risk of 59 for HIV-positive MSM, but the same study also highlighted a 6-fold increased relative risk in HIV-positive compared to HIV-negative IDU's. [5]

Population studies now estimate the incidence of anal cancer at 1.5 per 100,000 in the general population, but at 35 and 70 per 100,000 in the general population, gay men and HIV-positive gay men respectively. One cohort, in San Diego, reported an even higher rate of 224 in HIV-positive MSM. [6] This compares to an incidence of cervical cancer before the introduction of screening or 15 per 100,000.

Anal cancer does not appear related to CD4 count, and some studies have suggested that the incidence post-HAART may be increasing. [8] This can be balanced by evidence that suggests that, due to effective treatment, survival rates in the HAART era now approximate to that in HIV-negative cohorts (of around 75% at two years). [8]

A limited number of studies support a similar etiology between cervical and anal cancer, with 5% patients diagnosed with AIN2/3 and a similar proportion of patient after surgery for anal warts, progressing to anal cancer. A UCSF study published in 1997 in HIV-

positive MSM suggested a progression rate of 20% from normal cytology to HSIL and a 60% progression rate for men diagnosed with LSIL to HSIL (with 5% reverting to normal). In 21 patients with invasive anal cancer (from the same UCSF cohort of 1700 men), the median time to progression from a diagnosis of HSIL was 47 months (range 4-139 months). [9].

However, natural history studies should now be considered unethical, as they would for cervical cancer, given the clear link between AIN2/3 and risk of progression to anal cancer and the availability of effective treatment.

Anal cytological screening is easy, well tolerated and acceptable to patients. Results show either normal cytology or one of three diagnosis: ASCUS, LSIL or HSIL (Abnormal Squamous Cells of Undetermined Significance; Low-grade Squamous Intraepithelial Lesions; or High-grade Squamous Intraepithelial Lesions).

In the screening algorithm developed by Joel Palefsky in the US, normal results should lead to repeat annual screening as routine follow-up. ASCUS, LSIL and HSIL should prompt high-resolution anoscopy, with repeat annual anoscopy for AIN1 and treatment for AIN2/3. [10] This is supported by several studies reporting acceptable rates of 34-83% sensitivity and 38-72% specificity for anal cytology compared to histology.

Finally, the recent availability of reasonable and established treatments for AIN2/3 (infrared coagulation with clearance rates 50-60% at one year; topical trichloroacetic acid; imiquimod with 40% resolution vs 8% control; and surgical anal mucosectomy), that argue for the reevaluation of anal cytological screening.

While cost-effectiveness is always a factor in screening programmes the presentation made the following points:

- The first cost effectiveness study reported that cervical screening (3-yearly) in HIV-negative women was estimated at costing USD\$180,000 per life year saved. This compared to approximately USD\$11,000 for anal cytology screening in HIV-positive men. [11]
- A more detailed and recent analysis from the same group estimated costs of USD \$16,600 and \$13,000 per Quality Adjusted Life Year saved (QALY) for annual or two-yearly screening in HIV-positive MSM. For HIV-negative MSM these costs were \$34,800 and \$15,100 respectively. [12]
- A recent UK study determined screening in HIV-positive men is estimated to cost UKP £39,400, and that this is apparently not cost-effective. [13]

While the BHIVA/BAASH guidelines have stated that the benefit of screening is 'not yet proven', a more positive set of guidelines from New York State has recommended screening in HIV-positive MSM, HIV-positive CIN/VIN, and HIV-positive people with a history of genital warts, although these recommendations are unlikely to be running in practice due to the demand this would place on anoscopy services.

For any screening to be effective it will be dependent on providing timely anoscopy follow-up for patient with abnormal cytology results.

C O M M E N T

Although the National Institute for Health Research (NIHR) has commissioned a new review to look at screening for anal cancer in the UK (currently in press), the degree to which HIV is addressed is unclear. [14]

This is difficult because an earlier review highlighted important reasons for making screening available to HIV-positive people and MSM. This earlier report was produced in 2003 and has not been reviewed since. [15]

The UK cost-utility study from Karnon et al is worrying for many reasons, especially if this is used as evidence against initiating a pilot screening programme. This paper has a complicated methodology, and some assumptions in their modeling are not fully explained.

- Mortality associated with anal cancer is based on data from 1996.
- All patients diagnosed with HIV before 1990 are assumed to have died by 2005.
- The disutility weighting for false-positive results is not clearly explained.
- It is odd to find worse outcomes from any screening programme, especially given the high relative risk in HIV-positive MSM. In this paper, no scenario produced better results from a screening programme compared to no screening.
- The paper uses triangular distribution and markedly different results could come from different distributional forms.
- In the explanation of calibration methodology, the rating scale used is not generally seen as most methodologically robust, and time trade off and standard gamble may be more appropriate.
- In the discussion, the authors recognise that they assumed higher HIV mortality than the US study, but they do not specify the rate used. They concede that this would reduce the effectiveness of screening, so this is an important figure to elaborate. They also do not state basis of expected mortality data, though it is used in several parts of the model, including reducing the effectiveness of screening in older MSM 'as they have fewer QALYs to gain'.

- **Finally, the paper makes a strange point about how MSM in the UK may not use a screening programme. This is supported by a reference to a study that reported that people get safer sex information from friends rather than clinics. The rationale for this is not clear. As people primarily use clinics for monitoring and treatment, accessing prevention information seems an inappropriate marker to use.**

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Once-daily darunavir/r monotherapy is suboptimal as initial regimen in treatment-naïve people

Simon Collins, HIV i-Base

A tiny pilot for a Phase 2 study in treatment naïve patients was stopped prematurely, concluding that once-daily darunavir/r was not sufficiently potent as initial treatment in treatment naïve patients for the study to continue.

Seven patients (with baseline viral load <100,000 copies/mL and CD4 counts > 100 cells/mm³ and no evidence of drug resistance) were started on open-label darunavir/r monotherapy. At week 4, all patients had >1log drop in viral load and by week 8, viral load was <400 copies/mL in 4/7. However, the trial was stopped as 5/7 patients had inadequate viral responses (together with the high level of screening failures - 38/45 screened - which would limit enrollment for the larger planned study).

All seven patients achieved viral loads <50 copies/mL following intensification with nucleosides. CD4 responses at week 12 were +167 cells/mm³. No grade 3-4 clinical or laboratory events were reported. No darunavir-associated mutations were seen in the two patients with genotype results.

C O M M E N T

Although these results were disappointing as initial therapy, an analysis of the MONET study that randomised people with undetectable viral load (<50 copies/mL) on any HAART regimen to either darunavir/r as monotherapy or plus dual RTIs, reported non-inferiority (difference = -1.6; 95%CI -10.1 to +6.8%) in terms of the percentage of people in each group with <50 copies/mL at week 48 (86.2% vs 87.8% respectively). [2]

These results were supported by other analyses, which is important for the continued use of darunavir/r in the currently enrolling MRC PIVOT study of PI-monotherapy maintenance therapy. [3]

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Central fat accumulation remains a significant problem in patients starting HAART after 2005 with higher incidence in women compared to men

Simon Collins, HIV i-Base

A cross-sectional study from two large French hospitals presented at EACS was important for confirming that central fat accumulation (CFA), one of the symptoms associated with HIV-related lipodystrophy, remains a significant side effect, even for patients who have started treatment recently.

Isabelle Poizot-Martin and colleagues used waist circumference as a surrogate marker of CFA in 838 HIV-positive patients (71% male, 29% female) who started combination antiretroviral therapy (cART) before (Group 1, n=723) or after January 2005 (Group 2, n=115).

CFA was defined as >102/88 cms (using NCEPATPIII guidelines) or >94/80 cms (using IDF classification), for men/women respectively.

Median age (years) was 46 in Group 1 and 44 in Group 2 (p=0.004). Median CD4 count was 523 and 472 cells/mm³, respectively (p=0.06) and viral load was < 40 copies/mL in 84% of patients in each group. Exposure to cART was 11.6 vs 2.1 years for Group 1 and 2 respectively.

CFA was reported in significantly higher rates for women compared to men in both groups, but also at higher rates in women who started treatment after 2005 compared to women who started treatment earlier, as detailed in Table 1.

Table 1: Percentages of patients with CFA diagnosed by waist circumference

	Group 1		Group 2	
	NCEP	IDF	NCEP	IDF
Men	12.7%	29.2%	11.8%	37.6 %
Women	24.4%*	52.6%**	43.3%*	76.7%**

* p=0.028 ** p=0.013 (between group comparisons)

While there were significant differences in use of different drugs in Group 1 compared to Groups 2 (mainly a higher use of triple-nucleoside regimens: by 11 vs 2% of patients), there were no significant differences by sex, particularly for Group 2.

C O M M E N T

While further associations are limited in a single cross-sectional dataset, the conclusion that CFA remains highly prevalent in patients who started treatment recently, is important.

The different rates of CFA in women compared to men had been previously reported and clearly warrant further study.

The results support the importance for every new antiretroviral to include prospective monitoring of body fat changes within Phase 3 studies. It is difficult to understand how any new drug could be approved without data on the impact it has on lipodystrophy and body fat changes.

Ref: Poizot-Martin I et al. Abdominal adiposity remains highly prevalent in French HIV-infected patients having initiated antiretroviral therapy after 2005. 12th EACS. 11-14 November 2009, Cologne. Abstract PS11/1.

Alendronate improves bone mineral density in HIV-positive people with osteoporosis at 96 weeks

Simon Collins, HIV i-Base

A small randomised placebo-controlled study (ANRS 120) showed that alendronate therapy (70mg once-weekly) significantly increased bone mineral density (BMD) at the osteoporotic site after 96 weeks. All patients also received calcium carbonate 500mg and vitamin D 400 units daily. [1]

Rozenberg and colleagues randomised 44 patients (n=20 alendronate; n=24 placebo) with T-scores less than -2.5 at lumbar spine and/or total hip assessed by DXA. Mean age at baseline was 45 years, CD4 count was 422 cells/mm³ and 84% had viral load <400 copies/mL. Only two women were in this study.

At week 96, BMD increased at the osteoporosis site by 7.1% vs 1.0% in the alendronate and placebo groups respectively [mean difference 6.1% 95%CI 2.8 to 9.3%; p=0.003]. BMD increased by >2.5% in 86% vs 40% in each group respectively. A greater number of adverse events were reported in the placebo group (13 vs 6).

The authors concluded that alendronate improved BMD in HIV-positive people using antiretroviral treatment who were diagnosed with osteoporosis.

C O M M E N T

While this study confirmed results from an earlier 48-week randomised trial [2], and suggested additional benefits from longer treatment, the earlier study should have been sufficient not to require a placebo for any patients with diagnosed osteoporosis.

Alendronate is already included in HIV guidelines that discuss the management of osteoporosis.

However, until DXA screening is included in routine management, the majority of HIV-positive patients with low bone mineral density are unlikely to have their osteoporosis diagnosed unless it becomes symptomatic (ie post-fracture).

The recent EACS monitoring guidelines (November 2009) included the recommendation to use the FRAX online calculator to screen HIV-positive patients.

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Gender-based differences in patients receiving antiretroviral therapy

Polly Clayden, HIV i-Base

Several studies looked at the impact of gender on different aspects of antiretroviral treatment.

UK CHIC Study

The UK Collaborative HIV Cohort (CHIC) Study analysed the impact of starting HAART among heterosexuals initiating treatment between 1 January 1998 and 1 January 2007 at <350 CD4cells/mm³ and viral load (VL) >500copies/mL. [1]

The analyses used logistic and Cox regression models adjusted for age, ethnicity, calendar year, initial ART, previous AIDS and pre-ART CD4/VL. Sensitivity analyses were performed in which women who initiated HAART for the first time during pregnancy or became pregnant in their first year of HAART were excluded.

Of 3666 eligible patients for this study, 1487 (40.6%) were male and 2179 (59.4%) female. The investigators reported that men who started therapy in this group were significantly older than women, median 38 vs 33 years; had lower CD4 counts, 122 vs 160 cells/mm³ and higher viral load, 5.0 vs 4.7 log copies/mL, both p=0.0001.

Men were less likely than women to start with a nevirapine-based regimen (18.4 vs 34.7%).

They found no significant differences in initial viral load response, adjOR men vs women 0.95 (95% CI 0.87-1.03), p=0.19; or time to rebound, adjRH, 1.17 (0.93-1.47), p=0.19. However, men were less likely to stop a drug in their regimen, for reasons other than viral failure. (In this analysis, 79.4% of the group experienced initial viral load response (defined as <50 copies/mL) and 19.2% experienced viral rebound (two consecutive viral load >500 copies/mL).

CD4 counts increased across the cohort by a mean of 112 and 156 cells/mm³ at 6 and 12 months respectively. Men had significantly lower increases than women at both time points by 14.6 (p=0.005) and 12.1 (p=0.05) cells/mm³ respectively.

The overall findings remained unchanged when the investigators excluded pregnant women from the analysis. Of 2179 women included, 273 (12.5%) started HAART in pregnancy and 40 (1.8%) became pregnant within a year of starting.

The investigators noted that some gender differences became more pronounced and statistically significant in this sensitivity analysis.

Men were more likely to have viral rebound than women, RH 1.33 (1.04-1.71), $p=0.02$, but they continued to be less likely to discontinue treatment for reasons other than virological failure, RH 0.76 (0.65-0.88), $p=0.0002$. CD4 increases remained lower in men by 11.1 cells/mm³, $p=0.03$; and 10.9 cells/mm³, $p=0.07$, at 6 and 12 months respectively.

The investigators concluded that virological outcome was similar between men and women in this cohort. They suggested that the higher CD4 increase on treatment may be explained by their higher nadir and baseline CD4 count.

They also suggested that the finding that women were more likely to discontinue their treatment for reasons other than viral failure may be associated with a higher incidence of adverse events such as CNS toxicities associated with efavirenz. They wrote: "Further investigation into the reasons for discontinuation may shed light on the different CD4 responses and improve ART sequencing options for men and women."

STAR and STELLA cohorts

STAR and STELLA are two German prospective, multicentre cohort studies for antiretroviral naïve patients starting a lopinavir/r-based regimens.

A 48-week analysis comparing treatment outcomes, adverse events and self reported symptom distress, between men and women, was performed. [2]

Of a study population including 1136 patients, 984 were men and 172 were women. Men were older (median 41 vs 38 years, $p=0.001$), had higher median viral load (5.1 vs 4.9 log copies/mL, $p<0.001$), a lower CD4 percentage (12% vs 14%) and similar absolute CD4 counts (194 vs 214 cells/mm³).

At 48 weeks in ITT analysis, 308/467 (66%) men and 50/74 (68%) women had viral load <50 copies/mL. Median increases in CD4 count were 218 vs 198 cells/mm³ in men and women respectively.

Using the ASDM self-reported questionnaire to look at symptom distress revealed similar scores in men and women, 11.0 vs 12.5 respectively at baseline. Scores in both groups decreased significantly at week 48, by 3 and 2 in men and women respectively, both $p<0.01$.

Baseline symptoms of adverse events of any grade were documented in 16% men and 10% women, $p=0.05$. At 48 weeks 26% men and 15% women reported adverse events, $p=0.04$.

A similar proportion of men (7%) and women (5%) discontinued lopinavir/r for toxicities and 1% and 2% due to virological failure.

In Kaplan Meier analysis the investigators found the probability of remaining on treatment was similar, (76% vs 78%) in men vs women.

They reported no differences in virological and immunological outcomes and similar rates of discontinuation due to adverse events between men and women initiating lopinavir/r based regimens.

CASTLE study

The CASTLE study was a multinational noninferiority study comparing atazanavir/r- to lopinavir/r- based regimens both with background tenofovir and emtricitabine in 883 patients.

An analysis was performed at 96 weeks to look at virological, immunological and safety profiles by gender. [3]

Overall 277/883 (31%) patients in this study were women. Baseline characteristics were similar in men and women in this study.

As previously reported, once-daily treatment with atazanavir/r was noninferior to twice-daily lopinavir/r, 74% of patients receiving atazanavir/r and 68% of patients receiving lopinavir/r achieved VL <50 copies/mL at week 96; difference estimate 6.1% (95% CI, 0.3-12%, $p<0.05$).

Discontinuation rates were higher for women than men in both treatment groups: 21% vs 14% and 29% vs 18%, women vs men, in patients receiving atazanavir/r and lopinavir/r, respectively.

In ITT analysis, more men than women had VL <50 copies/mL at 96 weeks: 77% vs 67% and 71% vs 63%, men vs women, in patients receiving atazanavir/r and lopinavir/r respectively. These differences were not observed in on treatment analysis.

Mean CD4 cell increases from baseline, rates of adverse events and lipid profiles were similar between genders. GI adverse events and lipid profiles were lower in both men and women receiving atazanavir/r than lopinavir/r.

The investigators wrote: "Consistent with other ARV clinical trials, gender differences in treatment efficacy were primarily due to higher discontinuation rates in women."

GRACE

GRACE (Gender, Race and Clinical Experience) was a multicentre open label phase 2b study to access the safety and efficacy of duranavir/r plus optimised background regimen.

A post hoc analysis was conducted to investigate factors correlated with adherence in GRACE. [4]

In this study the mean age of patients was 42.9 years, 66.9% patients were women, and 61.5% and 22.4% of the total population were black and Hispanic respectively. At baseline women were younger on average and tended to have less advanced disease and be less treatment experienced than men.

The virologic response (VL<50 copies/mL) at week 48 was 53.4% in ITT analysis. See Table 1 for response rates by sex and race.

Table 1: Virologic response <50 c/mL at week 48 by sex and race, n (%)

	Black	Hispanic	Caucasian
Women	89/191 (46.6)	35/60 (58.3)	21/34 (61.8)
Men	39/73 (53.4)	24/36 (66.7)	18/31 (58.1)

The response rate in patients with ≥95% adherence was 63.1% compared to only 34.7% in those with <95% adherence.

In multivariate analysis the investigators found no significant differences between sexes or across race in GRACE. More IAS/USA major protease resistance associated mutations, participation at a non-academic site, fewer NRTIs in the OBR, being a non-smoker and having a CV medical history were predictive of ≥95% adherence.

References

All references are abstracts from the 12th European AIDS Conference (EACS), 11-14 November 2009, Cologne.

1. Barber T et al. Outcomes of first line highly active antiretroviral therapy (HAART) among men and women in the UK CHIC study. Abstract
2. Koegl C et al. No subjective or objective gender differences in ART-naïve patients initiating a lopinavir/ritonavir-based regimen. 48 week data from the German STAR and STELLA cohorts. Abstract PE 7.9/19.
3. Johnson M et al. Gender based differences in antiretroviral-naïve patients treated with ritonavir-boosted protease inhibitors: results from the CASTLE study through 96 weeks. Abstract PE7.3/8
4. Squires K et al. Rates and predictors of adherence in treatment experienced women and men in GRACE (Gender, Race And Clinical Experience). Abstract PE10.1/2.

Pilot PK study of two generic paediatric formulations of lopinavir/ritonavir vs originator products

Polly Clayden, HIV i-Base

Affordable protease inhibitors in suitable formulations for children are urgently needed.

De Kanter and colleagues from the University Nijmegen, the Netherlands, showed pharmacokinetic (PK) data from a phase I, open-label crossover study to evaluate two generic paediatric formulations of lopinavir/ritonavir developed by Cipla Pharmaceuticals (Lopimune tablets and granules 100/25mg). This was a pilot study designed to exclude large (>40%) differences in the exposure to lopinavir achieved using the generic formulations compared to the originator product (Kaletra).

Twelve HIV-negative adult volunteers were randomised to receive the following sequences of regimen ABC, ACB, BCA, BAC, CAB, CBA: A=Kaletra tablets, B=Lopimune granules and C=Lopimune paediatric tablets. They were given single doses of medication (400mg lopinavir) on an empty stomach at one-week intervals and a 32-hour PK curve was recorded. A 32-hour PK curve was also recorded for 5/12 volunteers after receiving lopinavir granules and Kaletra oral formulation both with food.

The volunteers were a median age 24 (range 21-55) years, height 1.79 (range 1.63-1.95) meters and weight 72 (range 51-87) kg. One third of the group were women.

The investigators found the median lopinavir AUC_{0-t} was 71.8 h.mg/L (IQR 48.7-93.5) with Kaletra tablets (A), and 38.7 h.mg/L (IQR 28.7-52.2) and 58.7 h.mg/L (IQR 42.5-79.4) with Lopimune granules (B) and Lopimune tablets (C) respectively. With Kaletra tablets as a reference these differences were statically significant, B vs A, p=0.003 and C vs A, 0.015.

C_{max} median values were 7.2 mg/L (IQR 5.8-8.3), 4.6 mg/L (IQR 4.1-5.2) and 6.5mg/L (IQR 5.0-7.1); B vs A, p=0.003 and C vs A, p= 0.012.

The investigators also noted lower ritonavir concentrations with the Lopimune formulations compared to Kaletra.

A sub-group of volunteers received Lopimune granules (n=5) and Kaletra oral solution (n=4) with food. In this comparison, the median lopinavir AUC_{0-t} was 62.1 h.mg/L (IQR 43.8-126.3) with Kaletra tablets, and 58.5 (IQR 55.4-77.6) and 49.6 h.mg/L (IQR 39.1-58.1).

C_{max} median values were 7.2 mg/L (IQR 4.6-9.1), 6.4 mg/L (IQR 5.5-7.6) and 5.2mg/L (IQR 4.3-5.7).

The investigators concluded that it is possible to exclude large differences in PK parameters for the Lopimune paediatric tablets,

compared to Kaletra, when received on an empty stomach. Large differences can also be excluded for the Lopimune granules when these are received with food.

They added that, based on these results, it was acceptable to start PK and dose finding trials of the Lopimune paediatric tablets and granules even though the Cipla bioequivalence study was not yet complete.

C O M M E N T

This study did not test the effect of different compositions of meals on the absorption of LPV/r. They used a standardised “normal” European/Dutch breakfast, to see if the absorption would be better with food than without, as this is the case with the absorption of lopinavir from Kaletra oral solution. The absorption from the granules might be dependent on the amount of fat in the meal as is stated in the Summary of Product Characteristics.

Since this small study, the Cipla formulation has changed and has been slightly refined, so there is an ongoing bioequivalence study. CHAPAS 2, which will look at these products in children, is waiting on these results before it begins (probably around March). CHAPAS 2 will be able to investigate absorption among breastfeeding children and also those who are malnourished.

Ref: de Kanter et al. The pharmacokinetics of two generic co-formulations of lopinavir/ritonavir for HIV-infected children: a pilot study of pediatric lopimune formulations vs the branded product in healthy volunteers. 12th EACS, Cologne, November 11-14, 2009. Abstract PE15.2/1.

TMC278 did not show teratogenic potential in animal models

Polly Clayden, HIV i-Base

TMC278 (ripivirine) is a novel NNRTI currently under investigation. The embryo-foetal toxicity was evaluated in rats and rabbits.

In this study, pregnant Sprague-Dawley rats (by oral gavage) and New Zealand white rabbits (by oral dosing) received doses of TMC278 during the period of organogenesis (days 6-17 and 6-19 in rats and rabbits respectively).

Doses observed were: 400, 120 and 40 mg/kg/day in rats; and 20, 10 and 5 mg/kg/day in rabbits. Both animal models had a control group.

The investigators reported moderate maternal toxicity (reduced food consumption, and body weight gain, and increased thyroid weight) in rats at the two higher doses. In rabbits they did not observe any maternal toxicity.

They reported no teratogenic effect in either animal and there was no effect of treatment on pregnancy parameters.

In rats in the two higher dose groups they observed an increase in incidence of dilated renal pelvis (visceral variant) 120 mg/kg/day, $p < 0.05$ and 400 mg/kg/day, $p < 0.01$ compared to the control group. This was the only finding on embryo-foetal development in rats.

The maternal and embryo-foetal development no observable adverse effect level (NOAEL), was 40 mg/kg/day, associated with a maternal AUC_{0-24h} of 37 ug.h/mL.

With rabbits, the only finding was a slight increase in the incidence of minor variations of the left subclavian artery, $p < 0.05$ and hypoplastic interparietal bone, $p < 0.05$ compared to the controls in the group receiving 20 mg/kg/day.

The maternal toxicity and embryo/foetal NOAELs were 20 mg/kg/day and 10 mg/kg/day, respectively, which were associated with maternal AUC_{0-24h} of 232 ug.h/mL and 170 ug.h/mL.

The investigators concluded that TMC278 did not show teratogenic potential in rat and rabbit models at drug exposures 13-80 times higher than those in HIV-positive patients receiving 25 mg/qd at steady state (TMC278-C204 Study AUC_{0-24h} was 2.8 ug.h/mL).

Based on this data they suggest that further studies in women of child bearing potential are warranted.

Ref: Desmidt M et al. Absence of a teratogenic potential from a novel next-generation NNRTI, TMC278. 12th EACS. 11-14 November, 2009. Cologne. Abstract PE7.1/4.

No clinically relevant interactions between TMC278 and oral contraceptives (norethindrone plus ethinylestradiol)

Polly Clayden, HIV i-Base

An open label trial conducted by Crauwels and colleagues evaluated the pharmacokinetic (PK) interaction between TMC278 and norethindrone plus ethinylestradiol.

In this analysis, 18 HIV-negative volunteers received 1mg norethindrone plus ethinylestradiol 35ug (combined oral contraceptive pill, Ovysmen) once a day for three sequential 21-day cycles spaced with 7-day intervals. TMC278 was co-administered for the first 15 days of the third cycle at a once daily dose of 25 mg. TMC278 and Ovysmen were taken within 10 minutes after breakfast.

At day 15 of the second and third cycles 24 PK profiles of norethindrone, ethinylestradiol and TMC278 were obtained. Plasma samples were analysed using validated LC-MS/MS methods, with a lower limit of quantification of 1.0 ng/mL for TMC278, 50.0 pg/mL for norethindrone and 2.0 pg/mL for ethinylestradiol. Serum levels of progesterone luteinising hormone (LH) and follicle-stimulating hormone (FSH) were determined on days 1 and 14 of the second and third cycles.

PK parameters were calculated using non-compartmental analysis. Statistical analysis compared the test treatment, Ovysmen+TMC278 to the reference, Ovysmen alone.

The women in the study were a median age of 26 years, weight 69.5kg and BMI 24.6. The majority (67%) were white.

The investigators reported no effect on norethindrone PK when co-administered with TMC278. With ethinylestradiol, neither the C_{min}, nor the AUC_{24h} were affected and C_{max} increased by 17% in the presence of TMC278. This increase is not expected to have a clinically relevant effect. See Table 1 for results of PK parameter ratios for norethindrone and ethinylestradiol in the presence of TMC278.

Table 1: PK parameter ratios for norethindrone and ethinylestradiol in the presence of TMC278

Parameter	n/n	Norethindrone (90% CI)	Ethinylestradiol (90% CI)
AUC _{24h} pg.h/mL	14/15	0.89 (0.84-0.94)	1.14 (1.10-1.19)
C _{max} pg.h/mL	15/17	0.94 (0.83-1.06)	1.17 (1.06-1.30)
C _{min} pg.h/mL	15/17	0.99 (0.90-1.08)	1.09 (1.03-1.16)

Steady state PK parameters of TMC278 25mg/QD in the presence of noretindrone and ethinylestradiol were comparable to values observed in previous trials of TMC278 alone. TMC278 25mg/QD had no clinically relevant effect on FSH, LH or progesterone serum levels in the presence of noretindrone and ethinylestradiol.

The investigators concluded that the contraceptive efficacy of 1mg norethindrone plus ethinylestradiol 35ug is expected to be maintained in the presence of TMC278 25mg/qd without dose modifications.

Ref: Crauwels et al. Pharmacokinetic interaction study between TMC278 an NNRTI, and the contraceptives northindrone plus ethinylesradiol. Abstract PE4.3/3

Etravirine pregnancy data from five cases: no dose adjustment required

Polly Clayden, HIV i-Base

A pharmacokinetic (PK) and safety study of etravirine (ETR) was conducted in five pregnant women receiving this next generation NNRTI through compassionate use during the clinical development programme.

PK assessments were performed in the third trimester and/or time of delivery. Samples were collected 1, 3, 6 and 12 hours post dose. Cord blood samples were obtained where possible. Plasma concentrations were determined using high performance LC-MS/MS (LLOQ 2ng/mL).

A non-compartmental model was used for the PK analysis and compared with population PK data from earlier trials. The investigators noted that in these trials (DUET-1 and DUET-2) PK parameters did not differ significantly between men and women.

In this study three women received ETR throughout pregnancy and two only in the third trimester.

The investigators reported comparable values in all five women to historical controls. See Table 1.

Table 1: PK parameters of ETR in third trimester

Case	T _{max} (h)	C _{max} (ng/mL)	AUC _{12h} (ng.h/mL)	C _{0h} (ng/mL)
1	3	896	4,277*	387
2	6	1,210	6,448*	521
3	3	474	4,788	149
4	3	1150	8,870	898
5	3	445	3,041	434
Mean	-	835	5,485	478
SD	-	363	2,253	272
DUET population PK n=575				
Mean	-	-	5,506	393
SD	-	-	4,710	391

AUC=Area under the curve; C=concentration; T=time

* AUC 6h

Three of the women had caesarean sections (one preterm due to twins) and the remainder vaginal deliveries.

The babies were all healthy. One was born with a polyotia but was otherwise normal. No other abnormalities were reported.

The investigators concluded that ETR PK in five pregnant women is comparable to that in non-pregnant adults, which suggests that no dose adjustment is needed. In this small study ETR did not have an effect on foetal toxicity.

ETR in pregnant women will be evaluated further in an ongoing trial investigating PK parameters of darunavir/r and ETR during the second and third trimesters and up to 12 weeks postpartum. [2]

C O M M E N T

The importance of conducting these studies and reporting even no effect must be stressed as guidance in this area is vague for many antiretrovirals.

References

1. Izurieta P et al. Safety and pharmacokinetics of etravirine in pregnant HIV-infected women. 12th EACS. Cologne. 11-14 November 2009. Abstract PE4.1/6.
2. A study to assess the pharmacokinetics (blood levels) of TMC114 (darunavir) taken with TMC114r (ritonavir), and TMC125 (etravirine) in HIV-1 infected pregnant women
<http://clinicaltrials.gov/ct2/show/NCT00855335>

Other selected PK and drug interaction summaries from EACS

www.hiv-druginteractions.org

This report summarises drug interaction and pharmacology studies presented at this recent meeting. Unless stated otherwise, all references are to the 12th European AIDS Conference (EACS), 11-14 November 2009, Cologne.

Raltegravir and famotidine or omeprazole

The effect of famotidine (20 mg single dose 2 h before raltegravir) or omeprazole (20 mg once-daily for 5 days, 2 h before raltegravir) was studied in 18 HIV-positive subjects stable on raltegravir (400 mg twice-daily) regimens. Coadministration of famotidine increased raltegravir AUC, C_{max} and C_{trough} by 45%, 60% and 6% respectively. Omeprazole increased raltegravir AUC, C_{max} and C_{trough} by 39%, 51% and 24%, respectively. The increases were not clinically significant and raltegravir may be coadministered with famotidine or omeprazole without dose adjustment.

C O M M E N T

This effect is less than previously seen in healthy volunteers.

Ref: Rhame F et al. Effects of famotidine and omeprazole on raltegravir pharmacokinetics in HIV-infected persons. 12th EACS, 11-14 November 2009, Cologne. Abstract PE4.1/1.

P450 and P-gp activities in HIV-positive and HIV-negative subjects

The activity of CYP3A, 2D6 and P-gp were investigated in 30 HIV-positive, treatment naïve patients and 12 HIV-negative controls. Subjects were given a "phenotyping cocktail" containing midazolam (1.5mg, intestinal and hepatic CYP3A), dextromethorphan (30 mg, CYP2D6), digoxin (0.5 mg, P-gp) and IV midazolam (1.0mg, hepatic CYP3A).

The activities of CYP3A, CYP2D6 and P-gp were lower in the HIV-positive subjects, but with the exception of CYP3A, the differences were small. Total CYP3A activity was 0.493-fold lower in HIV-positive subjects than in HIV-negative controls.

Within group variability was greater than between group variability, making it unlikely that dose adaptations based on infection status would be useful.

Ref: Jetter A et al. Are there differences between healthy volunteers and HIV-infected patients in the activities of CYP3A, CYP2D6 and P-glycoprotein. 12th EACS, 11-14 November 2009, Cologne. Abstract PE4.1/9.

MVC and CYP450 inhibitors or inducers

Maraviroc trough concentrations were determined in HIV-positive subjects receiving maraviroc in combination with CYP450 inhibitors or inducers.

Median maraviroc trough concentrations were 83 ng/mL, with 24% being below target (50 ng/mL) in subjects receiving maraviroc 150 mg twice daily with a boosted PI (not TPV or APV). In subjects receiving maraviroc 300 mg twice daily with a boosted PI, the median trough concentration was 264 ng/ml and 9% were below target.

When maraviroc was administered as 300 mg twice daily without a boosted PI or NNRTI, median trough concentrations were 47 ng/mL and 55% were below target. Coadministration of maraviroc 600 mg twice daily with etravirine resulted in median trough concentrations of 77 ng/mL, of which 19% were below target.

C O M M E N T

There is data suggesting that the average concentrations (Cavg) may be a better parameter to correlate with viral response.

Ref: Sari-Chaaf Z et al. Maraviroc boosted (or not) by ritonavir? Pharmacokinetic results from routine therapeutic drug monitoring. 12th EACS, 11-14 November 2009, Cologne. Abstract PE4.2/1.

Abacavir and darunavir/r or raltegravir

This study investigated the steady-state plasma pharmacokinetics of abacavir (600 mg once daily) when co-administered with darunavir/ritonavir (900/100 mg once daily) or raltegravir (400 mg twice daily) to 19 HIV-positive subjects.

Abacavir AUC, Cmax and Cmin decreased by 27%, 22% and 38%, respectively in the presence of darunavir/ritonavir. When coadministered with raltegravir, the AUC and Cmax of abacavir increased by 3% and 6%, respectively; Cmin decreased by 17%. It is important to relate the change in plasma abacavir exposure to the active intracellular carbovir triphosphate and a study is in progress.

Ref: Jackson A et al. Pharmacokinetics (PK) of plasma abacavir (ABC) in the absence and in the presence of darunavir/ritonavir (DRV/r) or raltegravir (RAL) in HIV-infected subjects. 12th EACS, 11-14 November 2009, Cologne. Abstract PE4.3/2.

TMC278 and oral contraceptives

The pharmacokinetic interaction between TMC278 (25mg once daily) and an oral contraceptive containing norethindrone/ethinylestradiol (1/0.035mg) was studied in 18 HIV-negative females. Norethindrone pharmacokinetics were unaffected by TMC278 (11% decrease in AUC, 6% decrease in Cmax, 1% decrease in Cmin).

There was no statistically significant change in ethinylestradiol AUC (14% increase) or Cmin (9% increase), but Cmax increased by 17%, however, this is not expected to be clinically significant. Pharmacokinetics of TMC278 were within the expected range. There was no marked effect on FSH, LH and progesterone serum levels.

TMC278 and oral contraceptives containing norethindrone/ethinylestradiol can be coadministered without dose modifications.

Ref: Crauwels H et al. Pharmacokinetic interaction study between TMC278, a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI), and the contraceptives norethindrone plus ethinylestradiol. 12th EACS, 11-14 November 2009, Cologne. Abstract PE4.3/3.

Darunavir and raltegravir interaction

Darunavir trough concentrations were determined in 117 samples from 55 HIV-positive patients receiving darunavir containing regimens with either a NRTI or raltegravir.

Mean (\pm sd) darunavir concentrations were higher in the NRTI subjects than in the raltegravir subjects (4.20 ± 2.35 vs 2.63 ± 84 mg/L). However, the proportion of subjects with undetectable viral loads (<50 copies/mL) was higher in the raltegravir group than in the NRTI group.

After adjusting for time from last drug intake and concomitant drugs, a multivariate linear regression model confirmed raltegravir to be independently related to lower darunavir concentrations.

The mechanism of this unexpected interaction remains to be determined, but it does not appear to be virologically significant.

C O M M E N T

This data is consistent with a previous report from Garvey et al presented at the IAS meeting in Cape Town (IAS 2009, LBPEB08). The absolute darunavir concentrations in the Fabbiani study are higher than previously reported.

Ref: Fabbiani M et al. Unexpected drug interaction between darunavir and raltegravir. 12th EACS, 11-14 November 2009, Cologne. Abstract PE4.3/4.

Raltegravir and unboosted atazanavir

The steady state pharmacokinetics of raltegravir (400 mg twice daily) and unboosted atazanavir (300 mg twice daily) were determined in 22 HIV-positive subjects who switched from their current regimen.

Atazanavir geometric mean AUC, Cmax and Ctough were 14454 ng.h/ml, 2275 ng/ml and 419 ng/mL respectively. Raltegravir geometric mean AUC, Cmax and Ctough were 7112 ng.h/ml, 1680 ng/ml and 62 ng/ml. Three subjects (14%) had atazanavir trough concentrations below 100 ng/ml.

At the time of switch, 79% subjects had undetectable viral load, but at week 24, all subjects had undetectable viral loads.

C O M M E N T

These data are generally consistent with Zhu et al (CROI 2009, abstract 696).

Ref: Ripamonti D et al. Steady-state pharmacokinetics, efficacy, safety and tolerability of dual regimen with atazanavir (300mg bid) plus raltegravir (400mg bid) in HIV-1-infected patients: 24-week results (CARDS study). 12th EACS, 11-14 November 2009, Cologne. Abstract LBPE4.3/5.

Nevirapine and efavirenz concentrations, during and after stopping rifampicin

Concentrations (12 h post dose) of nevirapine (400 mg/day, n=71) and efavirenz (600 mg/day, n=71) were determined at 6 and 12 weeks after starting rifampicin and then after rifampicin had been discontinued. Mean \pm SD concentrations for nevirapine at weeks 6, 12 and after discontinuation were 5.6 ± 3.6 , 5.5 ± 2.6 and 6.7 ± 3.5 mg/L, respectively.

Efavirenz concentrations at the same time points were 4.5 ± 4.3 , 3.8 ± 3.5 and 3.5 ± 2.7 mg/L, respectively. Patients on efavirenz showed greater inter-patient variability whilst receiving rifampicin than patients on nevirapine.

Ref: Manosuthi W et al. Serial monitoring of drug concentrations while on and off rifampicin between standard doses of nevirapine-based and efavirenz-based antiretroviral regimens. 12th EACS, 11-14 November 2009, Cologne. Abstract PE4.6/1.

Traditional medicine use in Uganda

The use of African herbal medicines in HIV-positive subjects receiving antiretroviral therapy was assessed in four districts of Uganda by interviewing traditional medicine practitioners (n=25) and HIV-positive subjects (n=44).

Over 100 plant species were identified, with approximately 80% of preparations being taken orally.

Multi-plant preparations were common in 75% districts, with mono-plant preparations being predominant in one district. Plant parts frequently used were leaves (33%), stem bark (23%) and root bark (18%). The priority plants identified included Aloe sp, Erythrina abyssinica, Sarcocephalus latifolius, Psorospermum febrifugum, Mangifera indica, Warburgia salutaris and Albizia coriaria.

C O M M E N T

The widespread use of traditional medicines with largely unknown effects on drug disposition indicates the need for studies in this area.

Ref: Lamorde M et al. Traditional medicine practices in the context of HIV in Uganda. 12th EACS, 11-14 November 2009, Cologne. Abstract PE19.9/1.

CONFERENCE REPORTS

11th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV (IWADR)

26-28 October 2009, Philadelphia

Introduction

We continue our reports from the 11th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV, held this year from 26–28 October 2009 in Philadelphia, with this report on important new research for hepatitis C treatment.

- The HCV pipeline – efficacy and side effects of compounds in Phase 3 studies

The meeting organisers make nearly all oral presentations to be available as free access webcasts. The oral plenary lectures at the meeting are of a consistently high standard, often inviting experts from outside the HIV field to provide an overview on newly emerging issues relating to long-term HIV management.

<http://lipo09.events-register.com>

The HCV pipeline – efficacy and side effect of compounds in Phase 3 studies

Simon Collins, HIV i-Base

Christoph Sarrazin from Goethe Hospital, Frankfurt presented an update on recent research relating to HCV treatment. [1]

The context for the importance of new HCV treatment for use in coinfection, is the urgent need for more effective therapies; less than 50% of currently treated patients achieve a sustained virological response (SVR), with up to 25% being non-responders and another 25% relapsing. Many more patients are excluded from treatment because of co-morbidities, contraindications to treatment or an individual choice to defer treatment based on the side effect profile of pegylated interferon plus ribavirin. These factors all underline the need for better treatment for HCV.

As with HIV, a broad understanding of the HCV lifecycle has provided several targets for treatment, outlined in Table 1. Most antiviral pipeline compounds are either protease (NS3/4A), polymerase (NS5B nucleosides and non-nucleoside) or NS5A inhibitors, or they interact with host proteins or work via unknown mechanisms (silibinin, nitazoxanide etc). However, the development of many compounds have been stopped due to poor efficacy or tolerability, and most of those remaining are only in Phase 1 or 2 studies. Only two HCV antivirals are currently in Phase III studies, both of them protease inhibitors: telaprevir (VX-950) and boceprevir (SCH-503034).

Table 1: HCV lifecycle and target for drugs in pipeline

Lifecycle stage	Potential compound types	Compounds in development	Development stopped or on-hold
Cell entry	Interaction with receptors via immunoglobulins or specific HCV antibodies		
Uncoating			
Protein synthesis	Inhibited by IRES inhibitors and inhibitors interfering with translation factors		
Cleavage	NS2 and NS3 protease inhibitors and NS4A inhibitors	Phase 1: TMC435350; BMS-650032; PHX1766. Phase 2: ITMN 191/R7227; TMC-435350; BI201335; SCH900518 (narlaprevir); MK7009. Phase 3: telaprevir (VX-950); boceprevir (SCH-503034).	BILN 2061 (cardiac in monkeys); ACH-806 (Nephrotoxicity).
RNA replication	Helicase inhibitors, NS5A inhibitors, NS5B polymerase inhibitors, cyclophillin inhibitors, silibinin	NS5B inhibitors: Phase 1: VCH222; Phase 2: R7128; GS9190; ANA598; PF-00868554 (filibuvir); VCH916; ABT-333. Host protein/unknown: Phase 2: nitazoxanide; silibinin; Debio-025; NIM811; SCY-635.	NS5B inhibitors: NM283 (GI toxicity); R1626 (GI toxicity included grade 4 and deaths); BILB1941 (GI toxicity); HCV796 (hepatic toxicity); VCH759; VCH916. NS5A inhibitor: Phase 1: BMI700052.
Packaging			
Maturation			

Telaprevir and boceprevir were both highly active in early studies in HCV monoinfected, treatment-naïve patients with HCV genotype-1, producing rapid viral load drops (approximately 4 logs and 2 logs, respectively) after 3 days of monotherapy. [2, 3]

However, only a minority of patients had continued declines over 14 days. As with HIV monotherapy, a single hepatitis C antiviral is not sufficiently potent to eliminate the virus or even maintain viral suppression. The rapid emergence of resistance around the active binding site (at codons V36, T54, R155 and A156) leads to reduced antiviral activity. The long-term clinical implications of HCV antiviral drug resistance are unknown.

When telaprevir was combined with PEG-IFN as dual therapy in a Phase 1 study, reductions of up to 7 logs were maintained for all patients at day 14, but the PROVE-2 Phase 2 trial showed that ribavirin also need to be included for sustained and durable responses. Notably, the triple combination reduced both duration of treatment (from 48 down to 12 weeks) and the risk of viral breakthrough to 3%. See Table 2. [4]

Table 2: Percentages of pts with undetectable HCV PCR (<10 IU/mL) in the PROVE study

	Wk 4	Wk 12	SVR (24 wk f/u)	% VLbreak through
PEG-IFN + ribavirin (48wks)	13	43	46	-
telaprevir + PEG (12 wks)	50	62	36	24%
telaprevir + PEG + ribavirin (12 wks)	80	80	60	3%

Roche's INFORM-1 study provided an indication of the potential to combine new HCV drugs without the PEG-IFN plus ribavirin. INFORM-1 is a proof-of-principle study using a dual protease/polymerase inhibitor combination of R7227 plus R7128, presented at EASL in 2009 (5).

Treatment-naïve patients in the higher dose arms had HCV viral load declines of -5 logs, with up to 30% achieving undetectable levels, and with no evidence of early viral breakthrough. At the 2009 AASLD meeting, INFORM-1 data from treatment experienced patients (relapsers, non-responders and null responders) were presented; the median HCV RNA drop was >4 log. [6]

These were exciting 14 day results, but results from longer-term results on efficacy, resistance and tolerability are now awaited. BMS has initiated a Phase 2 study combining 790052, an NS5a inhibitor plus BMS-650032, an HCV protease inhibitor, in null responders.

These newest compounds are important for their activity against HCV genotype-1, currently the least responsive to PEG-IFN plus ribavirin. Both boceprevir and telaprevir, however, have reduced activity against HCV genotype-2 and virtually no activity against genotypes 3 and 4.

Adding boceprevir to the current standard of care in treatment-naïve patients with genotype-1 increased SVR response rates from approximately 40% to 56% at week 28 and to 75% at week 48 for the triple combination. [7]

Similar results were seen for telaprevir in the PROVE-1/2 studies, with SVR rates of 60-70% using only 12 weeks of triple therapy. [8, 4]

In PROVE 3, SVR rates of approximately 70% and 40% were seen at 12 weeks in previous relapsers and non responders respectively, using telaprevir triple therapy, and this compared to SVR rates of 20% and 9% using PEG-IFN plus ribavirin. Rates in relapsers, but not non-responders, increased slightly when treated to 24-weeks, but relapse rates in both groups decreased with longer duration of treatment.

The preliminary nature of these studies - none of which are in people with HIV coinfection - has only provided limited tolerability data. However, discontinuation rates were 18% in first 12 weeks in the Phase 3 telaprevir studies, compared to around 4% using PEG-IFN plus ribavirin, indicating that poor tolerability remains an important limitation. Other common side effects occurred in 20-30% more patients, including nausea (~50% vs 30%), pruritis (~45% vs 23%), diarrhoea (~40% vs 28%), rash (~60% vs 40%), moderate-severe rash (~25% vs 9%), vomiting (~24% vs 12%) and haemorrhoids (~15% vs 1%). [4, 8]

Many of the discontinuations were within the first four weeks, precluding the likelihood of a successful outcome from treatment, but later discontinuations were reported too, and as a result, future telaprevir studies will limit treatment to 8-12 weeks.

Boceprevir had a similar doubling of discontinuation rates in triple therapy compared to standard treatment arms: 15% vs 7% in patients using epoetin-alpha (EPO), and 38% vs 15% when EPO was not used. However, boceprevir had a comparable longer-term toxicity profile to dual PEG-IFN plus ribavirin therapy from week 24 to 48, allowing longer duration of treatment. Anaemia rates were higher (approximately 60% vs 34%), neutropenia (17-30% vs 12%; especially grade-2), vomiting (17-44% vs 5%) and taste changes (20-44% vs 9%) in the boceprevir groups. [7]

Very limited data on protease inhibitors in Phase 1-2 studies suggests specific side effects from these drugs; gastrointestinal complications and, for BI201335, jaundice relating to increased unconjugated bilirubin (16%) and severe rash (2.5%). Polymerase inhibitors include heterogeneous reports of nausea, neutropenia, headache, diarrhoea, dizziness (for nukes) and generalised erythema, mild rash, headache and fatigue (for non-nukes).

Both boceprevir and telaprevir require dosing three times a day (every eight hours with food). However, SCH900518 (narlaprevir) which is also dosed TID has been studied twice-daily with QD 100mg ritonavir boosting, suggesting a similar potential for boosting HCV protease inhibitors, as with some PIs used to treat HIV. Preliminary response rates look similar to boceprevir and telaprevir, perhaps with reduced discontinuations. Studies of the Roche compound R7227 are also planned using ritonavir boosting.

C O M M E N T

These preliminary results in HCV mono-infection, especially for relapsers and non-responders with genotype-1, are exciting and encouraging. They also highlight the importance of studying promising new HCV compounds in HIV/HCV coinfecting patients.

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TREATMENT ACCESS

FDA approval of generic ARVs

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

Drug and formulation	Manufacturer, Country	Approval date
3TC/AZT/nevirapine 150/300/200mg. Fixed Dose Combination	Strides Arcolab, India	22 December 2009

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

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

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

C O M M E N T

This brings the total of FDA approved generic drugs and formulations to 105 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/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm122951.htm>

PEPFAR launches five-year strategy

On 1 December 2009, the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) launched a five-year strategy outlining the direction of the program for its next phase.

The goals included, to:

- transition from an emergency response to promotion of sustainable country programs;
- strengthen partner government capacity to lead the response to this epidemic and other health demands;
- expand prevention, care, and treatment in both concentrated and generalised epidemics;
- integrate and coordinate HIV/AIDS programs with broader global health and development programs to maximise impact on health systems; and
- invest in innovation and operations research to evaluate impact, improve service delivery and maximise outcomes.

In addition, it announced new targets for the program around prevention, care and support, treatment, and sustainability. As a component of the Global Health Initiative, PEPFAR will be carefully and purposefully integrated with other health and development programs.

C O M M E N T

This announcement was seen as a disappointing by many people who expected a stronger commitment to the potential role for the US in global health.

This level of funding will result in reducing the numbers of HIV-positive people who will be able access the PEPFAR funded treatment programmes as new patients each year.

However, the US still donates far more to treatment programmes than other western countries, and activists outside the US also need to focus on increasing the levels of funding for treatment access by their governments.

Source: PEPFAR press release. (01 Dec 2009).

The PEPFAR strategy is published online:

<http://www.PEPFAR.gov/strategy>

Global Fund approves US\$2.4 billion in new grants

TheGlobalFund.org

In its ninth round of funding the Global Fund to Fight AIDS, Tuberculosis and Malaria has made an overall approval of grants with a two-year commitment of US\$2.4 billion.

This is the second largest ever approved by the Global Fund, following a US\$2.75 billion round in 2008. The Global Fund has now approved a total funding of US\$18.4 billion for 144 countries since it was created in 2002.

The Global Fund also approved the roll-out of the pilot phase of a facility to reduce prices for effective malaria medicines (AMFm). The Pilot phase will take place in nine African countries and Cambodia and be funded through US\$216 million in funding from UNITAID, the United Kingdom government and the Bill and Melinda Gates Foundation. It aims to provide access for everybody to effective artemisinin combination treatments for malaria and save lives by reducing the use of old, ineffective medicines.

The Global Fund Board decided to launch its next round of grants in May 2010. This round of funding will be considered for approval at a Board meeting to be held some time between November 2010 and January 2011.

Source: GFFATM Press release. Global Fund approves US\$2.4 billion in new grants. (12 Nov 2009).

http://www.theglobalfund.org/en/pressreleases/?pr=pr_091112

UNITAID decision to fund 'patent pool' to boost access to new medicines

UNITAID and MSF press releases

On 15 December 2009, UNITAID, an international health financing agency, agreed to fund a licensing agency that will be able to administer a patent pool for AIDS medicines.

This will offer licenses to generic manufacturers, and has the potential to reduce prices and facilitate the combination of drugs from different makers into fixed-dose combinations. This first step will mean that formal negotiations with drug companies can hopefully now begin.

UNITAID has identified 19 products from nine companies for potential inclusion into the pool. Companies that UNITAID has already consulted include Gilead, Tibotec, Merck and Sequoia.

This programme is supported by the Médecins Sans Frontières' Campaign for Access to Essential Medicines. "This is an important decision, but the pool will be judged on its outcome for patients," said Michelle Childs, Director of Policy & Advocacy at MSF. "We've been encouraged by the positive responses from a number of companies to our campaign in support of the pool. Now that the pool has been given a green light, patent holders need to move from expressions of general support to firm and formal license commitments. We urge them to do so. This needs to happen fast, as the clock is ticking for millions of patients."

"The Board has confirmed that this pool is for all developing countries, but as this is a voluntary mechanism, the ultimate outcome will depend on the decisions of patent holders. Countries can still use the legal mechanisms at their disposal such as compulsory licensing and pro-health patent laws to ensure people have access to the life-saving medicines they need."

Source: MSF and UNITAID press releases, (14/15 Dec 2009).

UNITAID Executive board approves breakthrough plan to make AIDS treatment more widely available at lower cost: patent pool could save over one billion dollars a year.

<http://www.unitaid.eu/en/The-Medicines-Patent-Pool-Initiative.html>

ANTIRETROVIRALS

GSK issues Dear Doctor letter in the US: fosamprenavir and cardiovascular risk

On 4 December 2009 GlaxoSmithKline (GSK) and FDA notified healthcare professionals and others of a potential association between fosamprenavir and myocardial infarction (heart attack) and dyslipidemia (abnormal concentrations of lipids or lipoproteins in the blood) in HIV-positive adults. GSK has modified the existing 'warnings and precautions' section of the prescribing information to note that increases in cholesterol have occurred with treatment, the importance of lipids management, and a recommendation that triglyceride and cholesterol testing be performed prior to initiating therapy with fosamprenavir and at periodic intervals during therapy.

The text of the Dear Healthcare Provider letter follows:

Dear Healthcare Professional:

Fosamprenavir calcium (Levixa) tablets and oral suspension: myocardial infarction and dyslipidemia

GlaxoSmithKline would like to inform you of data presented at the 16th Conference on Retroviruses and Opportunistic Infections (CROI 2009) relating to a potential association between fosamprenavir tablets and oral suspension and myocardial infarction in HIV infected adults.

Action being taken by GSK

GSK has added myocardial infarction and hypercholesterolemia to the Adverse Reactions section of the fosamprenavir prescribing information (Section 6.2 Postmarketing Experience). Elevations in triglyceride levels are already described in the Adverse Reactions section (Section 5.8 Warnings and Precautions, Section 6.1 Clinical Trials).

GSK has modified the existing Warnings and Precautions statement (Section 5.8 Lipid Elevations) in the prescribing information for fosamprenavir Tablets and Oral Suspension to highlight that increases in cholesterol have occurred with treatment. This statement highlights the importance of lipids management by including a recommendation that triglyceride and cholesterol testing should be performed prior to initiating therapy with fosamprenavir Tablets and Oral Suspension and at periodic intervals during therapy.

GSK is in communication with FDA and this issue will be closely monitored.

Key messages

- A case-control study nested in the French Hospital Database on HIV [FHDH ANRS CO4] has reported an association between exposure to fosamprenavir/amprenavir and an increased risk of myocardial infarction (Odds Ratio (OR): 1.52 per additional year of exposure; 95% CI, 1.19-1.95). [Lang S, Mary-Krause M, Cotte L et al. CROI 2009, Abstract #43LB]
- Myocardial infarction has already been identified as a signal for the protease inhibitor (PI) class in general; the reported association is plausible and may be related to the propensity for this drug class to raise blood lipids [The D:A:D Study Group 2007].
- Prescribers are reminded that HIV infection itself has been associated with lipid disorders and ischaemic heart disease.
- Triglyceride and cholesterol levels should be checked prior to initiating therapy with fosamprenavir and at periodic intervals during therapy. Appropriate clinical management of lipid disorders should be initiated as required.
- Other modifiable risk factors for cardiovascular disease (such as hypertension, diabetes and smoking) should also be monitored in HIV-infected subjects and managed as clinically appropriate.

Labelling recommendations

Details of the new labelling for fosamprenavir are described under "Action Being Taken by GSK." Please read the Prescribing Information for the full text describing these labelling changes.

Action required by healthcare professionals

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV-infected patients. Clinical examination should include evaluation for physical signs of fat redistribution.

Triglyceride and cholesterol levels should be checked prior to initiating therapy with fosamprenavir and at periodic intervals during therapy. Appropriate clinical management of lipid disorders should be initiated as required.

Other modifiable risk factors for cardiovascular disease (such as hypertension, diabetes and smoking) should be monitored in HIV-infected subjects and managed as clinically appropriate.

Supporting information

At an international HIV conference (CROI, February 2009), data from a case-control study nested within the French Hospital Database on HIV were reported [Abstract #43LB].

The objective of the study, requested by the European Medicines Evaluation Agency (EMA), was to analyse the effect of exposure to specific nucleoside reverse transcriptase inhibitors (NRTIs) and PIs on the risk of myocardial infarction. Several conditional logistic regression models were used to assess the association of (i) cumulative exposure to specific NRTIs, (ii) recent (current or within 6 months) and past exposure (>6 months ago) to specific NRTIs, and (iii) cumulative exposure to specific PIs on the risk of myocardial infarction. The study reported an association between an increased risk of myocardial infarction and cumulative exposure to fosamprenavir/amprenavir (OR 1.52 per additional year of exposure; 95% CI, 1.19-1.95).

Myocardial infarction has already been identified as a signal for the PI class in the ongoing observational Data Collection on Adverse Events of Anti-HIV Drugs (DAD) cohort. Specific analysis of ART drug classes showed the relative risk of myocardial infarction to be higher with PI therapy (16% increase per year) compared with other ART classes. The signal is plausible and may be partly explained by the propensity of the PI class to raise blood lipids.

Suppression of viral replication in HIV disease with antiretroviral therapy is of the utmost importance. Patients should NOT discontinue treatment on their own. All treatment decisions should be explored in consultation with healthcare professionals.

Physicians should continue to monitor a patient's cardiovascular risk as part of regular reviews and seek to adjust modifiable risk factors. The profile of each antiretroviral agent is different and treatment decisions should always be personalised for an individual patient with careful consideration of the overall absolute risks and the benefits of effective long term treatment.

Please refer to the full prescribing information for fosamprenavir.

Call for reporting

GlaxoSmithKline reminds healthcare professionals to continue to report adverse reactions to appropriate national safety databases.

References

Lang S, Mary-Krause M, Cotte L et al. Impact of Specific NRTI and PI Exposure on the Risk of Myocardial Infarction: A Case-Control Study Nested within FHDH ANRS CO4. 16th CROI, February 8 - 11, 2009, Montreal, Canada. Abstract 43LB.

Slides and audio from the oral presentation by D Costagliola in session "Oral Abstract: Pharmacogenetics, Pharmacoenhancement, and Complications of ART" on Monday, Feb 9, 2009 10:00 AM:

<http://app2.capitalreach.com/esp1204/servlet/tc?c=10164&cn=retro&e=10649&m=1&s=20415&&espmt=2&mp3file=10649&m4bfile=10649&br=80&audio=false>

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Source: FDA listserve (04 Dec 2010)

<http://www.FDA.gov>

GUIDELINES

US guideline update: treat when CD4 is <500 cells/mm³

On 1 December 2009, the US Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents were updated.

Changes are highlighted in yellow on the PDF file and include:

New section

Based on interests and requests from HIV practitioners, a new section entitled "Considerations in Managing Patients with HIV-2 Infection" has been added to the guidelines. This new section briefly reviews the current knowledge on the epidemiology and diagnosis of HIV-2 infection and the role of antiretroviral therapy in the management of patients with HIV-2 mono-infection and HIV-1/HIV-2 coinfection.

Key updates

Drug resistance testing In this revision, the Panel provides more specific recommendations on when to use genotypic versus phenotypic testing to guide therapy in treatment-experienced patients with viremia while on treatment.

- Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens (AIII).
- Addition of phenotypic testing to genotypic testing is generally preferred for persons with known or suspected complex drug resistance mutation patterns, particularly to protease inhibitors (BIII).

Initiation of antiretroviral therapy In this updated version of the guidelines, the Panel recommends earlier initiation of antiretroviral therapy with the following specific recommendations:

- Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness or with CD4 count < 350 cells/mm³ (AI).
- Antiretroviral therapy should also be initiated, regardless of CD4 count, in patients with the following conditions: pregnancy (AI), HIV-associated nephropathy (AII), and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (AIII).
- Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm³. The Panel was divided on the strength of this recommendation: 55% of Panel members for strong recommendation (A) and 45% for moderate recommendation (B) (A/B-II).
- For patients with CD4 counts >500 cells/mm³, 50% of Panel members favor starting antiretroviral therapy (B); the other 50% of members view treatment as optional (C) in this setting (B/C-III).

Patients initiating antiretroviral therapy should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers may elect to defer therapy, based on clinical and/or psychosocial factors on a case-by-case basis.

What to start in antiretroviral-naïve patients

Increasing clinical trial data in the past few years have allowed for better distinction between the virological efficacy and safety of different combination regimens. Instead of providing recommendations for individual antiretroviral components to use to make up a combination, the Panel now defines what regimens are recommended in treatment naïve patients.

Regimens are classified as “Preferred,” “Alternative,” “Acceptable,” “Regimens that may be acceptable but more definitive data are needed,” and “Regimens to be used with caution.”

The following changes were made in the recommendations:

- Raltegravir + tenofovir/emtricitabine” has been added as a “Preferred” regimen based on the results of a Phase III randomised controlled trial (AI).
- Four regimens are now listed as “Preferred” regimens for treatment-naïve patients:
 - i) efavirenz/tenofovir/emtricitabine;
 - ii) ritonavir-boosted atazanavir + tenofovir/emtricitabine;
 - iii) ritonavir-boosted darunavir + tenofovir/emtricitabine; and
 - iv) raltegravir + tenofovir/emtricitabine.
- Lopinavir/ritonavir-based regimens are now listed as “Alternative” (BI) instead of “Preferred” regimens, except in pregnant women, where twice-daily lopinavir/ritonavir + zidovudine/lamivudine remains a “Preferred” regimen (AI).

Additional updates The following sections and their relevant tables have been substantially updated:

- What not to use
- Management of treatment-experienced patients
- Treatment simplification
- Hepatitis C coinfection
- Antiretroviral-associated adverse effects
- Antiretroviral drug interactions
- Preventing secondary transmission of HIV

These and other DHHS guidelines are available on the NIH aidsinfo website

<http://www.aidsinfo.nih.gov>

Direct download (PDF):

<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>

C O M M E N T

The main concern in these guidelines is the strength of the statement for new recommendations for starting treatment.

Currently the document states that the whole panel recommends starting treatment for people with a CD4 count 350-500. This leaves no indication of support for the view that there is insufficient data to balance the risks against the benefits.

Although this is discussed in the main document in more detail, the summary of the guidelines does not accurately reflect the later discussion. The summary is far more widely read than the entire document, and it would therefore be helpful for this wording to be reconsidered.

This years recommendations are especially important as they coincide with the enrollment of the NIH-funded START study which may be the only opportunity to look at both the risks and benefits from a randomised study.

So while there is data supporting short-term safety, there is no data based on long-term risk.

An example of risk comes from the trials of the preferred regimens referenced with the latest data (STARTMRK, ARTEMIS etc). Viral suppression to <50 copies/mL (the primary goal of treatment) was not achieved by around 15% patients at 48 weeks and 20% by week 96. In the context of lifelong treatment, low levels of resistance currently reported, may become more serious if second-line treatment also fails. Population-based uptake of treatment in Western countries is also frequently associated with higher rates of failure.

A second example is that no combination has been shown not to cause fat accumulation, itself associated with additional longer-term health complications, as well as reduced quality of life. This complication may also be related to race and gender.

These potential risks from earlier treatment are not addressed in the main guidelines.

In addition, while the summary states that 'some people may defer treatment', this is suggested for 'clinical or psychosocial factors' and is tied to an earlier sentence about people who might have difficulty with adherence.

While the document is only produced as guidance, the DHHS guidelines are widely interpreted as indicating the minimum recommended standard of care, based on the best available evidence. Clinical trials, especially NIH funded trials, become unethical if they recommend less than the current standard of care for any participant.

While many clinicians, researchers and advocates believe that there is still equipoise on the use of treatment by people with counts 350-500, the current summary brings them into conflict with what are otherwise, one of the most useful documents for the management of HIV infection.

Given the summary has already been widely distributed and publicised, it would help if any subsequent update addresses whether a randomised trial in people with CD4 counts lower than 500 cells/mm³ remains ethical. Currently the guideline summary states that expert opinion believes that further research is unnecessary.

This is important in the context of the START trial which is just enrolling patients and which will be the most important study to inform on this and many other questions.

The history of previous recommendations from the DHHS panel on the when treatment should be started shows the importance of collecting evidence from a randomised study. Earlier recommendations to start at 500 and 350 have probably resulted in widespread complications from side effects and resistance.

Other changes in the guidelines are positive, especially the inclusion of a new section on HIV-2.

WHO publish major revisions to HIV management guidelines

Polly Clayden, HIV i-Base

At the end of November 2009 the WHO released three Rapid Advice documents to guide HIV treatment and prevention strategies. [1]

The documents were:

- Antiretroviral therapy (ART) for adults and adolescents [2]
- Treatment for pregnant women and prevention of infant infection [3]
- Infant feeding [4]

Rapid advice: antiretroviral therapy for adults and adolescents

Since the last guideline revision in 2006, new evidence has become available, particularly concerning the earlier initiation of therapy. This document makes key recommendations in eight areas.

1. When to start?

Antiretroviral therapy should be started in all patients with ≤ 350 CD4 cells/mm³ and with WHO clinical stage 3 and 4. (CD4 testing is required to identify patients with WHO clinical stage 1 and 2 who need to start treatment).

2. What to start?

The recommended first line regimens are:

- AZT+3TC+efavirenz (EFV)
- AZT+3TC+nevirapine (NVP)
- TDF+3TC or FTC+NVP
- TDF+3TC or FTC+NVP

3. ART for HIV/TB co-infection

ART should be started in all HIV-positive people with active TB. TB treatment should be commenced first and followed by ART as soon as possible. EFV is the preferred NNRTI.

4. ART for HIV/HBV co-infection

ART should be started in all HIV-positive people needing treatment for their HBV. Regimens should contain dual-HBV therapy including tenofovir (TDF) plus 3TC or FTC.

5. ART for pregnant women

Recommendations for when to start and what to start with are as for a non-pregnant adult except that they do not recommend

using efavirenz during the first trimester of pregnancy.

6. When to switch?

Where available they recommend viral load to confirm treatment failure (defined as persistently above 5000 copies/mL) and if this is available routinely, 6 month monitoring. Where viral load is not available they recommend use of immunological criteria to confirm treatment failure.

7. Second-line ART

Atazanavir/r (ATV/r) or lopinavir/r (LPV/r) are the recommended boosted PIs for second-line regimens. If d4T or AZT was used first-line, tenofovir plus either 3TC or FTC are recommended. If TDF was used first-line, then AZT+3TC or FTC.

8. Third-line regimens

This recommendation is not specific. New drugs such as integrase inhibitors and second generation NNRTIs and PIs are suggested. People on failing second line regimen with no available options are recommended to continue with that regimen.

C O M M E N T

These guidelines are produced to inform national providers of the best standard of clinical care. In aspects that are currently aspirational, guidance is included on how to change from existing practice, for example in moving from using d4T to alternative drugs.

Two clinical questions not addressed are:

i) Whether lopinavir/r (Kaletra/Aluvia) monotherapy may have an important role in second-line regimens, given the supportive data from several studies? This would reduce cost and RTI-associated toxicity from drugs that may only provide limited antiretroviral activity, especially if nucleoside resistance developed on first-line treatment. This could provide some support for future third-line treatment, when CCR5 and integrase inhibitors become available.

ii) Whether the recommendation to select a high cut-off for virological switching (>5000 copies/mL) might result in an unnecessarily high risk of accumulating resistance to first-line drugs. As viral load monitoring is sometime only 6-monthly, this could delay a more protective earlier switch. Viral load blips have been reported up to 2000 copies/mL, though are usually lower, so deciding a true virological rebound at 2000 copies/mL may be worth considering in order to protect future options.

Rapid advice: treatment for pregnant women and prevention of infant infection

Again, this Rapid Advice was informed by new data particularly showing the benefit of starting ARV prophylaxis earlier in pregnancy and extended prophylaxis to mothers or infants is effective in reducing transmission during breastfeeding. They noted, "For the first time there is enough evidence for WHO to recommend ARVs while breastfeeding."

The document addresses women who were both eligible and ineligible for ART for their own health and makes seven key recommendations.

1. As described in 5 above.
 2. Eligible pregnant women should start ART irrespective of gestational age and continue throughout pregnancy, delivery and then indefinitely.
 3. The preferred regimens for women eligible for treatment are:
 - AZT+3TC+NVP
 - AZT+3TC+EFV
- Alternative regimens are:
- TDF+3TC(or FTC)+NVP
 - TDF+3TC (or FTC)+EFV
4. Infants of mothers receiving ART for their own health should receive:
 - a. Daily NVP from birth until 6 weeks of age if breastfed.
 - b. Daily AZT or NVP from birth until 6 weeks of age if not breastfed.
 5. Women not eligible for ART for their own health should receive an ARV prophylaxis strategy. This should be started from as early as 14 weeks gestation or as soon as possible for women presenting later.
 6. ARV maternal prophylaxis option A:
 - Antepartum daily AZT
 - Single dose NVP from onset of labour
 - AZT+3TC during labour and delivery
 - AZT+3TC 7 days postpartum

Breastfed infants should receive daily NVP throughout the period and one week after breastfeeding. Non –breastfeeding infants should receive daily AZT +NVP from birth to 6 weeks of age.

7. ARV maternal prophylaxis option B:

- AZT+3TC+lopinavir/r (LPV/r)
- AZT+3TC+abacavir (ABC)
- AZT+3TC+efavirenz (EFV)
- TDF+FTC+efavirenz (EFV)

Breastfed infants should receive daily NVP from birth until 6 weeks of age. Non –breastfeeding infants should receive daily AZT +NVP from birth to 6 weeks of age.

Options A and B are summarised in Table1.

Table 1. ARV prophylaxis options recommended for HIV-infected pregnant women who do not need treatment for their own health

Option A: Maternal AZT	Option B: Maternal triple ARV prophylaxis
Mother	Mother
AZT from 14 weeks gestation sdNVP at onset of labour* AZT+3TC during labour and delivery AZT + 3TC 7 days post partum *sd NVP can be omitted if mother receives >4 weeks of AZT post partum	Triple ARV from 14 weeks until one week after all exposure to breast milk has ended AZT+3TC+LPV/r AZT+3TC+ABC AZT+3TC+EFV TDF+FTC+EFV
Infant	Infant
Breastfeeding: Daily NVP from birth until one week after exposure to breast milk has ended Non-breastfeeding AZT or NVP for 6 weeks	Breastfeeding Daily NVP from birth to 6 weeks Non-breastfeeding AZT or NVP for 6 weeks

C O M M E N T

The recommendations regarding the use of nevirapine and efavirenz are important in the new guidance for pregnant women. That the recommendations give high value to maternal health and the benefit that this has on transmission to her infant is most welcome. In the remarks in the guidelines it is noted that this also places relatively low value on the potential toxicity risks for the mother and unborn infant.

The adult ART guidance document highlights the low quality, conflicting evidence on the risks of efavirenz causing neural tube defects and that the overall rates of birth defects reported for efavirenz, nevirapine, lopinavir/r or tenofovir appear to be similar and also similar to rates reported for the general population. Initiation of efavirenz is not recommended in the first trimester and they remark that since the neural tube closes in the first 28 days and very few pregnancies are recognised by this time, the actual risks of starting efavirenz in the first trimester are hard to estimate.

Their review of nevirapine safety in pregnant women with CD4 counts 250-350 cells/mm3 did not confirm an elevated risk of serious side effects so the WHO panel concluded the benefits of using nevirapine in this situation outweigh the risks of not initiating ART.

This panel was unable to conclude whether it was better to use efavirenz or nevirapine in pregnant women after the first trimester and with higher or unknown CD4 cell counts and they added that over half the panel preferred efavirenz in these situations.

These recommendations will make things a lot easier from a programmatic point of view, whether national guidelines will follow suit remains to be seen.

Rapid advice: infant feeding in the context of HIV

This is a set of revised principles and recommendations intended for policy makers, academics and health workers in resource limited settings to assist national infant feeding strategies and implementation, in the context of HIV.

They draw on and further elaborate the revised WHO recommendations for ARVs to prevent mother to child transmission and in particular to prevent postnatal transmission through breastfeeding, which they describe as a major breakthrough that should contribute to improved child survival.

However, of particular importance to UK policy and clinical practice, they state: "In highly resourced countries in which infant and child mortality rates were low, largely due to low rates of serious infectious diseases and malnutrition, HIV-infected mothers are strongly and appropriately recommended to avoid all breastfeeding. In some of these countries, infants have been removed from mothers who have wanted to breastfeed despite being HIV infected and even being on ARV treatment. In these settings, the pursuit of breastfeeding in the presence of safe and effective alternatives may be considered to constitute abuse or neglect."

C O M M E N T

BHIVA will be issuing guidance as a response to these WHO recommendations for resource limited countries, which will continue to strongly recommend avoidance of breastfeeding for HIV-positive women (and will be available at the upcoming BHIVA conference). We are preparing information for the community to use with our patient guides.

We will review these recommendations in more detail in HTB South.

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Updated paediatric HIV treatment guidelines (PENTA, 2009)

Polly Clayden, HIV i-Base

The updated PENTA guidelines were published in the November 2009 edition of HIV Medicine. These guidelines offer practical recommendations for treating children with HIV in Europe.

The main changes since the 2004 guidelines are:

When to start?

Universal treatment is recommended as soon as possible after diagnosis for all infants less than 12 months of age. The guidelines stress particular urgency for infants infected despite prevention of mother to child transmission (PMTCT).

For children 12 months or older, HAART should be started in all symptomatic cases (CDC stage B or C, WHO stage 3 or 4). Children 12 months or older with no or minor symptoms (CDC stage A or N or WHO stage 1 or 2) treatment should be started when CD4 count or percentage falls below the following thresholds:

- | | |
|---------------|---------------------------------------|
| 1 to <3 years | CD4<25% or 1000 cells/mm |
| 3 to <5years | CD4<20% or <500 cells/mm ³ |
| Above 5 years | CD4 count <350 cells/mm ³ |

These treatment thresholds differ significantly from the 2004 guidelines, see Table 1 for comparison of PENTA guidelines 2004 and 2009. Some recommendations also differ from the WHO and US treatment thresholds, see Table 2 comparison of PENTA, WHO and US treatment thresholds.

In children aged more than 12 months with no or minor symptoms and CD4 counts or percentages above these thresholds, HAART should be considered if the viral load exceeds 100,000 copies/mL.

What to start with?

The guidelines recommend a regimen of two NRTIs and either an NNRTI or a boosted PI for ARV-naïve children with no evidence of resistance. They note that a PI may be preferred in children with anticipated poor adherence.

Abacavir and 3TC are recommended for children who are HLA-B *5701 negative and AZT and 3TC for those who are HLA-B *5701 positive.

Nevirapine is recommended for children <3 years and efavirenz for older children.

Lopinavir/ritonavir is recommended for young children. For older children alternative boosted PIs may be used, including fosamprenavir/r and duranavir/r which are licensed for children from 6 years, atazanavir/r (which is licensed in the US for children from 6 years but not in Europe) and saquinavir/r (which is not licensed for children but may be suitable for adolescents).

Table 1: Comparison of PENTA guidelines 2004 and 2009

	PENTA 2009	PENTA 2004
	0-11 months	0-11 months
Clinical	Treat all	Treat CDC stage B or C
Immunological (CD4%/count)	-	Treat <35%
Virological	-	Consider >1,000,000 copies/mL
	12-35 months	12-47 months
Clinical	Treat CDC stage B or C/WHO stage 3or4	Treat CDC stage C
Immunological (CD4%/count)	Treat <25% or <1000 cells/mm3	Treat <20%
Virological	Consider >100,000 copies/mL	Consider >250,000 copies/mL
	36-59 months	4-12 years
Clinical	Treat CDC stage B or C/WHO stage 3or4	Treat CDC stage C
Immunological (CD4%/count)	Treat <20% or <500 cells/mm3	Treat <15%
Virological	Consider >100,000 copies/mL	Consider >250,000 copies/mL
	5 years +	13-17 years
Clinical	Treat CDC stage B or C/WHO stage 3or 4	Treat CDC stage C
Immunological (CD4%/count)	Treat <350cells/mm3	Treat <200 cells/mm3 Consider 200-350 cells/mm3
Virological	Consider >100,000 copies/mL	Consider >250,000copies/mL

Table 2: Comparison of current PENTA, WHO and US treatment thresholds

	PENTA 2009	US 2008	WHO 2008
0-11 months			
Clinical	Treat all	Treat all	Treat all
Immunological (CD4%/count)			
Virological			
12-35 months			
Clinical	Treat CDC stage B or C/WHO stage 3 or 4	Treat CDC stage B	Treat WHO stage 4 and severe 3
Immunological (CD4%/count)	Treat <25% or <1000 cells/mm3	Treat <25%	Treat <20% or <750 cells/mm3
Virological	Consider >100,000 copies/mL	Consider >100,000 copies/mL	
36-59 months			
Clinical	Treat CDC stage B or C/WHO stage 3 or 4	Treat CDC stage B	Treat WHO stage 4 and severe 3
Immunological (CD4%/count)	Treat <20% or <500 cells/mm3	Treat <25%	Treat <20% or <350 cells/mm3
Virological	Consider >100,000 copies/mL	Consider >100,000 copies/mL	-
5years +			
Clinical	Treat CDC stage B or C/WHO stage 3 or 4	Treat CDC stage B or C	WHO stage 4 or severe 3
Immunological (CD4%/count)	Treat <350 cells/mm3	Treat <25% or <500 cells/mm3	Treat <15% or <200 cells/mm3
Virological	Consider >100,000 copies/mL	Consider >100,000 copies/mL	

Other recommendations

Recommendations on the use of resistance testing, TDM and HLA testing are informed by adult data and paediatric cohorts in Europe.

The guidelines highlight the paucity of data from RCTs on which to base recommendations for children and note that available trials tend to be small, therefore "... we continue to rely on cohort studies, extrapolation from adult data and expert opinion." They

recommend that wherever possible children should be enrolled in clinical trials.

Drug information will be available alongside the guideline, and will be kept updated, on the PENTA website www.pentatrials.org

C O M M E N T

WHO paediatric guidance is due for update imminently, and is likely to recommend earlier treatment in line with updated WHO adult guidance.

WHO and PENTA will provide different recommendations based on the same data. This reflects both the paucity of high quality evidence from randomised clinical trials, on which the guidelines are based, and that PENTA guidelines are intended for use in Europe while WHO guidelines will predominantly inform national guidelines in less well resourced countries, where the ability of treatment programmes to deliver care may also be an issue.

We intend to summarise and review new WHO paediatric guidance later in 2010 when it is published. PENTA guidelines are not likely to change when new WHO paediatric guidance is published, and remain the current recommendations for treating children with HIV in Europe.

Ref: PENTA Steering Committee. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric infection. *HIV Medicine* 2009, 10, 591-613.

SIDE EFFECTS

HIV disease and renal function

Simon Collins, HIV i-Base

Although earlier ARVs including AZT and indinavir were associated with renal toxicity, the focus on routine renal monitoring has increased significantly due to the widespread use of tenofovir. While there is limited data on the impact of HIV and treatment on renal function, several recent studies contributed new information in this area.

PI-initiated HAART shows eGFR improvement over seven years

Catherine Leport and colleagues from the APROCO-COPILOTE cohort published long-term results of renal function in over 1100 patients who started protease inhibitor (PI) based combinations between 1997 and 1999 in 47 French HIV centres. [1]

Changes in eGFR in this cohort, estimated by MDRD ignoring adjustment for race, increased by +0.72 mL/min/1.73m²/month (95%CI 0.40–1.03) from treatment initiation to month 16 and then remained stable +0.01/month (95% CI, –0.08 to 0.10) for up to 7 years. The proportion of patients with a GFR of <60 or 60–90 were stable over time at approximately 5% and 39%.

This rate increase was lower among men and those with low BMI, AIDS, or who had used indinavir.

The cohort was 77% male; median age was 37 years (IQR 32–43), ethnicity was 10% African/90% Caucasian; 21% had a prior history of AIDS, and median baseline GFR was 93 mL/min/1.73m² (IQR, 82–107). GFR was estimated using the abbreviated MDRD formula, ignoring adjustment for race.

After a median follow-up of 7.0 years (IQR 3.8–8.4), the median CD4 level increased from 273 cells/mm³ (IQR 126–421) to 524 (IQR 370–737).

The mortality rate was higher for patients with baseline eGFR <60: 4.1 per 100 vs 1.6% among those with baseline GFR of 60–90, and 1.8% among patients with GFR 90 (p=0.21, adjusted for baseline age, CD4 count, HIV RNA level, AIDS stage, and injection drug use).

The study also analysed the impact of individual ARVs, although noting that this requires caution in interpreting results from a cohort study.

Indinavir and nelfinavir were the first PI for 40% and 29% patients, respectively. At 7 years, only 13% patients were still receiving their initial PI. Overall, 532 patients were started on indinavir and received it for a median duration of 21 months (IQR 9–42 months), whereas from 2001 onwards, 214 patients received tenofovir for a median duration of 20 months (IQR 8–38 months).

Changes in eGFR over time did not differ between patients who initiated tenofovir, regardless of GFR (<90 vs 90), and those who never used tenofovir, and it did not differ for patients who received indinavir prior to tenofovir, compared with those who never received tenofovir (data not shown). This is a different finding to that reported in the Swiss Cohort Study. [2]

In the multivariate analysis of GFR evolution over time, male sex, AIDS stage, lower baseline BMI, and receipt of indinavir were associated with a poorer evolution of GFR during the first 16 months of treatment. Beyond 16 months, a poorer evolution of GFR was associated with African origin and baseline CD4 cell count 200 cells/mm³ but not receipt of indinavir or tenofovir.

Loss of kidney function despite successful HAART

A paper from Andy Choi and colleagues in the 23 October issue of AIDS reported risk factors associated with reduced kidney function in an HIV-positive cohort of patients both on- and off-HAART, including 7% untreated viral controllers.

They followed 615 patients for a mean of 3.4 (± 2.5) years. Mean age was 45 years and 13% were women. Half the group were white, 25% were black and 10% were Hispanic. 15% of the group has risk factors for kidney disease including HCV, hypertension, hyperlipidaemia and smoking.

In this study, in contrast to Leport et al, the overall rate of kidney function calculated by changes in eGFR, declined by -2.6 mL/min/1.73m² [95%CI: -3.0 to -2.1] per year. In multivariable adjusted analyses, predictors of eGFR decline included female sex, diabetes, and hyperlipidemia, but not CD4 cell count or viral load.

The impact of HAART, was assessed in a sub group of 82 patients who started HAART during the study. GFR declined an average of -4.7 (95%CI -6.7 to -2.6) per year during the 1.2 years before HAART, and this improved to -1.9 (95% CI -3.7 to -0.1) during a mean 2.9 years of follow-up after starting treatment. In adjusted analysis, HIV treatment was associated with a +2.8 (95% CI 0.8-4.7) per year improvement in eGFR slope. Although these patients benefited from HAART, they continued to lose kidney function at a rate of -1.9 (-3.7 to -0.1) per year.

When comparing 45 untreated to 173 treated viral controllers (defined as having a viral load <500 copies/mL), patients on HAART had greater eGFR declines (adjusted difference -4.4 (-6.7 to -2.1) per year in treated versus untreated controllers).

Intermittent viral blips in the treated group were also associated with more rapid rates of eGFR loss [-6.7 (-11.1 to -2.4) per year.

Hypertension and diabetes were both strongly associated with renal decline in treated patients [-4.0 (-7.6 to -0.5) and -5.6 (-10.3 to -0.8) per year, respectively].

Unfortunately this study was underpowered to look at the impact of individual drugs, especially indinavir and tenofovir, and had limited data on other important markers of kidney health or treatment in individual patients.

The study concluded that although HIV treatment appears to help curb kidney function decline, patients who achieved durable viral suppression continue to experience substantial loss of eGFR and that loss of kidney function may be attributable to treatment-related factors, intermittent viremia, and traditional risk factors for kidney disease.

End Stage Renal Failure in HIV-positive patients in the UK

A review of the clinical epidemiology of end-stage renal failure (ESRF) in the UK (defined as starting permanent renal replacement therapy (pRRT), was undertaken by Loveleen Bansi and colleagues from the UK-CHIC study, and published in the 27 November issue of AIDS. [4]

Results were collected from almost 22,000 patients attending seven leading HIV centres between 1998-2007. ESRF occurred in 68 patients (0.31%), 44 (65%) of whom were black. The prevalence increased in black patients from 0.26% in 1998/99 to 0.92% in 2006/07 ($p=0.001$ for trend) and from 0.03% to 0.11% in non-black patients ($p=0.07$ for trend). Patients with ESRF were more likely to be female (29 vs. 21%), of black ethnicity (65 vs. 25%), and have lower nadir CD4 cell count (median: 72 vs. 179 cells/mm³).

In multivariable analysis, black ethnicity was associated with a higher risk of ESRF [HR 6.93, 95%CI: 3.56, 13.48], and higher current CD4 cell count with a reduced risk per 50 cells/mm³ higher (HR: 0.83, 95%CI: 0.76, 0.95).

The most common renal diagnosis was HIVAN, (in 53% of all patients and 82% of black patients). All cases of HIVAN were in black patients.

Response to pRRT was generally good with 70% overall 5-year survival. This was significantly better for black patients compared to those of other ethnicities (85% vs. 43%, $p=0.001$).

The group used data from the HPA and Renal Registry to estimate 231 cases of ESRF occurred in HIV-positive patients in the UK over this period and that this accounted for 0.5% of the 45,500 people who received pRRT.

In summary, this analysis highlighted a prevalence of ESRF of almost 1% in HIV-positive black patients in the UK. The favourable comparison to US incidence rates that are 5-6 times higher and better response to pRRT (98% vs 30-40% 2-year survival) was accounted for by lower rates of IV drug use and HCV coinfection.

The discussion noted that prevalence rates may have been slightly underestimated and treatment responses overestimated given that a minimum of 3 months follow-up was required for this analysis, but that given the strong association with nadir CD4 count, this is another reason to aim for earlier HIV diagnoses in black patients in the UK.

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4. Bansi L et al on behalf of the UK CHIC/ESRF study group. Clinical epidemiology of HIV-associated end-stage renal failure in the UK AIDS. 23(18):2517-2521, 27 November 2009. doi: 10.1097/QAD.0b013e3283320e12.

PREGNANCY & PMTCT

Pregnancy not nevirapine associated with risk of hepatotoxicity in large cohort comparison

Polly Clayden, HIV i-Base

There is some uncertainty about the association between nevirapine, pregnancy and hepatotoxicity in HIV-positive women.

In a concise communication, published in the November 27 2009 edition of AIDS, David Ouyang and investigators from two large American multicentre cohorts, the Women and Infants Transmission Study (WITS) and the International Maternal Paediatric Adolescent Clinical Trials (IMPAACT) protocol P1025, showed findings from a study to estimate whether this association differs by pregnancy status in HIV-positive women.

The study compared pregnant women in WITS and IMPAACT to a non-pregnant reference group from the Women Interagency HIV Study (WIHS).

Cox proportional hazard models were used to investigate the association between nevirapine use and any liver enzyme elevation (LEE, grade 1-4) and severe LEE (grade 3-4). Potential confounders included pregnancy status.

The analysis included a total of 2050 HIV-positive women receiving HAART of which 60% were pregnant.

Pregnant women in this analysis were younger than non-pregnant, mean age 27.99 vs 35.96, $p < 0.001$. They had higher CD4, lower viral loads and had been HIV-positive for a shorter duration of time. They also had less chronic hepatitis and were more likely to be both ART and nevirapine naïve. A similar proportion of pregnant and non-pregnant women had been exposed to nevirapine, with a greater proportion of non-pregnant women having CD4 ≥ 250 cells/mm³. See Table 1.

Table 1. CD4 cell count of women receiving NVP by pregnancy status

	n	%	n	%	p
NVP	218	17.73	169	20.58	0.106
CD4 \leq 250c/uL	50	23.81	22	13.92	
CD4 \geq 250c/uL	160	76.19	136	86.08	0.018

Overall the investigators found pregnant women were significantly more likely than non-pregnant women to develop any LEE, 14.2 vs 9.1% respectively, $p = 0.0001$. They also had a higher rate of severe LEE, 1.2 vs 0.6%, although this difference did not reach statistical significance.

Multivariate analysis found pregnancy to be significantly associated with any LEE, RR 4.7 (95% CI, 3.39-6.53, $p < 0.01$ and with severe LEE, RR 3.8 (95% CI, 1.3-11.1). However, nevirapine was not significantly associated with any LEE, RR 1.17 (95% CI, 0.8-1.7) or severe LEE, RR 1.78 (95% CI 0.4-7.82) and this was regardless of pregnancy status. The investigators noted that due to concerns in the literature about nevirapine exposure at higher CD4 counts, these variables were included in the multivariate models despite not being significant in univariate analysis and they continued to demonstrate no association with LEE.

These investigators wrote: "While we support close monitoring for clinical or laboratory evidence of hepatotoxicity with any ART regimen, our results challenge the notion that NVP is uniquely associated with hepatotoxicity during pregnancy."

C O M M E N T

It seems likely that pregnancy does not increase the risk of nevirapine-related toxicity at CD4 counts below 250 cells/mm³ and is therefore safe to prescribe in pregnancy in accordance with current guidelines.

However, it gets more complicated with regard to safety of nevirapine in pregnant women with CD4 counts greater than 250 cells/mm³, and this study, along with others, is not showing any signal or nevirapine-associated toxicity in pregnancy.

It is also notable that expert panel reviews for new WHO guidance did not confirm an increase of serious adverse events and concluded that the benefits of using nevirapine in this situation outweigh the risks of not initiating ART (see our review of WHO guideline revisions).

Given the temporary pregnancy related immunodeficiency in addition to any HIV-related immunodeficiency it certainly seems sensible to re-run these analyses at higher CD4 counts - eg 400 cells/mm³.

Ref: Ouyang et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. AIDS 2009, 23:2425-2430.

Birth defects following efavirenz exposure in a South African Hospital

Polly Clayden, HIV i-Base

Although efavirenz is FDA pregnancy category D, the teratogenic risk is still uncertain. The Antiretroviral Pregnancy Registry has recorded birth defects in 14/477 (2.9%) live births. Data from the MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, University College London, showed birth defects occurred in 5/205 (2.4%) infants with early pregnancy exposure.

A paper in the January 2010 edition of AIDS authored by Ebrahim Bera and colleagues describes findings from a regional South African cohort of pregnant women exposed to efavirenz. This is the largest study to date of efavirenz based HAART exposure from the second trimester onwards.

This study evaluated data from the Efavirenz in Pregnancy Registry which was set up in January 2006. The registry is prospective and based at Frere Hospital in East London, a referral hospital for a large area of the Eastern Cape.

Women who conceived on efavirenz and presented in the first trimester were offered the choice of termination of pregnancy (to 20 weeks gestation) or switched to another drug. Women who presented at 14 weeks or later and eligible for HAART were initiated on an efavirenz-based regimen.

The investigators reported that between 1 January 2006 and 31 December 2008, 744 women were initiated on efavirenz-based regimens from the second trimester onward. Of these, 89 women were still pregnant at the time of evaluation and 32 were lost to follow up.

During the same period, 220 women conceived while receiving efavirenz based HAART and 42 nevirapine-based HAART. Of this group, 17 and seven women were still pregnant and eight and two women were lost to follow up receiving efavirenz and nevirapine respectively.

The investigators classified women who had received efavirenz-base HAART throughout the entire first trimester as "complete first trimester exposure" and those who substituted efavirenz for another drug as "partial first trimester exposure".

This analysis evaluated data from 851 women with pregnancy outcomes.

The 623 women initiated on efavirenz in pregnancy were a median age of 28 (IQR 25-32) years with median of 9 (IQR 4-13) weeks of HAART. Birth defects occurred in 16 live births, a prevalence of 2.6% (95% CI 1.5-4.2).

The 195 women who conceived while receiving efavirenz were a median age of 30 (27-34) years, with a median of 39 (37-40) weeks of HAART. Birth defects occurred in 5/184 live births and 1/4 stillbirths, a prevalence of 3.3% (95% CI 1.2-7.0). The investigators noted that 93% of this group, received efavirenz based HAART for longer than one month before conception and all pregnancies were unintended.

There were no significant differences in the prevalence of birth defects between the first and second/third trimester exposure (prevalence ratio 1.27; 95%CI 0.5-3.20, $p=0.301$). Neither were there differences between complete (4/131; 3.1%) and partial (2/53; 3.8%) efavirenz exposure (prevalence ratio 0.81; 95% CI 0.15-4.29, $p=0.556$).

The investigators also observed a birth defect in 1/33 live nevirapine exposed infants, a prevalence of 3.0% (95% CI 0.1-15.8). The prevalence ratio of birth defects following conception on efavirenz compared to nevirapine was 1.08; 95% CI 0.13-8.65, $p=0.69$. However the numbers of nevirapine exposures are too small to draw any conclusions.

The investigators suggested that these data provide some reassurance on second/third line trimester efavirenz use for pregnant women. There were too few first trimester exposures in this study to make any recommendations concerning the safety or teratogenicity of efavirenz during this period.

C O M M E N T

This data adds to, and is consistent with, the existing experience of first trimester exposure to efavirenz. This study also provides significant new data on second and third trimester only exposure that is generally reassuring.

Bera E et al. Birth defects following exposure to efavirenz-based antiretroviral therapy during pregnancy: a study at a regional South African hospital. AIDS 24(2):283-289, January 2010.

DRUG INTERACTIONS

Essential news from Liverpool University drug interaction resource (HIV-druginteractions.org).

Significant interaction between atazanavir/ritonavir and the antipsychotic drug quetiapine

Two case reports describe patients who experienced serious quetiapine adverse effects potentially mediated through an interaction with ritonavir-boosted atazanavir.

The first patient (57-year-old male with HIV and bipolar disease) developed rapid and severe weight gain when quetiapine was added to a stable atazanavir/ritonavir-based antiretroviral regimen. After the patient discontinued both quetiapine and ritonavir, his weight returned to its baseline value. The second patient (32-year-old female with HIV, anxiety disorder, and a history of intravenous drug abuse) developed increased sedation and mental confusion when an atazanavir/ritonavir-based antiretroviral regimen was added to her stable anti-anxiety drug regimen, which included quetiapine. Her symptoms resolved promptly after discontinuation of the quetiapine.

Use of the Naranjo adverse drug reaction probability scale indicated that the adverse effects experienced by the two patients were possibly related and probably related, respectively, to an interaction between quetiapine and atazanavir/ritonavir. Quetiapine is primarily metabolised by CYP3A4, thus quetiapine concentrations may have increased when used concurrently with atazanavir/ritonavir.

Clinicians should be aware of the potential for this interaction, and extreme caution should be used when prescribing quetiapine and other atypical antipsychotic agents in HIV+ patients who are receiving antiretroviral therapy.

Source: www.hiv-druginteractions.org (10 December 2009).

Ref: Pollack TM et al. Clinically significant adverse events from a drug interaction between quetiapine and atazanavir-ritonavir in two patients. *Pharmacotherapy*, 2009, 29(11): 1386-1391.

<http://www.ncbi.nlm.nih.gov/pubmed/19857154>

Summary of interactions between vicriviroc and other ARVs

A recently published review on vicriviroc contains a section summarising the metabolism of the compound (primarily metabolised by CYP3A4; not inducer or inhibitor of CYP3A4; not a substrate for P-gp) and drug-drug interactions.

Since vicriviroc is extensively metabolised the exposure is increased when given with ritonavir. In Phase II trials optimal dosing was achieved by co-administration with a ritonavir-boosted PI as part of the regimen (30 mg once daily with ritonavir based regimen).

Drug-drug interactions have been investigated between vicriviroc plus ritonavir and 11 other antiretrovirals (atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir, lopinavir, zidovudine/lamivudine and tenofovir). None of the agents evaluated required dose modification or monitoring when co-administered with vicriviroc; nor does vicriviroc require dose modification when given with any of the 11 agents. In contrast due to the inducing effect of efavirenz, co-administration of vicriviroc alone with efavirenz is not recommended.

Other interactions described are with midazolam, ketoconazole, rifabutin (increase ritonavir dose), rifampicin (not recommended), carbamazepine (increase ritonavir dose) and the oral contraceptives ethinyl estradiol and norethindrone (interaction needs careful monitoring due to the ritonavir effect).

Source: www.hiv-druginteractions.org (16 December 2009).

Ref: Kummerle T et al. Vicriviroc: a CCR5 antagonist for treatment-experienced patients with HIV-1 infection. *Expert Opin Investig Drugs*, 2009, 18(11): 1773-1785.

<http://www.ncbi.nlm.nih.gov/pubmed/19888873>

Significant interactions between tipranavir/ritonavir and statins

Data from lopinavir/ritonavir and rosuvastatin have shown that it is difficult to predict interactions between boosted protease inhibitors and statins. Since tipranavir/ritonavir has a net inhibitory effect on CYP3A4, it has the potential to increase atorvastatin concentrations. However, rosuvastatin is considered unlikely to interact with tipranavir/ritonavir since it is not a CYP3A4 substrate and is not extensively metabolised.

Two open-label, prospective, single-arm, two-period studies, were performed in HIV-negative volunteers. These studies looked to identify interactions between tipranavir/ritonavir (500/200 mg twice daily) and either rosuvastatin (10 mg single dose) or atorvastatin (40 mg single dose),

Coadministration increased rosuvastatin AUC by 37% and increased C_{max} by 2.23-fold. Atorvastatin AUC was increased by 9.36-fold and C_{max} increased by 8.61-fold, when coadministered. Tipranavir pharmacokinetic parameters were not affected by single-dose rosuvastatin or atorvastatin. The atorvastatin data are consistent with marked inhibition of CYP3A4 and some transport proteins. The rosuvastatin data are consistent with previous findings evaluating this interaction with lopinavir/ritonavir and most likely due to inhibition of OATP1B1 and BCRP.

Based on these interactions, the authors recommend low initial doses of rosuvastatin (5 mg) and atorvastatin (10 mg), with careful clinical monitoring of rosuvastatin- or atorvastatin-related adverse events when combined with tipranavir/ritonavir.

C O M M E N T

Although these studies have shown the nature and magnitude of the pharmacokinetic interaction, they do not give any information on the pharmacodynamic interaction (i.e. the cholesterol-lowering efficacy of each statin) when given with tipranavir/ritonavir.

Data from rosuvastatin/lopinavir/ritonavir have shown that although plasma concentrations of rosuvastatin were increased, the cholesterol lowering efficacy was decreased when given in combination.

Source: www.hiv-druginteractions.org (23 November 2009).

Ref: Pham PA et al. Differential effects of tipranavir plus ritonavir on atorvastatin or rosuvastatin pharmacokinetics in healthy volunteers. *Antimicrob Agents Chemother*, 2009, 53(10): 4385-4392.

<http://www.ncbi.nlm.nih.gov/pubmed/19667285>

No interaction between tipranavir/ritonavir and efavirenz

This study investigated the effect of steady-state efavirenz on steady-state tipranavir/ritonavir pharmacokinetics in 16 healthy adult female and male volunteers.

After dosing with tipranavir/ritonavir (500/200 mg twice daily with food) for 10 days, efavirenz (600 mg once daily) was added to the regimen for 14 days. Intensive pharmacokinetic sampling was done on days 10 and 24. The geometric mean ratios (90% confidence intervals) for AUC, C_{max}, and C_{min} comparing TPV/r alone and in combination with EFV were 0.97 (0.87 to 1.09), 0.92 (0.81 to 1.03), and 1.19 (0.93 to 1.54) for tipranavir, and 1.03 (0.78 to 1.38), 0.92 (0.65 to 1.30), and 1.04 (0.72 to 1.48) for ritonavir.

With the exception of a 19% increase in tipranavir C_{min}, which is considered not to be clinically relevant, efavirenz had no effect on the steady-state pharmacokinetics of tipranavir or ritonavir. Tipranavir/ritonavir can be safely coadministered with efavirenz and without the need for a dose adjustment.

Source: www.hiv-druginteractions.org (07 December 2009).

Ref: la Porte CJ et al. Lack of effect of efavirenz on the pharmacokinetics of tipranavir-ritonavir in healthy volunteers. *Antimicrob Agents Chemother*, 2009, 53(11): 4840-4844.

<http://www.ncbi.nlm.nih.gov/pubmed/19721063>

CANCER AND HIV

Outcomes from screening study for anal cancer in HIV-positive compared to HIV-negative patients

Simon Collins, HIV i-Base

A recent paper in the September 2009 issue of *Gut* reported significantly poorer diagnostic results from colonoscopy screening in HIV-positive compared to HIV-negative controls. This included higher prevalence of lesions, larger and more advanced lesions and that these were occurring at a younger age in the HIV-positive group.

Bini and colleagues from New York performed coloscopy screening for colonic neoplasms in 136 asymptomatic HIV-positive men older than 50 years and 272 HIV-negative controls matched for age, sex and family history. All participants were patients at a single VA site, with screening performed from 2002-2004. Exclusion criteria included previous screening (5-10 years) or positive faecal occult blood test.

The median duration of infection in the HIV-positive groups was 11 years (IQR 7-14), median CD4 count was 346 cells/mm³ (IQR, 236-707) and around 90% were on HAART, 73% of who had had undetectable viral load.

The study found a significantly higher prevalence in HIV-positive patients (62.5% vs 41.2% ($p < 0.001$)). This remained highly significant after adjustment for potential confounding variables, including age, sex, race/ethnicity, current alcohol use, current smoking, use of NSAIDs and aspirin, family history of colorectal cancer and history of screening.

Compared with control subjects, HIV-positive patients had significantly increased odds of having a neoplastic lesion (OR = 2.38; 95% CI, 1.56 to 3.63). This association remained highly significant after adjustment baseline characteristics (OR = 3.00; 95% CI, 1.83 to 4.93) and after further adjustment for tobacco, alcohol, aspirin and NSAIDs (OR = 2.84; 95% CI, 1.74 to 4.62).

Compared with controls, HIV-infected patients were significantly less likely to have hyperplastic (benign) polyps and were more likely to have adenomas 6-9 mm in diameter. More HIV-infected subjects than control subjects had two or more adenomas detected (41.2% vs 30.9%, $p = 0.04$).

Among the 11 adenocarcinomas that were diagnosed, HIV-positive patients were significantly younger than those without HIV (52.4 (SD 1.3) vs 60.3 (SD 4.0) years, $p = 0.002$), a difference of 7.9 (95% CI, 3.6 to 12.2) years. Late-stage adenocarcinoma of the colon (stage III or IV) was more common in HIV-positive subjects (3/5 (60.0%)) than in controls (1/6 (16.7%)), although this difference was not statistically significant ($p = 0.24$).

The study found no association between neoplastic lesions of the colon and duration of HIV infection, CD4 count, or viral load, but a protective effect was reported in HIV-positive people on HAART (OR = 0.13; 95% CI, 0.02 to 1.02).

The authors concluded that their findings suggest that screening colonoscopy should be offered to HIV-positive patients, although the age of initiation and the optimal frequency of screening require further study.

C O M M E N T

These add to the growing evidence supporting a screening programme for HIV-positive people as a targeted high risk group. See coverage in the EACS conference report earlier in this issue of HTB. [2]

References

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http://www.natap.org/2009/HIV/100809_03.htm
2. Bower M. Screening for non-AIDS malignancies: if and how? 12th EACS, 11-14 November 2009, Cologne. Webcast:
<http://www.multiwebcast.com/eacs/2009/12th/4149>

TRANSMISSION AND PREVENTION

Male circumcision: new data supporting protective mechanism

Simon Collins, HIV i-Base

The protective mechanism for reducing heterosexual HIV transmission to circumcised men has been attributed to two factors relating to the properties of the inner foreskin: a thinner keratin layer reducing the physical barrier and a higher concentration of CD4 and Langerhans cells that are primary targets for infection. A third factor may be that the foreskin prolongs the time that fluid that contains HIV remains in contact with genital tissue. In theory, the size of the foreskin should also positively correlate to the risk from these mechanisms, and this is supported by results from a study published in the 23 October edition of the journal *AIDS*. [1]

HIV infection rates were collected from 965 men in Rakai, Uganda, who were recruited for two randomised circumcision studies. These men were initially HIV-negative and followed for a total of 3920 person years, prior to circumcision as part of the trial protocol. The results from these trials have already been reported. [2, 3]

After circumcision, the foreskin surface area was calculated (length x width; cm²) and infection rates prior to circumcision were calculated by quartile. Men who became infected compared to those who remained HIV-negative were found to have a significantly greater foreskin surface area (mean 43.3 (± 2.1) vs 36.8 (± 0.5) cm² ($p < 0.01$)).

HIV incidence/100 person years (PY) was 0.80, 0.92, 0.90 and 2.48 for men with foreskin surface areas in the lower (7.0-26.3 cm²), second (26.4-35.0 cm²), third (35.2-45.5 cm²) and upper quartiles (45.6-99.8 cm²) respectively.

The incidence rate ratio (IRR) of HIV acquisition, after adjusting for age, education, religion, number of sex partners and condom use, was significantly higher for men in the highest compared to the lowest quartiles of foreskin surface area (IRR 2.37; 95%CI 1.05-5.31).

There was, however, no significant difference in HIV incidence between the lower three quartiles. In the adjusted analysis, older

age (IRR 4.16; 95%CI 1.55, 11.19, and IRR 4.00; 95%CI 1.46, 10.74; for ages 25-30 and >30 respectively, each compared to 15-24 years), lower education level (0.40; 0.18, 0.91; secondary/tertiary vs primary/none) and catholic religion (IRR 0.37; 0.16, 0.82; Catholic vs non-Catholic) were also significantly associated with risk of HIV acquisition.

The authors concluded that their findings, in addition to the observational studies and randomised trials, add plausibility to the hypothesis that the foreskin is a tissue vulnerable to HIV acquisition.

They suggested that minimising retention of residual foreskin tissue after male circumcision using dorsal slit and sleeve procedures rather than the forceps-guided procedure (which leaves 0.5-1.0 cm of mucosal skin proximal to the corona) is a theoretical concern. However, they also reported that they did not observe any increased risk of HIV acquisition among men with smaller foreskin surface areas that were substantially larger than residual tissue retained after circumcision surgery.

C O M M E N T

While the study states that these findings need to be replicated in other studies, it is difficult to see how this could be supported.

Firstly, although circumcision studies have shown protection against HPV, HSV and syphilis, men primarily want to be circumcised in order to reduce their risk of HIV infection, and should be told if they are HIV-positive at the time of surgery. It is unclear whether the men in this study would have undertaken circumcision, had they been made aware that they had already caught HIV prior to the intervention.

Secondly, now that circumcision had been proven to reduce heterosexual transmission in high prevalence settings, it is difficult to see why participants would be followed for any significant period prior to surgery.

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2. Gray RH et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; 369:657-666.
3. Wawer MJ et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai Uganda: a randomised controlled trial. *Lancet* 2009; 374:229-237.

A caution for male circumcision programmes: high complication rates highlighted outside a trial setting

Simon Collins, HIV i-Base

Important limitations to the protective benefits from circumcision, prompted by a 2008 WHO review by Robert Bailey and colleagues, of complications during male circumcision in Kenya [1], were discussed in a recent editorial article in the 2 January 2010 journal *AIDS*. [2]

The original study, available online without subscription, deserves reading in full by anyone rushing to roll-out circumcision programmes on a community level.

The WHO study prospectively followed approximately 1000 men (IQR ~13-15, range 5-21 years), who were circumcised in July-August 2004, who were interviewed about complications 30-89 days after surgery. Twenty-four men were directly observed during circumcision and after 3, 8, 30 and 90 days.

The participants had either a traditional circumcision performed in a village or within a household compound, or a medical circumcision performed by someone the participant considered to be a clinician in a hospital, health centre, dispensary or private office. The researchers also interviewed 21 traditional and 20 clinical people who carried out the circumcisions.

After interviewing approximately two-thirds of participants and directly following the 24 cases, the researchers found very high rates of complications and decided to directly examine and interview the remaining 298 men, (range 45 - 89 days after circumcision).

One or more complications were reported by 35% men circumcised traditionally and by 17% men circumcised medically (OR 2.53; 1.89-3.38; $p < 0.001$). These rates were significantly higher than the approximate 1-3% observed in clinical trials, or in infants circumcised in developed countries.

Although rates for each complication were not given, the most common self-reported complications were excessive bleeding, infections and excessive pain, with bleeding the most common. Pain upon urination, incomplete circumcision requiring repeat surgery, and lacerations of the glans, the scrotum and the thighs were also reported. Many traditional circumcisions continued to bleed and needed medical support.

Infections were equally common among subjects circumcised medically and traditionally. Those circumcised traditionally were more likely to report receiving antibiotics from local practitioners, often from "travelling nurses" with few or no qualifications. These informal practitioners often sold injections to address infections and bandaged the wound after applying gravacine (a talcum powder with penicillin). Whether it prevented infections we cannot be sure, but it tended to cake in the wound, delay healing and result in thick scarring and, in a few cases, permanent discolouration.

In 24% of the traditional cases and 19% of the medical cases, the wound had still not healed after 60 days ($p=0.056$) in contrast to 96% healed by 30 days in the randomised male circumcision in Kisumu, Kenya.

In the interviews with 298 men, traditionally circumcision was much more likely not to have healed (21% vs 10%, AOR 0.43; 0.22–0.84, $p=0.014$), to have significant swelling (14% vs 5%, AOR 3.20; 1.27–8.07, $p=0.014$), to have a culturally unacceptable amount of foreskin remaining (12% vs 3%, AOR 5.32; 1.54–18.31, $p=0.008$); and to higher trend to have lacerations (17% vs 10%, AOR 1.91; 0.93–3.91, $p=0.077$), and keloid scarring (17% vs 10%, AOR 1.99; 0.98–4.06, $p=0.059$).

Compared to developed country settings, delayed healing, swellings and lacerations were also prevalent among those circumcised medically.

The researchers concluded that “extensive training and resources will be necessary to build the capacity of health facilities in sub-Saharan Africa before safe circumcision services can be aggressively promoted for HIV prevention” and that “the rate of serious complications from traditional circumcisions should also serve as an alarm to ministries of health and the international health community that focus cannot only be on areas where circumcision prevalence is low”.

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PRO 2000 microbicide gel does not pan out

Richard Jefferys, TAG

Earlier this year at the Conference on Retroviruses & Opportunistic Infections, Salim Abdool Karim presented data suggesting that a vaginally applied microbicide gel called PRO 2000 might offer some protection against HIV infection in high-risk women. [1]

The results were not statistically significant but represented a trend, suggesting a 30% reduction in risk of acquisition of the virus. Some commentators at the meeting noted that because this study had two separate control arms (a placebo gel and no gel), comparing the total number of control participants from both of these arms with the group that received PRO 2000 would render the result statistically significant. To his credit, Karim emphasised that such an analysis was not a pre-specified part of the protocol and was therefore inappropriate. He also pointed out that there was a larger, ongoing phase III study of PRO 2000 involving over 9,000 women that would provide a definitive answer as to the product’s efficacy.

The results from this trial, called MDP-301 and run by the UK Medical Research Council in close collaboration with Imperial College in London and investigators in four African countries, were announced on 14 December. Disappointingly, the hint of efficacy seen in the smaller phase IIb was not duplicated: there were 130 HIV infections among the 3,156 women that received PRO 2000 gel, and 123 infections in the group of 3,112 women that received placebo gel.

The first news story reporting the result appeared in the Times newspaper (UK edition) the day before and broke the embargo on the MRC releases by several hours; it was subsequently taken offline before being reinstated. The article dramatically - but erroneously - characterises the PRO 2000 result as “a significant setback.” The whole purpose of large phase III efficacy trials is to definitively answer the question of whether an intervention works and, quite often, they don’t. In the case of PRO 2000, the microbicide is one of the last in a pipeline of products with relatively limited direct antiretroviral activity and, over the past several years, there has been increasing recognition in the field that more specific products are needed. Several such antiretroviral microbicides, such as the gel form of the drug tenofovir (Viread) are now in trials.

Source: TAG weblog (14 Dec 2009)

Further information on the MDP-301 trial:

Background materials from the trial’s sponsor, the Microbicide Development Programme of the UK Medical Research Council:

<http://www.mdp.mrc.ac.uk>

AVAC’s PRO 2000 resource page:

<http://www.avac.org/ht/d/sp/i/3426/pid/3426>

Global Campaign for Microbicides:

<http://www.global-campaign.org/MDP301.htm>

References

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<http://www.retroconference.org/2009/Abstracts/36659.htm>

Source: TAG basic science weblog (19 Feb 2009).

BASIC SCIENCE

Recent basic science updates from Richard Jefferys excellent web log.

Bridging the neurology-immunology barrier

The Cell Press journals *Neuron* and *Immunity* have collaborated to produce a timely free-access special issue focusing on the interrelatedness of neural and immune systems. [1]

The editors of *Neuron* write: "The brain was once thought to be a largely 'immune-privileged' system. Traditionally, research has reflected this segregation, with neuroscientists focusing on the nervous system and immunologists focusing on the immune system. Yet as science in both realms has moved forward, it has become clear that the nervous and immune systems interact on many levels, in both disease states and under healthy conditions. It is also clear that molecules traditionally viewed as neural- or immune-specific play important and often distinct roles in the other system. Experimental evidence of interactions between the neural and immune systems continues to accumulate, and the two research communities are beginning to communicate more as well. In this same spirit, *Neuron* and *Immunity* have coordinated to bring together a compilation of articles on selected topics related to the interface between the nervous and immune systems."

The issue includes articles addressing "Immune Activation in Brain Aging and Neurodegeneration" and "Neuroimmune Crosstalk in HIV Infection." [2, 3]

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[http://www.cell.com/neuron/fulltext/S0896-6273\(09\)00753-3](http://www.cell.com/neuron/fulltext/S0896-6273(09)00753-3)

Free journal on immunology and cardiovascular disease

The January 2010 issue of the journal *Clinical Immunology* is offering free access to a series of articles addressing the immunology of cardiovascular disease. Among a range of related subjects, the reviews address data on the roles of innate and adaptive immunity in the development of atherosclerosis and the status of experimental immunotherapeutic approaches to treating the disease.

Reference

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<http://www.sciencedirect.com/science/journal/15216616>

Early predictors of disease progression

Richard Jefferys, TAG

Recent research involving SIV-infected macaques has suggested that the early loss of a particular type of memory CD4 T cell (known as a "central memory" T cell or T_{cm}) may be a key predictor of the subsequent pace of disease progression. T_{cm} are a long-lived subset of memory T cells that can proliferate robustly in response to antigen. T_{cm} proliferation generates a fleet of T cells belonging to a shorter-lived subset called "effector memory" (T_{em}) cells. T_{em} are generally viewed as first-responders that can rapidly execute anti-pathogen functions, while T_{cm} provide a stem-cell like renewal source for new T_{em} if their numbers need to be bolstered. Studies in HIV-infected people have consistently shown a loss of T_{cm} and increase in T_{em} (which equates to a decrease in long-lived resting T cells and an increase in short-lived activated T cells), but whether changes in the numbers of different T cell subsets during early infection can predict disease progression has not been thoroughly evaluated.

A new study published in the *Journal of Infectious Diseases* set out to answer the question of whether quantifying T_{cm} in early infection provides prognostic information. To provide sufficient statistical power to ensure confidence in the findings, a total of 466 individuals were studied, among whom 101 progression events occurred.

It turned out that the proportion or absolute number of T_{cm} did not correlate with subsequent disease progression (defined as the time to AIDS or death), but several other parameters did. These included the proportion of naïve CD8 T cells, with a greater proportion being strongly associated with slower disease progression ($p < 0.001$); this correlation remained significant after adjustment for CD4 T cell count. The numbers of CD8 T cells expressing the IL-7 receptor (CD127) were also linked to the rate of progression; having fewer of these cells correlated with a faster disease course.

Immune activation was assessed by measuring the proportion of CD4 and CD8 T cells expressing the proliferation marker Ki67.

In both subsets, higher proportions of Ki67-expressing cells equated to faster progression, and for CD8 T cells this relationship held up after adjustment for baseline CD4 T cell count, age, and viral load. The median time to AIDS or death among subjects with the highest levels of Ki67-expressing CD8 T cells (based on dividing participants into quartiles) was 4 years for those in the top quartile compared to 10 years for those in the lowest.

Finally, measures of cell-associated viral load (CAVL: the proportion of CD4 T cells containing HIV DNA) were correlated significantly with progression in those participants sampled within 225 days of their estimated date of seroconversion (225 days was the median time after the estimated date of seroconversion that samples were obtained). Among participants sampled later, CAVL was not significantly correlated with rate of progression, suggesting an important impact of the early spread of HIV among CD4 T cells on subsequent disease course. The researchers also evaluated CAVL in different CD4 T cell subsets: naïve, central memory, transitional memory and effector memory. To their surprise, naïve CD4 T cells showed relatively high rates of infection, albeit around 10-fold lower than the memory subsets. Because resting naïve CD4 T cells are known to be very resistant to HIV, the researchers speculate that the infected naïve cells may have been rendered susceptible by immune activation (naïve CD4 T cells have been shown to become susceptible to R5-using HIV after they receive activation signals).

The authors conclude by stating: “we find that quantification of Tcm cells in early infection does not provide predictive power for progression. However, measures of homeostasis and activation, including CD127 expression and Ki-67, do provide such information and should be studied further to determine their role in clinical monitoring of HIV-1 progression...Future efforts to identify markers of subsequent progression should focus on measures of activation and homeostasis during the earliest stages of infection.”

Source: TAG Basic Science Weblog (13 Jan 2010).

References

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<http://www.journals.uchicago.edu/doi/abs/10.1086/649430>

OTHER NEWS

International AIDS Conference to be held in the US after over 20-year ban

The International AIDS Society has announced that the 2012 International AIDS Conference will be held in Washington, D.C. This will mark the first time the meeting has been held in the United States since 1990, when it was held in San Francisco.

The decision came largely as a result of the lifting of restrictions for people with HIV entering the United States, which was announced by President Obama in October.

The US HIV travel ban was consistently opposed by HIV activists and the decision taken by the IAS to refuse to hold meetings in the US was widely supported.

The 2012 meeting, held from 22-27 July, is expected to attract more than 25,000 delegates from nearly 200 countries, including more than 2,500 journalists.

Source: Press release, International AIDS Society. The IAS announces Washington, DC, as site of the 19th International AIDS Conference in July 2012: removal of entry restrictions on People Living with HIV by the U.S. allows for return of conference after 22-year absence. (30 Nov 2009).

The IAS maintains a detailed global database on HIV-related travel restrictions:

<http://www.hivtravel.org>

Changes at the European Medicines Agency (EMA)

On 8 December, the European Medicines Agency officially unveiled a package of changes with the launch of a new organisational structure and new visual identity.

Changes include:

- a change in name (from EMEA to EMA) and website address
- integration of human pre- and post-authorisation activities into one unit
- the creation of a new unit for patient health
- a dedicated group for the management of product data

Established in 1995, this is only the second time there has been a major re-organisation of the Agency's services.

A new public website for the Agency is nearing the end of development and will be launched in 2010. With the current website being visited more than 700,000 times each month, the new site is being designed with the needs of the public in mind, offering improved navigation and search functionality, providing better access to information on public-health issues.

Source: EMA press release: European Medicines Agency launches new organisational structure and new visual identity. (8 Dec 2009).

<http://www.ema.europa.eu>

ON THE WEB

Conference reports and online abstracts:

Webcasts from 11th Lipodystrophy Workshop

11th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV

26-28 October 2009, Philadelphia, USA

It is an incredibly useful feature of this small specialised meeting that the organisers arrange for nearly all oral presentations to be available as free access webcasts.

The oral plenary lectures at the meeting are of a consistently high standard, often inviting experts from outside the HIV field to provide an overview on newly emerging issues relating to long-term HIV management.

<https://lipo09.events-register.com/lipodystrophy/default.cfm?itemtypeid=15&title=Webcasts%20and%20videos>

Webcasts from 12th EACS

11-14 November, Cologne

Presentations from this conference are now available online.

This year a comprehensive programme of lectures and sessions available as webcasts and podcasts and include many of the slide sets:

<http://www.europeanidsclinicalociety.org>

<http://www.multiwebcast.com/eacs/2009/12th>

Access requires a free one-time registration using the invitation code: EACS2009

The abstracts from the meeting are currently only available in a subscription issue of HIV Medicine (2009, volume 10, issue S2).

How to access the webcast?

- 1) Go to: www.europeanidsclinicalociety.org
- 2) Click on the Webcast link to the left
- 3) Click on the webcast banner
- 4) Click Sign In and enter your username and password

How to access a single presentation?

- 1) Click on the presentation you would like to access below
- 2) Enter your username and password when prompted

Reports and journals:

PLoS Medicine

Volume 6(11) November 2009

The unintended consequences of clinical trials regulations. McMahon AD et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000131>

Alex McMahon and colleagues critique the International Conference on Harmonisation (ICH) guidance on good clinical practice (GCP), arguing that it is having a disastrous effect on noncommercial randomised clinical trials in Europe.

Effects of genital ulcer disease and HSV-2 on the efficacy of male circumcision for HIV prevention: analyses from the Rakai trials. Gray RH et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000187>

Ron Gray and colleagues analyse data from two circumcision trials in Uganda to assess how HSV-2 status and genital ulcer disease affect the procedure's ability to reduce HIV infection.

Community resources and publications:

Flat-lined: how flat NIH funding undermines research on HIV, TB and viral hepatitis

Lydia Guterman, TAG

The goal of this funding analysis is to provide a comprehensive picture of the current state of U.S. National Institutes of Health (NIH) research investment in HIV/AIDS and three of its most common coinfections (hepatitis B, hepatitis C, and TB) after five years of flat funding at NIH (2004–2009).

In FY 2007, NIH spent approximately 10% of its budget on HIV/AIDS but only 1.1% of all research investment in HBV, HCV, and TB combined. More than half (52%) of all programs for AIDS and these three diseases were administered by the National Institute of Allergy and Infectious Diseases (NIAID).

With flat funding, new initiatives and expansions of research on HIV/AIDS and the three most common coinfections cannot be funded. As the real value of the budget contracts, it is likely that more conservative research proposals by experienced researchers will trump higher risk (and potentially higher reward) proposals submitted by early-career researchers. This discourages innovation and has likely already led to missed opportunities for the funding of novel approaches in the prevention and treatment of HIV/AIDS and its common coinfections.

<http://www.treatmentactiongroup.org/publication.aspx?id=3052>

PDF download

http://www.treatmentactiongroup.org/uploadedFiles/About/Publications/TAG_Publications/2009/tag%20flatlined%202009%205.28web.pdf

Clinical management of the HIV-positive woman

TheBody.com

A podcast discussion with Kimberly Smith and Valerie Stone

<http://broadcaster.thebody.com/t?ctl=179F25:B33203735488890861B00D26D4C955E3&>

Recent years have brought HIV health care providers a deeper understanding of the unique challenges involved in providing care to HIV-infected women. Although there remains a dearth of information regarding the impact of HIV and antiretroviral therapy on women, there is much that we do know. For instance, research has shown us that HIV-infected women can have a high rate of cervical cytological abnormalities and certain gynecologic complications. We are well aware that reproductive counseling is an essential part of care for HIV-infected women. In addition, the burdens of child and family care often create obstacles to adherence and continuation of care. These and other issues make it more important than ever that today's HIV health care providers have as complete an understanding as possible of the ideal manner in which to treat their HIV-infected female patients.

UK patient survey: you, your GP and HIV

This survey has been compiled by the Forum Link Project, a network that currently links patient support groups from 15 HIV clinics. The survey has been designed by HIV-positive people and to help understand people's relationship with their GP and how we would like to see Primary Care services develop in the future.

We believe this is the first online survey in the UK of GP services in relation to HIV care, that is organised, compiled and run by HIV-positive people. The data collected will be used by Forum Link members during consultations currently being undertaken by various Patient Groups and PCTs.

The survey is anonymous and is online here:

<http://www.forum-link.org/research/gp/survey>

Medical resources:

HIV inSite resources

Health care of the HIV-positive transgender person

Barry Zevin, MD. September 2009. [RealAudio with slides]

<http://hivinsite.ucsf.edu/InSite?page=cfphp-zevin>

Dosing of antiretroviral drugs in adults with renal insufficiency and haemodialysis

UCSF Center for HIV Information

<http://hivinsite.ucsf.edu/InSite?page=md-rr-18>

FUTURE MEETINGS

2010 conference listing

The following listing covers some of the most important upcoming HIV-related meetings and workshops.

Registration details, including for community and community press are included on the relevant websites.

16-19 February: 17th CROI, San Francisco.

<http://www.retroconference.org/2010>

17-19 March: 8th European Drug Resistance Workshop, Sorrento, Italy.

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

7-9 April: 11th International Workshop on Clinical Pharmacology

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

25-29 April: 21st International Harm Reduction Conference, Liverpool.

<http://www.ihra.net>

31 May-2 June: 6th International HIV /HCV coinfection Workshop, Israel.

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

24-25 June: 5th International Workshop on Hepatitis C - Resistance and New Compounds, Boston.

23-24 June: 5th International Workshop on Clinical Pharmacology of Hepatitis Therapy, Boston.

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

15-16 July: 5th International Workshop on HIV Transmission - Principles of Intervention, Vienna.

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

16-17 July: 2nd International Workshop on HIV Pediatrics, Vienna.

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

18-23 July: XVIII International AIDS Conference (AIDS 2010), Vienna.

<http://www.aids2010.org>

12-15 September: 50th ICAAC, Boston.

<http://www.icaac.org>

11 September: 3rd International Workshop on Clinical PK of TB Drugs

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

7-11 November: 10th HIV International Congress on Drug Therapy in HIV Infection, Glasgow

<http://www.hiv10.com>

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.

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

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

Sections include:

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

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

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

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

Generic clinic forms

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

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

<http://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 since 2002. It now includes over 300 members from over 100 organisations. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

The CAB has a separate website, where reading material, reports and presentations from these meetings are posted. Membership is free,

<http://www.ukcab.net>

World CAB - reports on international drug pricing

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

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

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

i-Base Treatment Guides

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

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

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

Translations of i-Base 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.

HTB South

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

ARV4IDUs

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

Treatment information request service - 0808 800 6013

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

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

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

Online Q&A service

An online 'question and answer' service that now has over 900 questions online. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).

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

Recent questions include:

- Doubts when I'm told that my life expectancy is good...
- What is the prognosis if diagnosed with these symptoms?
- What is the risk of infecting my girlfriend with HIV?
- News reports of research that 'could' be a cure
- Does treatment work if you start with a low CD4 count?
- Can hepatitis B reactivate?

- Does yohimbe interact with HIV meds?
- Pregnancy without viral load results
- Should I start treatment at CD4 320?
- How do I time my meds when travelling?
- Is a viral load result of 50 really a blip?
- Does skipping a dose have an immediate effect?
- Does masturbation have any effect on HIV-positive people?
- Personal results from a recent diagnosis...
- Should I start treatment in South Africa with a CD4 of 320?
- How can I increase my sexual desire?
- How often can I have sex?
- Can I get pregnant with a CD4 count of 360?
- What are the alternatives to Sustiva (efavirenz)?
- How long do I need to stay on HIV drugs?
- Can I study in India if I am HIV-positive?
- The condom broke with a partner who does not know I am HIV-positive...
- My CD4 is 347... do I need to start treatment?
- How can I work in Saudi Arabia?

Find HTB on AEGiS

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

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

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

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

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

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

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

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

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

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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.

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1 5 10 25 50 100 Other _____

Guide To HIV, Pregnancy and Women's Health (January 2009)
1 5 10 25 50 100 Other _____

NEW: Introduction to Combination Therapy (June 2008)
1 5 10 25 50 100 Other _____

Changing Treatment - Guide to Second-line and Salvage Therapy (September 2008)
1 5 10 25 50 100 Other _____

Guide To Avoiding and Managing Side Effects (May 2008)
1 5 10 25 50 100 Other _____

Guide To HIV and hepatitis C coinfection (May 2007)
1 5 10 25 50 100 Other _____

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

Phoneline support material (pls specify required number of each)

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

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

1 Sheet 1 pad 5 pads 10 pads Other

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