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(hyperlinked)

EDITORIAL

This issue of HTB includes reports from the recent BHIVA meeting in Cardiff.

Data were presented from the BHIVA pregnancy audit and provides a fascinating insight into current practice in this country and will inform the revised BHIVA pregnancy guidelines.

Included as a supplement with this issue of HTB is a report from an international community meeting held 'to enable HIV-positive people and advocates from the developing world to voice their concerns about drug pricing and esearch practices in their regions to senior executives of the multinational pharmaceutical industry'.

Twenty-seven individuals from 21 countries gathered in San Francisco, California in advance of the annual Retrovirus Conference, the year's most important scientific conference on HIV, to meet with officials responsible for global marketing and pricing policies at Roche, GlaxoSmith Kline, and Boehringer Ingelheim.

The report contains an edited digest of the discussions and additional copies are available from the website or the i-Base office.

This issue also includes a letter from Dr Sarah Fidler relating to an earlier article on antiretroviral treatment in primary infection. It rightly highlights the newly enrolling Spartac study that will hopefully provide definitive answers to this important area.

We always welcome correspondence related to articles in HTB and will publish these whenever possible.

CONFERENCE REPORTS

10th Anniversary Conference of the British HIV Association (BHIVA)

15–17 April 2004, Cardiff

Unless otherwise stated, all references are to the programme and abstracts of the 10th BHIVA conference, which are available online as a pdf file at the bhiva website:

http://www.bhiva.org

Pregnancy 2003-4 audit

Polly Clayden, HIV i-Base

Data from the BHIVA pregnancy audit - a case note review of pregnancies among women with HIV in Britain between October 2002 and September 2003 - were presented at this meeting. This review was performed in order: "To enable BHIVA guidelines to be reviewed in the light of current practice and the most recent evidence." It also gives an insight into the extent to which the current guidelines are being followed.

The audit evaluated questionnaires from 99 centres nationwide: 19 in London, 79 elsewhere and one unstated. Eighty centres submitted data for 504 pregnancies. Four pregnancies were excluded from the analysis due to: one maternal and foetal death at 24 weeks gestation caused by multi organ failure attributed to TB drugs and/or nevirapine; two pregnancies were terminated and one was not delivered during the audit period.

Management and communication

The majority of centres (87) managed pregnancy and delivery working with a multi-disciplinary team and 81 respondents were satisfied with communication among healthcare professionals. A large number (79) of respondents said that post-natal ward midwives would be informed of a woman's HIV status, eight said problems had arisen through relevant staff not being told of a woman's status and 11 through staff using this information inappropriately.

Diagnosis and patient demographics

The majority of centres (82) used an "opt out" system of antenatal HIV testing, 11 reported an "opt in" system and six did not know/answer. Of the group of women evaluated 208 (42%) knew their status before pregnancy; 249 (50%) were diagnosed in the first or second trimester; 233 (47%) by routine antenatal screening; 37 were diagnosed in the third trimester but >7 days pre-delivery; 3 (0.6%) within seven days pre-delivery and 2 (0.4%) post-delivery.

The majority of patients, 390 (78%) were black African; 60 (12%) were white; 21 (4%) were black Caribbean (20 patients were described as "other" and there were no data for nine).

Most of the women were either in the 20-30 year old age group - 239 (48%) or the 30-40, 215 (43%) age group. Only two (0.4%) were under 15, 23 (5%) were age 15-20 and 8 (2%) were over 40 years old. (There were data missing for 13 [3%] women).

Maternal health and use of antiretrovirals

Almost half (49%) of the women – both off and on treatment - had a CD4 count of >350 cells/mm^3 near the beginning of their pregnancy, 2% had 0-50 cells/mm^3; 18% 51-200 cells/mm^3; 27% 2001-350 cells/mm^3 and 4% were not known.

At the start of pregnancy, 104 (21%) women were already receiving antiretrovirals. Treatment varied widely and there were a few worrying reports: two women were receiving dual therapy (although had undetectable viral loads); 11 were on efavirenz (two with detectable viral loads) at the start of pregnancy and five at the end of pregnancy; six were receiving ddI and d4T together (two with detectable viral loads) and four were still using ddI/d4T at the end of their pregnancy.

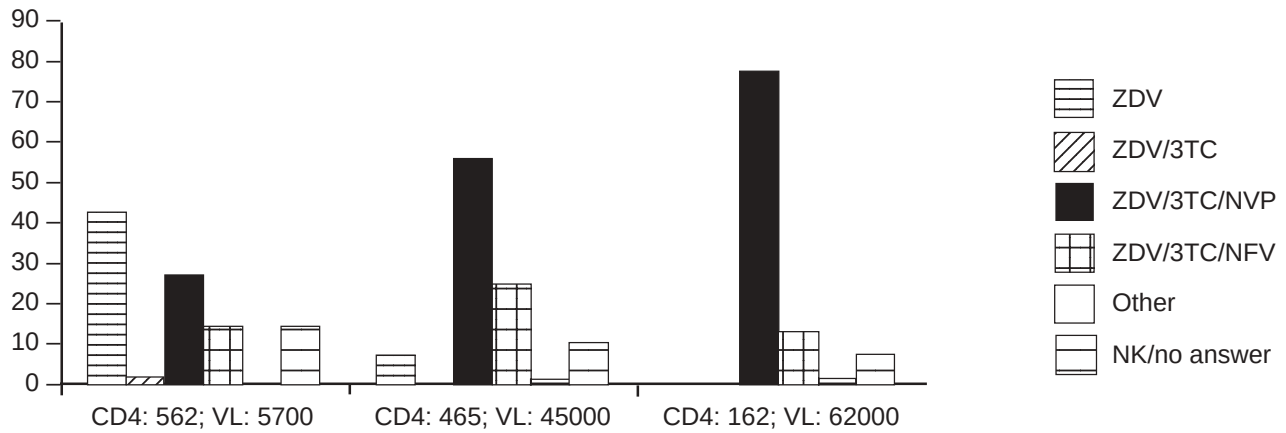
At the end of their pregnancies, 484 women were using antiretroviral treatment or prophylaxis. The data were unclear for eight patients.

Half the women received ZDV/3TC/NVP; 14% ZDV monotherapy; 10% ZDV/3TC/NFV; 2% ABC/ZDV/3TC; 2% ZDV/3TC/LPVr. Two percent of women received no antiretrovirals, including one with HIV2 and four very late presenters. There was no analysis to evaluate how many women with higher CD4 counts who did not require treatment for their own HIV received triple therapy.

These findings are consistent with respondent's replies when questioned about what they would do in various scenarios. The investigators noted that one respondent, when asked how they would treat a woman with a CD4 count of 562 cells/mm^3 and a viral load of 5,700, proposed dual therapy of AZT and 3TC. (See Figure 1 below).

Respondents were also asked what they would do for a subsequent pregnancy for a woman who did not require treatment for her own health. Thirty-seven percent of respondents replied that they would base their strategy on a resistance test and/or adherence and viral load on previous ART and 20% that they would offer the standard therapy or the same as in the previous pregnancy.

Figure 1: Stated preference of ART by clinicians in three hypothetical scenarios



Mode of delivery

In answer to a question about a hypothetical scenario involving a woman on HAART with stable, undetectable viral load, 55% of respondents reported that they would recommend an elective Caesarean section; only 9% and 7% would favour a planned vaginal delivery in women with previous uncomplicated births and first pregnancies respectively. Sixteen per cent were neutral and the remainder reported no policy or did not answer.

Of the reported pregnancies 422 (85%) were planned for Caesarean section and in 43 (9%) it was not considered to be indicated as 38 had a pre-delivery undetectable (<50 copies) viral load, three with viral load less than 1000 and two not known. The majority of women (35) in this group were on HAART, two were receiving ZDV monotherapy and one ZDV/3TC dual therapy. Nine women (2%) declined a Caesarean section, two had no plan and data were missing for 22.

Actual mode of delivery reports 335 (67%) by elective caesarean; 70 (14%) after onset of labour; 54 (11%) vaginally and 41 (8%) "Not known". Fifty-eight (14%) of planned Caesarean sections resulted in Caesarean section after onset of labour and eight (2%) delivered vaginally.

Deliveries in women planned for elective Caesarean

	Completed weeks of gestation						
Actual mode of delivery	**<36**	**37**	**38**	**39**	**>40**	**Not Known**	**Total**
Elective CS	17	22	205	49	9	23	325
CS in labour	23	15	11	5	2	2	58
Vaginal	4	1	3	-	-	-	8
Not known	6	2	9	4	-	10	31
Total	50	40	228	58	11	35	422

The investigators added there is: "Possible need for guidance on when to perform planned CS – many women labour early, so best done at 38 weeks, not later."

Pregnancy outcomes

The majority of deliveries (48%) occurred at 38/40 weeks, which reflects the use of elective Caesarean, 11% were at or before 36-40 weeks and 9% at 37-40 weeks. Initial results suggest 10 stillbirths: nine at or before 36-40 weeks and one at 37-40. The investigators are following this up.

Foetal and neonatal abnormalities

The investigators reported 15 abnormalities among foetuses and neonates, these were described as follows:

- 2 babies known to have HIV
- 2 (one a twin) died of neonatal TB
- 1 spina bifida, possible sacral myelomeningocele
- 1 trisomy 21 & AV canal defect
- 1 congenital jejunal atresia
- 1 cleft palate
- 1 diaphragmatic hernia
- 1 clicky hip, absent red reflex, later found normal
- 1 intra-uterine growth retardation
- 1 "small with infection"
- 1 "flat" baby incubated in neonatal intensive care
- 2 unclear

Breast feeding

In answer to a question about support currently offered for infant feeding the investigators reported: "Centres varied greatly in the support offered for bottle-feeding." And in answer to a hypothetical question about a mother's reluctance to bottle feed: seven replied that this was patient choice; 14 respondents cited child protection; 21 referred to the use of antiretrovirals maintaining maternal viral load below detection at 50 copies/mL; four mentioned antiretroviral prophylaxis for the baby and three suggested pasteurising expressed milk.

Conclusions

The investigators described these findings as "broadly positive" but cited areas in which they felt stronger guidance to be needed. In particular: appropriate use and stopping of nevirapine; avoidance of ddI and d4T together; appropriate use of planned vaginal delivery; timing of elective caesarean section; management of women who wish to breast rather than formula feed and management of subsequent pregnancies.

C O M M E N T

Nevirapine has been widely prescribed in combination therapy during pregnancy in the UK and elsewhere. In the UK triple therapy has generally been prescribed only once the CD4 count has fallen below 350 and usually when closer to 200 cells/mm^3. Since the recent caution

from Boehringer this remains an option for pregnant women with CD4 counts below 250 cells/mm^3 but the more difficult question is how best to manage those pregnant women with high CD4 counts for whom a short course of combination therapy is considered the best option.

The unquantified risk of fulminant hepatitis with nevirapine in pregnancy, as well as the difficulties of preserving future options when discontinuing combinations with widely differing half-lives – a troubling finding was that when asked about stopping nevirapine 15% of respondents said that they would stop all drugs together - means that other options, need to be found. While protease inhibitors appear to be the best alternative there is relative paucity of data on their pharmacokinetics during pregnancy, and the importance of transplacental transfer of antiretrovirals should also be considered especially if delivery is likely to occur before viral replication has been controlled.

Conversely these data probably highlight the relative safety of using nevirapine in pregnancy and it is important to note that this audit was performed prior to the updated safety warning.

Perhaps the most important initial finding of the audit is the observation of 10 stillbirths in 500, a rate almost 4 times the national rate of 5.6/1000 (http://www.statistics.gov.uk). Further analysis is urgently required to determine whether this is due to recognised social and medical factors, confusion over reporting and methodology ("miscarriages" were censored in this analysis) or whether current intervention strategies are in anyway implicated. The investigators are following this up.

Finally this audit also highlights the need for strong support packages for HIV positive mothers to encourage bottle feeding. This includes clear information about the risk of breastfeeding, counselling and practical interventions such as formula and sterilising equipment for those mothers with limited resources, until there are robust data to support the early studies suggesting that breastfeeding by a mother with an undetectable viral load using antiretrovirals carries zero risk of transmission.

Revision of the BHIVA Pregnancy Guidelines is currently underway.

Ref: BHIVA clinical audit committee. Oral presentation, BHIVA Plenary Session 3, 10th BHIVA conference 2004.

More positive children are surviving into adult life and require tailored services

Graham McKerrow, HIV i-Base

HIV-positive children are surviving into adult life and many adolescents in a UK cohort have been heavily pretreated with antiretroviral therapy with suboptimal responses and will challenge therapeutics in adult services, according to a cohort study. Teenagers need help transferring from paediatric to adult services, as well as information and tailored services to increase independence and choice, according to another study.

The Collaborative HIV Paediatric Study (CHIPS) looked at the evolving UK cohort of children at 18 centres in the UK and Ireland. [1] Of 759 children, 179 (24%) are adolescents between 12 and 19 years. 99 (56%) of the adolescents are female, 107 (61%) are of Black African origin, 47 (27%) are white, 151 (86%) were infected via vertical transmission, 11 (6%) via blood transfusion. 38% were born in the UK and Ireland, and 137 (78%) are being treated in London.

63 adolescents developed CDC stage C disease during follow-up and 4 have died during their adolescent years since 1996.

At last follow-up, 36 (20%) had never received antiretroviral therapy, 114 (64%) were on highly active antiretroviral therapy, only 66 (46%) of whom started HAART as their first regimen, the remainder receiving prior mono and/or dual therapy. More than one quarter of all adolescents in the cohort have been treated with more than 8 ARVs. Almost half of those on treatment have suboptimal virological response.

20 (11%) transferred to adult care services, with a median age at transfer of 17.0 years (range 15.3-18.8).

2 reported pregnancies, both were previously treatment naïve and received AZT (zidovudine) monotherapy during pregnancy.

CJ Foster and colleagues conclude: "HIV-infected children are surviving into adult life. In this cohort, many have been heavily pre-treated with antiretroviral therapy with suboptimal responses, and will challenge therapeutics in adult services.

D Melvin of St Mary's Hospital, London, and colleagues conducted a self-administered anonymous patient questionnaire to identify teenagers' views on healthcare concerns and service provision at two London clinics. [2]

19 teenagers (9 female) aged 13 to 19, all with vertically acquired HIV, responded. Most requested general information on healthy living and sexual development and sex education. Older teenagers (16 years or over) wanted more information on ARV treatment and HIV disclosure and the importance of understanding its implications. Most were told their HIV diagnosis with a healthcare professional present, but there was a wide variety of opinions on which age this was best done, although most said it should not be before 11. Most did not want school/college/work to be informed.

Services were rated highly by all except one respondent and the priorities included being able to meet the doctor alone and getting know regular clinic staff. Older teenagers wanted teenager-only clinics operating outside college hours and younger teenagers wanted a gradual introduction to adult services. Older adolescents were concerned about relationships, HIV

transmission and having children; younger adolescents were worried about managing work and HIV secrecy at school as well as arguments with parents.

The authors conclude: "Addressing the needs of vertically infected adolescents has implications for both paediatric and adult HIV services. Transition should be viewed as a process throughout the adolescent years rather than a one off transfer of care".

C O M M E N T

There is currently much discussion around best practice for the transition of adolescents from paediatric to adult care. CHIVA (Childrens HIV Association; http://www.bhiva.org/chiva) and i-Base recently convened a meeting to look at evolving models and produce guidelines that are currently in preparation.

References:
1. Foster CJ, Lyall EGH, Dierholt K et al. HIV infected adolescents: an evolving UK cohort. Abstract 017
2. Melvin D, Prime KP, Dodge J et al. One size fits all? The changing needs of HIV-positive teenagers. Abstract P25

Other news from the BHIVA conference

Simon Collins, HIV i-Base

Atazanavir switch appears tolerable and effective

Clinical results were presented on patients who had switched to atazanavir (ATZ) on the named patient/early access programme at Brighton, East Sussex and St Mary's Hospital, London. Limited data – largely relating to toxicity and viral load response - can be collected from these programmes. However, these results can give some support when considering a switch to this newly available once-daily protease inhibitor (PI) in situations not covered by the registrational studies.

Results were presented on 76 patients who received ATZ for a median of 15 weeks (range 1–47). The median time on antiretroviral therapy was approximately five years and the duration of prior PI therapy almost two years. Reasons for starting ATV included pill burden (20), once-daily therapy (21), adherence issues (9), hyperlipidaemia (20), gastrointestinal disturbance (11), lipodystrophy (6) and virological failure (13). Two patients died (unrelated to ATV); six stopped ATV because of patient choice (3), hypersensitivity (1) jaundice (1) and myositis (1). One patient was lost to follow-up.

Of the 28 patients who switched to ATZ with a viral load of <50 copies/ml, 27 remained undetectable. Of the 44 starting with detectable viraemia, 22 are now undetectable and the remaining 16 on therapy have experienced significant viral load reductions.

Hyperbilirubinaemia occurred in 64%, resolving in 61%; three patients experienced clinical jaundice. Hyperlipidaemia improved in 61%, with 38% of these patients able to stop lipid-lowering agents. Improvements in gastrointestinal symptoms occurred in 54%.

Ref: McDonald C, Mackie N, Smyth C et al. Clinical experience of atazanavir: tolerable and effective. Oral Abstract O2.

Therapeutic drug levels can continue three weeks after stopping efavirenz

The STOP study received an oral presentation at this year's Retrovirus conference and is covered in detail in the April issue of HTB (Vol 5, No 3), but has particularly important implications for treatment in the UK.

Ten patients who were discontinuing or switching efavirenz, largely due to toxicity, had plasma drug levels measured weekly, while continuing on background or switched treatment, in order to collect detailed data relating to efavirenz clearance.

Efavirenz clearance was within the expected range for five patients (half-live ~50 hours), but five had efavirenz half-life >100 hours (median 123, range 114-229). Four of these were black African women who at baseline had efavirenz levels ~10,000 ng/ml (10-fold higher than minimum target) perhaps explaining the need to change for toxicity. Three women maintained therapeutic levels >1000 ng/ml 2 weeks after stopping EFV.

Current guidelines (BHIVA, 2003) suggest EFV can be stopped 7 days before shorter-acting nucleoside but these extended PK data suggest the stop window should be increased to 2–3 weeks for some patients (or efavirenz switched to nelfinavir or other shorter lasting drug for the last 3 weeks).

Ref: Taylor S, Allen S, Smit E et al. The Stop Study: after discontinuation of efavirenz (EFV), plasma concentrations can persist for >2 weeks. Oral abstract O6.

Use of detuned HIV test to establish recent infection

Accurately identifying recent HIV infection provides the opportunity to track more accurately the rate that HIV progresses in any individual. In addition to allowing entry into primary infection studies, it will also impact on the importance of earlier treatment. Anecdotally, many patients appear to progress to requiring treatment far earlier than the previous estimate of 5-8 years, and data in this area would also help address whether this is occurring.

STARHS (Serologic Testing Algorithm for Recent HIV Seroconversion) can diagnose infection within the previous 4–6 months in people who have tested HIV-positive with the routine EIA antibody test but who have not produced sufficient antibodies for this less sensitive (detuned) EIA test. Martin Fisher and colleagues reported on use of this simple test at Brighton Hospital.

Incident cases from 1996 to 2002 were determined by conventional methods (HIV-negative test within 18 months, evolving antibody response or incomplete Western blot), by STARHS and by both methods combined.

Of 486 individuals newly diagnosed during the study period 387 (89%) underwent STARHS serum analysis. New diagnoses identified as incident by conventional methods increased from 0/50 (1996) to 18/82 (2002). STARHS identified a further 48 incident infections (11% of total new infections; 48% of total incident), ranging from 2/50 (1997) to 14/82 (2002). Using a combination of conventional methods and STARHS, RHI increased over time from 9/50 (1996) to 32/82 (2002) [P<0.001].

This test is available free from the Health Protection Agency laboratory in Colindale (formerly PHLS) on 020 8200 4400 x 4262. It is not available as an initial HIV diagnostic test but only to gauge recent infection in a patient with a confirmed HIV diagnosis. There are also limitations, including only being validated for subtype-B infection. The test cannot be used for patients who have already started antiretroviral treatment or who are diagnosed with ongoing AIDS-related illnesses. The 6-month window period used in STARHS analyses for calculating population-based HIV incidence is the mean for a tested population. Although individual results would be distributed on either side of the mean and this window may not always be applicable for every individual infection, it is routinely used when accessing recent infections for individuals entering trials of primary HIV infection.

Ref: Fisher M, Dean G, Cooper V et al. Adjunctive use of the Serological Testing Algorithm for HIV Seroconversion (STARHS) identifies a high and increasing proportion of newly diagnosed infections as incident. Oral abstract O8.

Tenofovir for treatment of HBV in coinfected patients

Gilleece and colleagues from the Chelsea and Westminster Hospital presented results from an open-label study of 40 HIV/HBV coinfected patients (39 men, 1 woman) using tenofovir 245mg as part of or in addition to their antiretroviral therapy.

31 patients were 3TC-experienced, with a median exposure of 72 weeks (range 6–270). 60% of those who underwent HBV DNA polymerase sequencing had a mutation in the YMDD motif.

The median HBV viral load fell from 250 x 10^6 to <10,000 copies/ml at 96 weeks. 25/40 (63%) had an undetectable HBV by 48 weeks. 14/14 (100%) who reached 96 weeks had an undetectable HBV DNA level. Eight individuals became HBeAg-negative between 36 and 96 weeks, and six seroconverted to HbeAb-positive. Three of these six had lamivudine resistant mutations at baseline. All eight individuals remained HbsAg-positive.

The median CD4 count rose from 271 (baseline) to 386 (48 weeks) and 488 cells/mm^3 at 96 weeks. Similarly, the CD4% rose from baseline to 96 weeks (19.2% to 24% to 22.5%).

C O M M E N T

Several previous reports have highlighted the activity of tenofovir against HBV. [2, 3, 4] It is not clear whether any of those patients show a viral non-response as reported from adefovir where 15-20% show an HBV-RNA decrease of < 1 log (Van Bömmel, AASLD 2003).

It was also unclear whether there was any viral load rebound suggesting development of resistance.

References:

1. Gilleece Y, Nelson MR, Clarke A et al. Tenofovir in the treatment of hepatitis B (HBV)/HIV co-infected individuals. Oral abstract O19.
2. Dore GJ, Cooper DA, Pozniak, AL, et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and -experienced patients coinfected with HIV-1 and hepatitis B virus. J Infect Dis. 2004;189:1185-1192.
3. Benhamou Y, Katlama C, Rozembaum W, et al. Efficacy of tenofovir disoproxil fumarate (TDF) for hepatitis B virus (HBV) in human immunodeficiency virus (HIV) infected patients. Hepatology. 2003;38(suppl 1):712A. 54th AASLD, 2003. Abstract 1155.
4. Efficacy of Tenofovir Disoproxil Fumarate in Hepatitis B Virus in HIV-co-infected Patients: The TECOVIR Study. 11th CROI, Feb 2004, San Francisco.

Sub-type-B infection in UK traced to 1975-1982

Hue and colleagues from Oxford University and University College London reconstructed a phylogenetic tree including 1784 *pol* gene sequences from subtype B viruses throughout the world, together with more than 1645 sequences from UK isolates, in order to identify independent introductions of HIV-1 within the UK.

Using a coalescent-based approach, incorporating a calculated rate of nucleotide substitution of the subtype B *pol* gene they identified four large viral lineages, indicating multiple, independent introductions of subtype B HIV-1 into the UK, dated to the period 1975–1982. Each strain showed an initial exponential phase of growth from time of introduction until the late 1980s, after which the effective population size appeared to plateau until the present, possibly due to altered sexual behaviour.

Apart from seroconversion symptoms or cases of rapid HIV progression, HIV is generally reported as taking 5-8 years to progress to clinical symptoms. An idea of the history of HIV in the UK is important for many HIV-positive people who are long-term diagnosed. It is also helpful to remember that many people were infected long before there was any knowledge of HIV as a new virus and that infection predated the availability of the first HIV test in 1985 by many years.

Ref: Hue S, Pybus OP, Pillay D. Use of coalescence theory to estimate time of introduction of HIV-1 strains into the UK, and subsequent population growth dynamics. Oral abstract O11.

HIV still missed by GPs

Gilbert and colleagues from the Health Protection Agency reported on UK nationals who have a low or unacknowledged risk of HIV and present late in the course of HIV infection, often after frequent attendances to general practitioners (GPs).

Information from 286 in-depth interviews with low or unacknowledged risk individuals and those diagnosed because of HIV-related symptoms (n=157, 55%) was compared with data about people diagnosed for other reasons.

A greater proportion of those diagnosed late were male and older, or in a long-standing relationship.

Of the 157 late diagnoses, 95 were considered to have acquired HIV heterosexually, 74 in the UK and 21 abroad, 16 through 'high-risk' behaviours, 16 heterosexually by a 'high-risk' partner and the remainder through an unusual, other or unknown route. No partners had informed them of their HIV status.

Greater awareness by GPs of common symptoms indicative of immune suppression could result in avoidable morbidity and premature mortality. The study also concluded that sensitive partner-notification practices that enable a greater number of individuals to inform their partners should be explored.

Ref: Gilbart VL et al, CDC HPA London.Late diagnosis of HIV infection among individuals with low or unacknowledged risks in England, Wales and Northern Ireland. Oral abstract O15.

ANTIRETROVIRALS

Antiviral activity of foscarnet in salvage therapy

Graham McKerrow, HIV i-Base

Another small study has reported short-term antiviral activity from foscarnet use in salvage therapy for seven patients with multi-drug resistant HIV-1.

Sophie Mathiesen and colleagues in Denmark used foscarnet as induction therapy or as maintenance therapy in different dosing regimens for seven severely immunocompromised patients harbouring three or more nucleotide excision mutations (NEM). During induction the median decrease in viral load was 1.8 log and increases in CD4 cell counts ranged from 0 - 136 cells/mm^3.

The patients were foscarnet naïve although heavily pre-treated having received ARVs for a median 9 years (range 7-11), and had been exposed to 14 (12-14) different ARVs. They had multidrug-resistant virus harbouring 7 (5-9) NRTI mutations including 3 or more NEM, 9 (6-12) PI mutations and 2 (1-3) non-NRTI mutations.

Before treatment with foscarnet, the HIV RNA level was 165,000 copies/ml (93,000-1,440,000) and the CD4 count was 17 cells/mm^3 (9-56). All patients continued their HAART regimens, with minor adjustments, during foscarnet treatment. Six patients received foscarnet as induction therapy (60 mg/kg three times a day) for 14 days (5-17).

At the end of foscarnet induction, viral load had decreased 1.8 logs (1.2-3.2) and CD4 cells had increased 8 cells/mm^3 (-19-56). Four patients initiated foscarnet as maintenance therapy, three as a rollover from induction, with various dosing regimes.

The patients had received maintenance therapy for 1-8 weeks. Treatment was interrupted in 2 patients because of renal impairment or infection originating from the intravenous device.

The authors write: "Maintenance therapy was associated with increases in CD4 cell counts despite the fact that the initial decrease in viral load during induction therapy was not fully sustained. The blunted virological response during maintenance therapy could be caused by the reduced doses of foscarnet, the prolonged dosing interval or the development of resistance. The rapid virological rebound when foscarnet was stopped further indicates that the decline in viral load can be ascribed to the effect of foscarnet."

The authors advise: "Foscarnet toxicity and the risk of severe infections related to intravenous administration represent a major limitation in clinical practice. Therefore, regardless of the promising antiretroviral properties, treatment with foscarnet should be instituted with great caution and restricted to patients with severely deteriorated immunology and no other treatment options left. The objective of therapy should be to identify tolerable maintenance doses that provide a reasonable improvement in the CD4 cell count."

C O M M E N T

Foscarnet was assessed for antiretroviral activity in vivo in a number of pilot studies or as part of CMV-therapy. There was never a profound effect reported in patients on monotherapy or as part of a multiple drug regimen in salvage therapy.

Foscarnet has to be given IV two to three times a day in the induction phase of CMV treatment and also requires careful preadministration of probenecid to limit renal toxicity. Its optimal antiretroviral use is unknown.

The development of an orally available prodrug of foscarnet was stopped by AstraZeneca the manufacturer after CMV-retinitis became a rare disease.

Although the potential antiviral activity indicated by this study could be useful in a few patients, the significant toxicity indicates that they are likely to those with CD4 counts <50 who also require treatment for active CMV.

Ref: Mathiesen S, Roge B, Weis N et al. Foscarnet used in salvage therapy of HIV-1 patients harbouring multiple nucleotide excision mutations. AIDS: Volume 18(7) 30 April 2004 pp 1076-1078

RESISTANCE

Kaletra therapy fails woman with subtype C virus with multiple mutations

Graham McKerrow, HIV i-Base

The importance of studying pattern of natural polymorhisms and development of resistance in response to treatment in non-B subtypes was highlighted in a case report of a South African patients with dominant subtype C virus using a lopinavir/r (Kaletra)-based combination.

Francesca Conradie and colleagues in Johannesburg report in the 30 April issue of AIDS on the failure of Kaletra in a 25-year-old woman. The failure, they write, appears to be the result of an accumulation of multiple PI mutations and a single reverse transcriptase mutation. Kaletra is a potent antiretroviral drug with a high resistance barrier, and primary failure has not previously been described in an antiretroviral naïve patient.

This patient received treatment (stavudine, didanosine and hydroxyurea) for two weeks in June 2000 but the treatment was stopped when she developed eosinophillic folliculitis. She had a baseline CD4 count of 282 cells/mm^3 and her viral load was 325,000 copies/mL. In November 2000, she was started on Kaletra, AZT (zidovudine, ZDV) and 3TC (lamivudine), and by week 16 her viral load was less than 50 copies/mL.

At one year, her viral load was undetectable and her CD4 count was 395 cells/mm^3. At 2 years, her viral load had rebounded to 908 copies/mL although her CD4 count had increased to 451 cells/mm^3. Self-reported adherence was greater than 95% but adherence counselling was intensified. Five months later, her viral load had increased to 16,200, and her CD4 count was still 451 cells/mm^3. She had generalised lymphadenopathy with a large node in her armpit. One month later the viral load was 12,800 copies/mL. The patient said she was completely adherent in the previous month. Lymphadenopathy persisted.

After resistance studies, the regimen was changed to AZT, abacavir and nevirapine.

Viral genotyping on a stored sample from before November 2000, showed M361 and L63P mutations, which are naturally

occurring polymorphisms in subtype C viruses, in the protease gene.

Viral genotyping on a sample taken on the failing regimen, showed the only reverse transcriptase mutation was M184V. The PI mutations identified were M36I, I54V, L63P and V82A. The PI sequences were sent to the Stanford database for drug resistance, which found several more mutations associated with PI treatment.

Conradie and colleagues write: "Mutations in the protease gene that are known polymorphisms but are also secondary mutations associated with PI resistance were present before starting treatment and may have made the accumulation of additional mutations more likely. In addition, poor adherence with suboptimal lopinavir levels may have contributed to the development of resistance. This observation supports the hypothesis that resistance to lopinavir requires the accumulation of a series of mutations, and demonstrates that well-described PI resistance mutations can accumulate when on lopinavir-ritonavir therapy and can contribute to virological failure. A signature mutation for lopinavir resistance was not identified."

C O M M E N T

It is important to note that this patient primarily responded to therapy despite high viral load.

The interesting news is that mutation pattern leading to lopinavir resistance may be different in genotype C patients.

It seems strange however, that the patient did not acquire NRTI mutations beyond M184V which are usually more rapidly acquired than PI mutations in the presence of replicating virus.

Ref: Conradie F, Sanne I, Venter W et al. Failure of lopinavir-ritonavir (Kaletra)-containing regimen in an antiretroviral-naive patient. AIDS: Volume 18(7) 30 April 2004 pp 1084-1085

SIDE EFFECTS

Oral uridine treats mitochondrial toxicity

Graham McKerrow, HIV i-Base

A case report of a 54-year-old Caucasian man in Germany indicates that oral uridine may be effective in life-threatening mitochondrial toxicity related to pyrimidine nucleoside analogues such as zalcitabine (ddC, Hivid) or stavudine (d4T, Zerit).

Several investigators have found beneficial effects of uridine in vitro and in animals, but Ulrich Walker and colleagues report in the 30 April issue of AIDS the case of a man who has been on antiretroviral medication since being diagnosed with HIV-1/AIDS four years ago. He was on a stavudine-containing regimen, which was then switched to lamivudine 150 mg twice a day, stavudine 40 mg twice a day, abacavir 300 mg twice a day and efavirenz 600 mg a day. His initial CD4+ count of 25 cells/mm3 had risen to 682 two years ago. HIV was undetectable in the blood.

The authors report that after several months, he developed myalgias and a continuous increase in creatine kinase, lactate and transaminases. Abdominal ultrasound revealed signs of massive liver steatosis. The patient was started on NucleomaxX, a food supplement consisting of Mitocnol, an extract from sugar cane with a high content (17%) of nucleosides, for suspected stavudine-related mitichondrial toxicity. Drinking the contents of a single 36g sachet of NucleomaxX increases physiological serum concentration of uridine in humans from approximately 5 uM to more than 100 uM. The patient had 3 sachets a day for 4 days. At his next visit two weeks later, liver and muscle enzymes, and the myalgias, had improved, despite unchanged medication. Lactate had normalised after 7 weeks. Stavudine was then switched to tenofovir. There were no subsequent clinical or laboratory abnormalities, viral load remained below the limit of detection at < 50 copies/ml, and ultrasound showed substantial improvement of steatotic signs.

Ref: Walker U, Langmann P, Miehle N et al. Beneficial effects of oral uridine in mitochondrial toxicity. AIDS: Volume 18(7) 30 April 2004 pp 1085-1086

Links:

http://www.i-base.info/pub/htb/v4/htb4-7/potential.html

http://www.i-base.info/pub/htb/v4/htb4-7/Uridine.html

http://www. NucleomaxX.com

LIPODYSTROPHY

Phase II results show ThGRF could be safe, effective treatment for lipodystrophy, says company

Graham McKerrow, HIV i-Base

Theratechnoligies, a Canadian biotech company, is trumpeting the preliminary Phase II trial results of its ThGRF, a stabilised analogue growth hormone-releasing factor (GRF) that looks promising for the treatment of HIV-associated lipodystrophy patients with excessive visceral fat.

The preliminary results suggest that ThGRF is safe and effective, concentrating its effect on reducing visceral fat while preserving subcutaneous fat. This would make it particularly useful in treating people with an accumulation of visceral fat (lipohypertrophy) together with a loss of subcutaneous fat (lipoatrophy). It demonstrated good glycaemic control, even among glucose intolerant and diabetic patients. About 40% of HIV-associated lipodystrophy patients are either glucose intolerant or diabetic.

ThGRF induces the production and secretion of growth hormone in a specific, physiological and pulsatile fashion, which, says the company, makes it a strong candidate as a potential treatment for many diseases related to aging and obesity as well as HIV-associated lipodystrophy.

The double-blind, randomised, placebo-controlled study conducted in seven centres in Canada and the USA, enrolled 61 patients, all on stable antiretroviral therapy, in parallel groups, who received a daily subcutaneous injection of ThGRF 1 mg, 2 mg or placebo, over a period of 12 weeks.

The researchers report that the 2 mg dose produces a marked increase in levels of IGF-1 (a dependable indicator of bioavailable growth hormone in the human body) (+80%, $P < 0.01$ vs placebo), and "highly significant" effects on body composition (lean body mass: +1.7kg, $P < 0.01$ vs placebo; total body fat mass: 1.4 kg, $P < 0.02$ vs placebo).

Dr Steven Grinspoon, Director of the Programme in Nutritional Metabolism, and Associate Professor of Medicine at Harvard Medical School and Lead Investigator for the US, said: "The selectivity on visceral fat mass as well as the decrease in the VAT/SAT [visceral fat/subcutaneous fat] ratio are noteworthy … and suggest that the physiological mode of action of ThGRF translates into clinical advantages over other approaches for patients with HIV-associated lipodystrophy. ThGRF may also prove useful to alter fat distribution from the trunk and viscera in non-HIV-infected patients with the metabolic syndrome."

A company statement says: "Based on these positive results, the company and its clinical experts consider that ThGRF is well suited for Phase III testing as a novel approach to treat HIV lipodystrophic patients with excessive visceral fat, an unmet clinical need."

More details and a webcast will be posted for 90 days at the following links:

http://www.vcall.com/CEPage.asp?ID=87905

http://www.theratech.com

C O M M E N T

The same results however with the potential of reducing subcutaneous fat have been reported for recombinant human Growth Hormone (r-hGH).

It would be interesting to know the effect of ThGRF on glucose metabolism or the frequency of arthralgia, two adverse events of r-hGH. In addition a reduction 1.4 kg visceral fat is fairly moderate and is in the range of the changes reported for exercise or metformin, and less than that reported for r-hGH.

Reversibility of lipoatrophy in HIV patients 2 years after switching from a thymidine analogue to abacavir

From HIVandHepatitis.com

The HIV-associated lipodystrophy syndrome affects approximately 50% of HIV-positive patients, particularly those receiving antiretroviral therapy based on nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs).

The selection of an optimal treatment regimen for HIV infection is influenced by increasing evidence that particular antiretroviral drugs may exacerbate lipoatrophy and associated metabolic abnormalities.

However, because of cross-resistance among antiretroviral drug classes and other treatment toxicities, it is likely that, in a lifetime, HIV patients will have to take drugs that are associated with the development of the lipodystrophy syndrome.

A number of cohort studies have suggested that long-term exposure to thymidine-based analogues results in lipoatrophy that is associated with mitochondrial toxicity and lactic acidemia.

The PIILR extension study examined lipoatrophic patients on a protease inhibitor-sparing antiretroviral regimen for at least 12 months, who then ceased stavudine (d4T) or zidovudine (AZT, ZDV). This study resulted in significant improvements in lipoatrophy but an unacceptable rate of HIV virological rebound.

More recently, replacement of d4T or ZDV with abacavir (ABC) in randomised controlled trials has been shown to lead to modest improvements in fat mass over a relatively short period of time.

The initial MITOX (mitochondrial toxicity) study reported a significant increase of 0.4 kg (11%) in limb fat in the ABC-treated subjects at 24 weeks, as well as significant relative increases in subcutaneous thigh and abdominal fat mass. However, this difference in limb fat was not apparent clinically.

The objective of the current study was to determine if long-term improvement in HIV lipoatrophy can be attained by substitution of the thymidine analogues ZDV or d4T with ABC. Long-term follow-up (104 weeks) of this randomised, open-label study (MITOX) appears in the 30 April issue of *AIDS*.

Seventeen HIV clinics in Australia and London enrolled 85 patients with HIV lipodystrophy who were randomised to switch from a thymidine analogue to ABC, while continuing all other antiretroviral therapy (ABC arm) (n = 42) or continue current therapy (ZDV/d4T arm) (n = 43).

At week 24, all control patients could switch to ABC. Of the original 111 patients randomised, 85 had long-term follow-up data, with 77 having imaging data available at 104 weeks.

The primary endpoint was time-weighted change in limb fat mass, measured by dual-energy X-ray absorptiometry (DEXA).

At week 104, the mean increase in limb fat for the ABC and ZDV/d4T group was 1.26 +/- 2.02 kg and 0.49 +/- 1.38 kg, respectively. The time-weighted change for limb fat was significantly different between the two arms (0.43 kg; *P* = 0.008).

On-treatment analysis demonstrated a trend for increased limb fat in patients in the ABC arm.

Interestingly, visceral fat accumulation, buffalo hump, self-assessed lipodystrophy or the lipodystrophy case definition score (LCDS) did not improve.

The authors conclude: “In patients with moderate-to-severe lipodystrophy, significant improvements in subcutaneous fat continued over 104 weeks after switching from a thymidine analogue to ABC. Nevertheless, the lipodystrophy syndrome was still evident, indicating additional strategies need evaluating.”

Ref: Martin A et al (for the Mitochondrial Toxicity (MITOX) Study Group). Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *AIDS* 18(7): 1029-1036. April 30, 2004.

Source: HIVandHepatitis.com

COMMENT

The increase in subcutaneous fat seemed to be linear over time in this study, which may point at a continuous biological effect. This may be the good news, because the gain itself although statistical significant was clinically not relevant. A severely wasted leg may have lost 4-5 kg of fat which means that the gain of 1.2 kg is about 20% needed to return to normal.

These results were presented at the 2003 Workshop on Lipodystrophy and included in the reports from that meeting in the August/ September 2003 issue of HTB:

http://www.i-base.info/pub/htb/v4/htb4-7/Mitochondrial.html

It is to be hoped that the high profile already given to the results from this study, and the caution against use of d4T in the 2003 BHIVA guidelines should mean that few patients with lipoatrophy are still using d4T. The publication of the full results in AIDS is therefore welcomed.

PRIMARY INFECTION

Rapid clearance of HIV-1 is associated with decreased risk of AIDS

Graham McKerrow, HIV i-Base

A study of 22 patients with acute infection from the Trinidad Seroconvertor Cohort in Port of Spain, Trinidad, concludes that efficient, early clearance of HIV-1 strongly predicts subsequent risk of progression to AIDS. This finding is consistent with a growing body of evidence suggesting that effective immune responses during the earliest phase of infection are important determinants of disease progression.

William Blattner and colleagues in Trinidad and the United States found that 10 patients developed AIDS-defining events. In univariate analysis, progression to AIDS was associated with rate of initial HIV clearance ($P = .002$), virus load during set point ($P = .008$), and CD4+ cell count during steady state ($P = .04$).

Multivariate analysis showed that a rapid rate of initial clearance was the sole independent predictor of subsequent progression to AIDS and was associated with a 92% reduction in the risk of AIDS. The rate of initial clearance was inversely correlated with the number of early symptoms ($r = -0.66$; $P = .0008$). However, symptoms did not predict subsequent risk of AIDS.

Ref: Blattner W, Oursler KA, Cleghorn F et al. Rapid clearance of virus after acute HIV-1 infection: correlates of risk of AIDS. JID 2004;189:1793-1801

C O M M E N T

This study presents interesting data, but in clinical practice the monitoring of CD4 will be still the most relevant strategy. There will be considerable variation in the natural course of the disease even after inclusion of viral clearance in patients with known time of infection.

IMMUNE BASED TREATMENT

HIV patients get long-term boost with short, intermittent drug regimen

US National Institutes of Health (NIH) scientists report that brief, widely-spaced courses of the experimental immune-boosting drug interleukin-2 (IL-2) allow people with HIV to maintain near normal levels of a key immune system cell for long periods. The researchers, from NIH's National Institute of Allergy and Infectious Diseases (NIAID) and the Warren G. Magnuson Clinical Centre, describe their findings in the 1 May issue of the journal *Blood*.

"These data provide strong evidence that IL-2 therapy, which can be self-administered by patients, could be an important adjunct to highly active antiretroviral therapy (HAART)," says NIAID Deputy Director John R La Montagne.

The new report summarises the experience of 77 HIV-positive individuals who enrolled in extension phases of three long-running AIDS clinical trials. Participants were taught to inject themselves subcutaneously with IL-2 twice daily in 5-day-long cycles. Cycles were initiated as often as necessary to maintain levels of CD4+ cells at predetermined, individually tailored amounts. IL-2 can boost CD4+ cell levels, with the goal of improving overall immune health.

Immune-stimulation therapy, such as IL-2, might play a substantial role in treating patients with this condition, notes Richard Davey Jr, an NIAID AIDS clinician who headed the studies reported in Blood. Indeed, during the early 1980s NIH physicians pioneered the use of long courses of IL-2 to treat individuals whose immune systems had mysteriously failed. Scientists now know those people were suffering from AIDS, but at the time the virus had yet to be identified.

Today, HIV patients receiving IL-2 therapy typically begin with 5-day-long cycles every other month while taking drugs, such as HAART, on a sustained basis. According to Dr Davey, this regimen often raises an HIV patient's CD4+ cell levels well into the normal range after only a few cycles. The new research suggests IL-2 therapy can then be administered much less frequently without loss of benefit.

Most studies to date have looked at IL-2 therapy over only relatively short periods, says Dr Davey. In contrast, the average length of patient follow-up described in the current paper is about six years. Patients in these trials have received an average of 10 IL-2 cycles during the course of their involvement, with most of the cycles occurring in the initial years of participation. Of the original 77 volunteers, 61 achieved and maintained normal or nearly normal levels of CD4+ cells for periods ranging

from two to 91 months between IL-2 cycles. During the most recent period of study, the average time between cycles was more than 3 years. (Of the 16 people no longer participating, one died, one developed non-Hodgkin's lymphoma, eight elected to follow other treatment plans and six experienced CD4 cell count declines that did not respond to IL-2 therapy.)

"Patients described in this study are still being followed," says Dr Davey. "There are also trials planned or underway to learn if IL-2 therapy could delay or obviate the need for continuous HAART, thereby sparing persons with HIV disease from the serious side-effects that HAART can cause. The early experience from some small preliminary studies in this area suggests that this may indeed be a possibility, although larger trials are clearly needed to explore this fully."

Source: NIAID press release (edited)

Ref: CE Farel et al. Induction and maintenance therapy with intermittent interleukin-2 in HIV-1 infection. *Blood* 103:3282-86. Published online January 15, 2004.DOI: 10.1182/blood-2003-09-3283.

C O M M E N T

CD4 guided IL2 administration reduces IL-2 side effects considerably. However the clinical benefit of this strategy remains to be proven. It is always nice to look at higher CD4 numbers, but the clinical implications will not become clear until long-term follow-up results become available from the ongoing ESPRIT and SILCAAT studies.

HEPATITIS COINFECTION

The 39th Annual Meeting of the European Association for the Study of the Liver (39th EASL)

14-18 April 2004, Berlin, Germany

Although coinfection with HIV only covered a minority of the studies presented at the 39th EASL, reports on new drugs to treat HBV or HCV monoinfection indicate the most hopeful pipeline for coinfected patients. Full abstracts from the meetings are not available on the conference website, but coverage of many of the HIV and hepatitis coinfection and new agent studies have been grouped by subject and are reported or included as abstracts on the HIVandHepatitis.com website:

http://www.hivandhepatitis.com/2004icr/39easl/main.html

Extensive coverage, again grouped by subject, is also provided on the NATAP website:

http://www.natap.org

These include:

- Albuferon: new HCV drug dosed every 2-4 weeks by subcutaneous injection
- Model to predict outcome of Pegasys plus ribavirin therapy
- Small, unrandomised study compares Pegasys to PegIntron
- Daily cannabis smoking as a risk factor for fibrosis progression in chronic hepatitis C
- Long-term outcome of HBeAg-negative patients with cirrhosis treated with lamivudine monotherapy: a 5 year prospective cohort

Tenofovir blocks viral replication in HBV monoinfected and in HIV-HBV coinfected patients with lamivudine resistance

From HIVandHepeatitis.com

Researchers evaluated the additional effect of tenofovir (Viread) on hepatitis B virus (HBV) viral dynamics after HBV DNA breakthrough during lamivudine (Epivir-HBV) therapy.
Eleven chronic HBV patients (five HIV coinfected) with breakthrough HBV DNA and the presence of a YMDD mutation received "add-on" tenofovir 300 mg once daily, while maintaining their existing therapy, including lamivudine.

Sequential sera, taken at day 1; t=0 and t=8 hours, day 2, 4, 7, 10, 14, 21, 28 and thereafter every 4 weeks, were tested for HBV DNA using PCR. Mean baseline log HBV DNA was 8.31 +/- 1.07 (median 8.62; range 6.48-9.76 log HBV DNA).

Application of tenofovir resulted in a mean log HBV DNA decline of 2.54 +/- 0.91 after 4 weeks of tenofovir treatment and a mean decline of 4.95 +/- 0.90 log HBV DNA after 24 weeks of treatment.

The authors conclude: “These data show that tenofovir is capable of blocking viral replication in patients with lamivudine induced mutant viruses in HBV patients as well as in HBV/HIV co-infected patients.”

Ref: de Man RA et al. Viral dynamics with frequent sampling during tenofovir therapy in patients with lamivudine-resistant hepatitis B virus mutants. Abstract 427. 39th EASL, 14-18 April 2004, Berlin, Germany.

Compared to Caucasians, Africans have significantly higher rates of fibrosis and cirrhosis despite lower levels of HBV replication

From HIVandHepeatitis.com

It is believed that low HBV replication (<105 copies/ml) is indicative of mild histological lesions. In this study, French researchers aimed to assess the relationship between viral replication, histological lesions and race in HBV patients of diverse ethnic backgrounds.

The study group consisted of 552 chronic HBsAg carriers without other viral co-infection who had a liver biopsy. Viral replication was assessed in 516 patients by hybridisation and/or PCR assays.

Race was defined as African (Af, Blacks), Caucasian (Cc, Whites), Asian (As). Overall, Af had more frequent low viral replication (75%) than Cc (43%) or As (34%) (p<10-3). Despite low viral replication, 20% of patients had significant fibrosis (F2F3F4), including 7.5% with cirrhosis.

Among all patients with F2F3F4, 35% had low level replication and 16% no replication (<200 copies/ml). A third of cirrhotic patients had a low level of replication and 11% no replication.

The interactions between viral replication and liver lesions were also modified by race. In F2F3F4 patients, the proportion of those with low viral replication was 49% in Af, which was significantly higher than in As (25%, p<0.02) or Cc (26%, p=0.03). Non-Af race was associated with F2F3F4 (p=0.01) independent of male sex (p<10-3) and age (p<10-3). However, after adjustment for the level of viral replication the race effect disappeared.

The authors conclude: “A significant proportion of patients with chronic hepatitis B have advanced fibrosis despite a low level of HBV replication. Differences between Af and As patients suggest a considerable clinical impact of different HBV genotypes.”

Ref: Ratziu V et al. Low HBV replication and liver fibrosis: the impact of race in a study of 552 chronic hepatitis B patients. Abstract 440. 39th EASL, 14-18April 2004, Berlin, Germany.

Undetectable HIV viral load in HIV-HCV coinfected patients slows liver fibrosis progression rate

From HIVandHepatitis.com

In the pre-HAART era, HIV-HCV-coinfected patients were reported to have a faster fibrosis progression rate (FPR) than HCV-monoinfected patients. One preliminary study suggested that HAART might slow down FPR. The study was conducted in New York City and at four sites in Puerto Rico.

In the current study, overall, 685 consecutive HCV-infected patients, 297 HIV-positive and 388 HIV-negative, who underwent a liver biopsy (Ishak scoring) were analysed. A known date of HCV infection was available in 675.

The patients’ mean age was 46.9 years, 21.1% were female, genotype 1 was present in 79.0%, median HIV RNA level was 420 copies/ml, and median CD4+ cell count was 401/mm3. There was no difference between HIV-HCV-coinfected and HCV-monoinfected patients in fibrosis progression rate (0.138 vs. 0.128 Ishak fibrosis units/year [IshFU/yr], p=0.21), fibrosis stage (2.88 vs. 2.86 Ishak fibrosis units, p=0.87) and necroinflammatory grade (6.92 vs. 6.50 Ishak necroinflammatory units, p=0.088).

In HIV-HCV-coinfected patients, log10 HIV RNA level was strongly correlated with FPR, but CD4+ cell count only weakly.

HIV-HCV-coinfected patients with any HIV viral load >400 copies/ml had a faster FPR than coinfected patients with undetectable plasma HIV RNA and than HCV-monoinfected patients who in turn had a similar FPR as HIV-HCV-coinfected patients with <400 copies/ml (p=0.253).

HIV viral load is strongly correlated with FPR in HIV-HCV-coinfected patients, but CD4+ cell count only weakly. Undetectable HIV viral load is associated with slower FPR than with any HIV level and the same as in HCV-monoinfection.

Ref: N Bräu and others. Control of HIV viral load through Highly Active Antiretroviral Therapy (HAART) slows down liver fibrosis progression in HIV/HCV-coinfection and makes it the same as in HCV-monoinfection. The Puerto Rico-New York Hepatitis C Study Group. Abstract 91. 39th EASL, 14-18 April 2004, Berlin Germany.

C O M M E N T

This study confirms previous data published by Benhamou et al Hepatology 1999 and Quirishi et al. in The Lancet 2003 showing that patients on effective antiretroviral treatment have a slower fibrosis progression and a lower incidence of liver failure. A methodological problem is that in principle only studies with paired biopsies and not cross sectional studies can answer the questions of fibrosis progression accurately.

OTHER NEWS

US government stops scientists attending International AIDS Conference

Graham McKerrow, HIV i-Base

The United States government has slashed its budget for sending scientists to the International AIDS Conference (IAC) in Bangkok in July, a move that will prevent the attendance of many who have had papers accepted for presentation. It is said to be a reprisal for a demonstration at the IAC two years ago against Tommy Thompson, the US Secretary for Health and Human services.

Two years ago the US department of Health spent $3.6 million sending 236 people to the IAC conference in Barcelona, but the Department of Health and Human Services (DHHS) has announced that it will spend only $500,000 to send 50 US scientists and 80 from Africa.

The DHHS prevents scientists from presenting their work if their travel is not paid for by the government so many who have had their papers accepted by the conference organisers for presentation, will not be able to do so. The department will pay for 20 scientists from the Centre for Disease Control (CDC), 20 from the National Institutes of Health and 10 from the DHHS.

According to Science, a confidential email sent in March by Jack Whitescarver, the Director of the NIH Office of AIDS Research, quoted DHHS official William Steiger as saying the decision to cut the number of government scientists "was as a result of the treatment the Secretary received in Barcelona and DHHS opinion that this meeting is of questionable scientific value". A speech in Barcelona by Tommy Thompson was drowned out by the shouts and whistles of 40 protesters who invaded the stage.

A spokeswoman for CDC told the journal Science that the agency would select scientists according to "which [talks] are most important". NIH refused to comment.

Meanwhile, the US government is also criticised in an article for the American Foundation for AIDS Research (AmFAR) which says the President's Emergency Plan for AIDS Relief (PEPFAR) emphasises abstinence and fidelity, advocating condoms for only those who engage in high-risk behaviors. "PEPFAR therefore ignores the group most vulnerable to HIV today — young married women." The full report is at the AmFAR link below.

Webcasts and other coverage of the XV International AIDS Conference will be available online at http://www.kaisernetwork.org/aids2004. Kaisernetwork.org will serve as the conference's official webcaster.

Link:

http://www.aids2004.org/

http://www.amfar.org/cgi-bin/iowa/td/feature/record.html?record=119

EMEA releases recommendations for better information for patients

The European Medicines Evaluation Agency (EMEA) has released recommendations on improving information for patients. Drawn up in collaboration with patients' organisations, the recommendations fall into three main areas; providing information adapted to patients' needs, developing appropriate communication tools, and increasing public awareness on the use of drugs and EMEA activities.

Patient information is a priority for the EMEA and the Agency has continuously strengthened its interaction with patients since its creation in 1995. An EMEA/CPMP (the agency's Committee for Proprietary Medicinal Products) working group with patients' organisations was set up in 2003 to look at issues including further improvements in the areas of transparency and dissemination of information, product information, pharmacovigilance and interaction between the EMEA/CPMP and patients' organisations.

The group has now made detailed recommendations and proposals for action. Some recommendations, such as the provision of patient-friendly general and product-specific information material or the re-structuring of the EMEA website to facilitate access to information for patients can be implemented within the current legal framework, while others such as public hearings during the scientific evaluation process would require amendments to legislation.

Several of these recommendations require consultation with the European Commission and Member States' competent authorities in order to arrive at a harmonised approach at European Union level. This includes harmonisation of the information provided on the package leaflet or improvement of public access to information on adverse drug reactions. Patient information has also been put at the top of the political agenda as a result of the recent review of EU pharmaceutical legislation, the work of the G10 High Level Group on Innovation and the Provision of Medicines, and recent discussions in the Council of Health Ministers. The recommendations from the EMEA working group are the first element of the Agency's response to the G10 recommendations and the resolution of the Council of Health Ministers of 1 and 2 December 2003.

The document 'EMEA/CPMP Working Group with Patients Organisations – Outcome of Discussions: Recommendations and Proposals for Action' (EMEA/CPMP/5819/04/Final) is available to download as a pdf file:

http://www.emea.eu.int/pdfs/human/patientgroup/581904.pdf

Comments should be sent by 30 June 2004 to:

patients@emea.eu.int

Source: EMEA Press release (pdf file)

http://www.emea.eu.int/pdfs/general/direct/pr/1072004.pdf

CORRESPONDENCE

Response to report from 11th CROI on treatment in primary infection

Dr Sarah Fidler

Keith Henry, reporting from the 11th CROI conference, in HTB April 2004, claimed that there is little benefit from treating acute HIV infection. [1]

This conclusion was based upon data presented by Prof. Bruce Walker and his colleagues, who have reported little clinical advantage from antiretroviral intervention with structured treatment interruption (STI) with/without vaccine in small cohorts of treated seroconverters over the past 3-5 years [2]. However, none of these studies have been sufficiently powered to address definitively the role played by antiretroviral treatment in acute HIV infection and none have had a randomised untreated comparison arm. Primary HIV infection is very heterogeneous, and leads to a wide range of clinical outcomes. [3] For example, it is reasonably well established that symptomatic seroconversion carries a worse prognosis than asymptomatic seroconversion. HIV-specific CD4+ T-helper responses have been shown to correlate with good virological control in acute infection [4, 5], and several small studies support the hypothesis that preservation of these CD4+ T-helper responses with early ART may influence virological control. [6-9] However, more recent work has demonstrated limited longevity of these responses, although this remains controversial. [10]

The clinicians' dilemma as to whether to offer ART intervention in patients presenting with acute HIV infection remains unanswered. The only way to address this is with a large-scale randomised clinical trial appropriately powered to definitively answer this question.

The Spartac trial, is a Welcome Trust funded 5-year multi-centred randomised study, which started in 2004 with sites in the UK, South Africa, Russia and Australia and will answer this question.

Clinicians and patients wishing to find more information about taking part in this study should contact Dr Sarah Fidler [s.fidler@imperial.ac.uk, Tel: +44 20 7594 3903]; or Dr Judy Fox [Tel: 20 7886 1466] or Mr Ken Legg [Tel: 20 7886 6790] at St Marys Hospital clinical trials unit Paddington, London.

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ON THE WEB

Conference abstracts:

Conference abstracts on AEGiS

The ongoing project by AEGiS to archive of important HIV/AIDS conference abstracts in a single online database resource continues to add conferences monthly.

IAS World AIDS Conferences are now either completely archived, or in progress from 1989 to present and the 1st and 2nd HIV Pathogenesis and Treatment Conferences (Buenos Aires, 2001 and Paris, 2003) are both now posted.

The database also includes Retroviruses Conferences (CROI) from 1997 onwards and specialised meetings such as the international resistance and lipodystrophy workshops organized by IMP and the ECAS and Glasgow European Conferences.

http://www.aegis.org/conferences/

Treatment Access:

MSF's 'Untangling the web'

http://www.accessmed-msf.org/prodpublications.asp?scntid= 22420041625454&contenttype=PARA&

Download pdf file of this report:

http://www.accessmed-msf.org/documents/untanglingtheweb6.pdf

The sixth edition of MSF's "Untangling the web of price reductions: a pricing guide for the purchase of ARVs in developing countries" was published in pdf format in April 2004.

This new edition contains updated information on prices for eligible countries (including price/unit and price/patient/year) for both adult and paediatric formulations and updated information and clarifications on the conditions and restrictions applying to these offers.

Untangling the web will be printed as part of the joint WHO-UNICEF-UNAIDS-MSF project 'Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS', due out next month. We expect that the printed version will be available in a month.

Botswana Generic report

The draft report of the FDC meeting in Gaborone, Botswana held on 29-30 March is available at:

http://www.globalhealth.gov/fdc.shtml#Draftdocument

Journal articles:

AIDS journal articles free online after one year

AIDS, the official journal of the International AIDS Society, is now free after one year. Articles older than 12 months will be freely accessible through the journal website:

http://www.aidsonline.com/pt/re/aids/issuelist.htm

http://www.aidsonline.com

This offer extends access options made through two projects HINARI (www.healthinternetwork.org/index.php) and AGORA (www.aginternetwork.org/en/) that provide at greatly reduced costs on-line subscriptions to institutions within countries whose resources would otherwise prevent them from subscribing and accessing journal content from the publisher of AIDS, Lippincott Williams and Wilkins.

Online medical resources:

HIV inSite Knowledge Base

New or updated chapters from April and May include:

Clinical overview of HIV disease

http://hivinsite.ucsf.edu/InSite?page=kb-03-01-01

Genotypic testing for HIV-1 drug resistance

http://hivinsite.ucsf.edu/InSite?page=kb-03-02-07

Non-antiretroviral medication-related adverse events during treatment of HIV-related infections and complications

http://hivinsite.ucsf.edu/InSite?page=kb-03-01-07

Adverse events of antiretroviral drugs

http://hivinsite.ucsf.edu/InSite?page=ar-05-01

Dosing of antiretroviral drugs in renal insufficiency and hemodialysis

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

thebody.com

Five people, five treatment interruptions, five outcomes

http://www.thebody.com/confs/retro2004/sti_cme_studies.html?m46h

We can read research about experimental HIV treatment strategies until our eyes glaze over, but sometimes it's more interesting — and more educational — to hear a doctor talk about some of the patients who have actually taken part in them. Dr. Gerald Pierone brings us in for a closer look at five people who took doctor-guided HIV structured treatment interruptions under a variety of circumstances.

JournalView: a new way to keep up with the latest in HIV medicine

http://www.thebody.com/redirect/journalview/april04.html?m46h

The Body Pro, The Body's sister site for HIV healthcare professionals, has launched JournalView, a new, monthly analysis of HIV research authored by an HIV physician. Every month, JournalView will scour top medical journals and other publications, selecting key findings and providing expert commentary on their importance to the world of HIV medicine. Click on the link above to read JournalView's inaugural issue!

Pharmacokinetic Factors In HIV Therapy

An online programme reviewing key issues in HIV pharmacology, and the role of pharmacokinetic factors in the outcomes of antiretroviral therapy. Site requires on-time free registration.

http://clinicaloptions.com/pk0510

Pharmacokinetic and pharmacodynamic principles: a guide for HIV healthcare professionals

Key pharmacokinetic and pharmacodynamic parameters; Characteristics of drug concentrations at steady state, and impact of different dosing regimens; Relationship between antiretroviral concentrations and treatment outcomes.

Factors associated with pharmacokinetic variability in HIV-infected patients

Clinical relevance of interpatient variability in drug concentrations; Factors contributing to PK variability in HIV-infected patients; PK variations associated with demographics, hepatitis and renal disease, pregnancy, and pediatrics.

Integrating pharmacokinetics into treatment decisions: strategies for optimal patient care

PK parameters that may predict clinical outcomes; Advantages and disadvantages of various boosted-PI regimens; Recently observed drug-drug interactions between antiretroviral agents.

Interactive guide to antiretroviral dosing

Interactive tool to access information on dose adjustments recommended for FDA-approved antiretrovirals in specific clinical scenarios (eg, hepatic or renal insufficiency; pediatrics; body weight).

Online publications:

IAVI Report online

http://www.iavireport.org/

The new IAVI Report Online is a centralized online source of information on all aspects of AIDS vaccine research and prevention

Visitors to the website will be able to subscribe to any of the IAVI Report products in a variety of electronic and print formats, all free of charge.

VAX articles are translated from English to French, German, Portuguese and Spanish.

New PRN Reports on line

Update on the treatment of acute and early HIV infection

Martin Markowitz, MD & Bruce D. Walker, MD, Summary By Tim Horn

http://www.prn.org/prn_nb_cntnt/vol9/num2/markowitz_walker_v9n2_frm.htm?notify04-134

Pharmacokinetics, pharmacogenetics and HIV: the aim to optimize antiretroviral therapy

David J. Back, PhD, Summary by Tim Horn

http://www.prn.org/prn_nb_cntnt/vol9/num2/back_frm.htm?notify04-134

Diagnosis and management of HPV-associated anogenital dysplasia in HIV-infected men and women

Joel Palefsky, MD, FRCP(C), Summary by Tim Horn

http://www.prn.org/prn_nb_cntnt/vol9/num2/palefsky_frm.htm?notify04-134

GMHC Treatment Issues - March/April 2004

Bi-monthly treatment newsletter which this issue focuses on employment and back-to-work issues.

http://www.gmhc.org/health/treatment/ti/ti1803.html

TAGline – May 2004

From the Treatment Action Group (TAG), Vol 11, Issue 5.

http://www.thebody.com/tag/may04/contents.html

- Abbott, Trimeris/Roche pricing decisions rekindle old R&D cost questions
- Letters to the editor
- Hydroxyurea: little-noticed ban of little-used drug triggers little-known investigation

MEETING ANNOUNCEMENTS

XV International AIDS Conference

11-16 July, 2004

The first conference of its kind to be held in Southeast Asia, the IAS World AIDS Conference will be held in Bangkok, Thailand.

Free press registration may still be available for community press. For details see the conference website:

http://www.aids2004.org/

2nd European Advanced HIV Course

August 25-27, 2004

Deadline for application: 30 May, 2004

The European AIDS Clinical Society (EACS) is running its second course on 'Antiretroviral Therapy and Comprehensive Care for People living with HIV/AIDS' focused on the clinical management of HIV, in Montpellier (South of France) from 25th to 27th August 2004.

For further information please call the EACS office for an application form:

sylvie-chatelin@eacs.ws

or download it from our website:

http://www.eacs.ws

Australasian HIV and HCV conferences

4th Australasian Hepatitis C Conference

31 August - 2 September 2004

Canberra Australia

This Conference is the leading Australasian gathering for Hepatitis C Research, Public Health Policy, Prevention, Treatment and Community Responses

16th Annual Conference of the Australasian Society for HIV Medicine (ASHM)

2 – 4 September 2004

Canberra Australia

Australia's largest HIV Conference. The theme for the 16th ASHM Conference is *Positive Partnerships – From Policy to Primary Care* and the conference will focus on how Australia has responded to HIV and where we need to go in the future. While some of this focus will be on our policy responses, it is equally embracing of management and prevention strategies.

For further information on both conferences or to register contact: conferenceinfo@ashm.org.au (email) or +61 2 9368 2714 (phone) or visit:

http://www.ashm.org.au/conference2004

JOB VACANCY

Treatment Information Officer

HIV i-Base has a vacancy for a part-time treatment information officer.

17.5 hours, 19-24k pro rata (negotiable based on experience)

The job description for this post includes providing treatment information and support to HIV-positive people via the i-Base phoneline and information request service. Currently the phoneline operates 12-4pm on Mondays, Tuesdays and Wednesdays.

The post also includes writing articles for Positive Treatment News and involvement in other i-Base projects.

A good level of treatment knowledge is necessary for this position but training will also be provided. The post offers an excellent opportunity for people who already have a good understanding of the issues involved to both increase their knowledge and contribute to an important service.

The post requires a high level of motivation and the ability to work within a small committed organisation. Personal experience of HIV is important and applications are particularly encouraged from HIV-positive people.

For further details or an information pack, please contact:

Simon Collins at i-Base on 020 7407 8488

or visit the i-Base website at

http://www.i-Base.info

New closing date for applications: 11 June 2004

PUBLICATIONS AND SERVICES FROM i-BASE

The i-Base website

Our web address is:

http://www.i-Base.info

All i-Base publications are available at our website, which is accessed by people all over the world; we have more than 5,000 successful page requests per week from about 80 countries on all continents.

The site gives details about i-Base, the UK Community Advisory Boards (UK-CABs), 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).

World CAB Report: focus on international drug pricing

Report from a meeting in Febraury 2004 of community advocates and three major pharmaceutical companies that focussed on pricing issues and global access to treatment. Included as a supplement with this issue of HTB.

Introduction to Combination Therapy

This non-technical patient guide to treatment is available in 12 languages. It explains what combination therapy is, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and how to avoid drug resistance.

Printed and pdf versions of this booklet are available in Bulgarian, Chinese, English, French, Georgian, Italian, Latvian, Macedonian, Portuguese, Russian, Slovak, and Spanish. To order copies, see below and the back page.

Guide to HIV, pregnancy & women's health

This patient guide helps women get the most out of HIV treatment and care before, during and after pregnancy. It should help whether you are on therapy or not and includes information for your own health and for the health of your baby.

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

Guide to changing treatment: second-line and salvage therapy

This is a non-technical patient guide to second-line and salvage therapy. This booklet helps patients in discussions with doctors, and covers what you can do if your viral load starts to rise, and the importance of considering or finding out why your current combination failed. To order copies, see below.

Guide to avoiding & managing side effects

This is a comprehensive 36-page guide that is aimed at helping anyone using HIV drugs to get the most out of their treatment, the most out of their relationships with their doctor and other health professionals, to get better medical care to improve their health and, most importantly, to enjoy a better quality of life.

It is written by people who are HIV-positive, who have been on most of the treatments, who have had many of the side effects and who have learnt to negotiate their own healthcare.

Chinese, French, Italian and Spanish translations of this booklet are also available. To order copies, see below.

Italian treatment guides

We have Italian versions of our three treatment guides: Introduction to Combination Therapy, Guide to Changing Treatment and Guide to Avoiding and Managing Side Effects. For details of what is in each guide, see under the separate headings on these pages. The Italian guides are available in a single printed publication (to order, see below) or from our website.

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.

Copies can be ordered using the form on the back page or by visiting our website (details below).

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: see below for details.

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 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.

UK-Community Advisory Board: reports and presentations

The UK-Community Advisory Board (UK-CAB) is a network for community treatment workers across the UK. Each meeting includes two training lectures and a meeting with a pharmaceutical company.

Reports and presentations for the eighth meeting, held on 27 February 2004, are posted to the i-Base website. The training session at this meeting included the second part of an introduction to statistics, given by Dr Caroline Sabin from the Royal

Free Hospital. In the afternoon session, the CAB met BMS to discuss the new protease inhibitor, atazanavir.

http://www.i-base.info/ukcab/feb04/index.html

Transcriptions and slides of training sessions from previous meetings also on the site include:
- Genetics, resistance and HIV - Professor Clive Loveday
- Approaches to Salvage Therapy - Dr Mike Youle
- Pregnancy, HIV and Women's Health - Dr Karen Beckerman
- Fertility treatment and sperm-washing techniques - Dr Leila Frodsham
- Access to treatment for UK visitors, refugees and asylum seekers - Linda McDonald
- Resistance, Lipodystrophy and IAS Report - Simon Collins
- TB and HIV coinfection - Dr Anton Pozniak

Find HTB on AEGiS

AEGiS.com - 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.com/pubs/i-base/2004

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

http//www.i-base.info/forms/index.html

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

All publications are available free of charge — including bulk orders for the UK or single copies for other countries.

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h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website:
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Also available in FRENCH, ITALIAN, SPANISH, PORTUGUESE, CHINESE, and GREEK *as pdf files on the i-Base website*

Changing Treatment - Guide to Second-line and Salvage Therapy *(November 2003)*

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Guide To Avoiding and Managing Side Effects *(August 2002)*

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Also available in SPANISH as a print version and in FRENCH, SPANISH, ITALIAN, CHINESE *as pdf files on the i-Base website*

Paediatric HIV Care - March 2001 - Report from i-Base Paediatric Meeting

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

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