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EDITORIAL

This issue contains further reports from the IAS conference in Rio, specifically looking at hepatitis coinfection and resistance studies.

Two new features are now available relating to subscribing to HTB on the i-Base website. One is an RSS new feeder, which will allow main contents of each issue to be available through a news reader on your web-browser. The second is a similar facility for use on handheld PDA organisers.

There is also a new Portuguese translation of the June 2005 Introduction to Combination Therapy guide. This is available as a pdf file on the i-Base home page, and would be useful for UK clinics with Portuguese speaking patients.

We would like to use the rest of this editorial space to raise the issue of access to treatment for asylum seekers in the UK and related to the policy of dispersal, and to ask for your help. We have heard of many distressing individual examples and it is important to collect more detailed examples of current practice.

A survey is being organised by the National AIDS Trust to ensure that asylum seekers living with HIV have access to adequate and ongoing HIV treatment and care, and that no harm should be caused to asylum seekers during the process of dispersal to new areas of residence.

This survey of health professionals is to collect information in order to provide recommendations for the National Asylum Support Service about improving procedures, ensuring continuity of HIV care and treatment through the dispersal process.

The questionnaire has already been distributed to some members of BHIVA, however NAT would welcome the views of other health professionals who have worked/are working with asylum seekers living with HIV.

The questionnaire can be downloaded at www.nat.org.uk.

Please contact NAT policy officer Hannah Bate on 020 7814 6756 for further information, or email:

hannah.bate@nat.org.uk

Completed copies of the survey need to be returned by Monday 17th October to the same email address, or by post to National AIDS Trust, New City Cloisters, 196 Old Street, London EC1V 9FR.

Thank you for your help.

CONFERENCE REPORTS

Further Reports from 3rd IAS Conference on AIDS Pathogenesis and Treatment

Rio de Janeiro, Brazil, 24-27 July, 2005

The following two articles from HIVandHepatitis.com cover the hepatitis coinfection and the resistance studies presented at this conference.

Abstracts can be accessed free online via:

i) the conference schedule planner

<http://www.ias-2005.org/planner/>

This link via the 'programme at a glance' planner to each section of the programme. It includes online links to most of the individual abstracts and some of the powerpoint presentations used for the oral sessions.

ii) the 'abstracts on demand' website

<http://www.abstractsondemand.com/ias2005>

Although there is a commercial aspect to the site, you do not need to log in or create an account to use the site. Individual abstracts are searchable and readable online without charge – select the option to make a new book but don't proceed to checkout.

iii) the AEGiS conference database

<http://www.aegis.org/conferences/iashivpt/2005>

The AEGiS online conference database will provide all abstracts online, and although the full programme had not been archived by the time we went to press, it is expected to be available shortly. Careful proofing undertaken by AEGiS often means that many abstracts are more accurate on this excellent non-commercial website.

Management of hepatitis C and B in HIV-coinfected individuals: an overview of studies presented at the 3rd IAS Conference

Mark Nelson and Laura Waters, for HIVandHepatitis.com

Introduction

Although the advent of HAART has resulted in a considerable reduction in mortality and morbidity associated with HIV infection, advances in the management of hepatitis B and C both in mono- and co-infected patients continues to somewhat lag behind. This is particularly true for those coinfected with HIV and HBV or HCV, despite the high incidence of coinfection worldwide.

Liver disease remains a major cause of mortality amongst HIV-infected individuals living in developed countries with access to HAART, as well as being a significant cause of morbidity in coinfected individuals.

The 3rd International AIDS Society Conference in Rio de Janeiro included a number of presentations on coinfection, particularly HCV with new subanalyses of the APRICOT trial, and new data on the safety of antiretrovirals (ARVs) in coinfected individuals. Several epidemiological studies highlighted the high rates of concomitant HCV and HBV in HIV-infected subjects and the need for enhanced vaccination programmes in emerging HIV populations.

Unless otherwise stated, all references in this article are to the Program and abstracts of the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment. July 24-27, 2005. Rio de Janeiro, Brazil.

Epidemiology of HCV

The difficulties of instituting risk reduction programmes amongst intravenous drug users (IDUs) were outlined in a poster by Aquino et al. [1] Low rates of HIV infection (approximately 1%) in a Philippine IDU population led to a reluctance from the local authorities to support risk management programmes. The authors used HCV testing as a marker of risky injecting practice and 80% tested positive for HCV antibody.

Hadi et al performed a prospective follow-up amongst an IDU population in Pakistan. [2] Levels of baseline HCV and HIV infection were 42% and 3.4% respectively amongst the 500 individuals recruited to the study and the group reported high levels of risky behaviours such as sharing of injecting equipment. During follow-up the incidence of HCV and HIV were calculated to be 22 and 1.7 cases/100 person years.

Gabelia et al analysed the risk factors for HIV and HCV infection in 2406 adults in Georgia, including over 900 IDUs. [3] High injecting frequency and sharing of drug using equipment were strongly associated with HCV positivity (overall rate in IDUs 58.2%), as was previous imprisonment. Rates of HIV infection in the IDU population were much lower at 0.5% and there appears to be a low rate of spread of the infection in this group. This contrasts with a longitudinal study in Vancouver suggesting increasing HIV incidence amongst IDU over the last decade. [4]

Armenia, until recently, had no access to ARVs. 74 HIV-positive patients were screened for eligibility for therapy (based on CD4 count and symptoms) and 29/74 were diagnosed with HCV, highlighting the high rates of HCV coinfection in many regions and the increased risk of complications secondary to disease progression and drug associated toxicity in the dual infected population. [5]

An Argentinean cohort analysis by Fay et al assessed the frequency of HCV antibody positivity in 250 HIV infected patients between 1997 and 2004. Forty-eight per cent were coinfected with HCV, 87.5% of whom had evidence of active disease; HCV RNA detectability was not related to risk group. Genotype 1 was the most prevalent subtype (72%), again not influenced by risk group. Fifteen per cent of HCV infected individuals were found to have a positive HCV RNA but negative antibody leading the authors to recommend HCV RNA testing as a screening test in this population. [6]

Finally, a prospective serological study of 312 individuals attending an out-patient unit in St Petersburg detected coinfection with HIV and either HCV or HBV in 37%; in total 27.1% tested positive for HIV-1 antibody and 26.9% of these had a positive HBV surface antigen and 80.8% a positive HCV antibody (over 75% of these individuals had a positive HCV RNA). This study reiterates the frequency of HIV/HCV coinfection in many populations. [7]

In contrast, a Romanian study by Benea et al found relatively low rates of HCV infection in their HIV-positive cohort (6.82%), reflecting the low levels of IDU-associated infection. [8]

Silva et al found that in a cohort of 2005 individuals 48% had not been screened for HCV and of those who had undergone testing, 10.9% were HCV-positive. All clinicians should test newly presenting individuals for hepatitis A, B and C, and vaccinate and retest as appropriate. [9]

HCV therapy

It is well established that rates of success when treating HCV are lower in those coinfected with HIV than in mono-infected individuals. Neumann et al studied HCV kinetics in an attempt to predict rates of sustained virological response (SVR) in

a group coinfecting with HIV and HCV (genotype 1). Twenty-three patients (11 Caucasian and 12 African-American) were treated with weekly Pegylated interferon alpha-2b (PegIntron) dosed at 1.5mcg/kg and 1200mg ribavirin once daily for 48 weeks. [10]

HCV RNA quantification assays were performed to monitor viral kinetics during therapy. The results revealed a rapid early phase decline in HCV RNA between day 1 and 3 followed by a transient day 3-7 rebound in 22/23 patients. The day 1-3 decline and the mean decline at day 7 were significantly greater in Caucasians.

A second phase decline occurred between week 1 and 4, again significantly faster in Caucasians; this second decline correlated with viral load at day 3 ($p < 0.003$).

A number of factors were found not to correlate with viral kinetics including age, gender, baseline ALT and CD4 cell count. Sustained viral response (SVR) was achieved in 4/21 patients; absence of SVR could be predicted with 100% negative predictive values by a viral load > 5 log copies/mL at day 28 or day 3.

High rates of HCV RNA clearance in response to weekly Peg-IFN (Alpha-2b) 1.5mcg/kg and daily ribavirin (800-1000mg/day) were demonstrated in an open-label, prospective study amongst 17 HIV/HCV coinfecting individuals in Moscow. [11]

In this population, 87% were IDUs and approximately 50% were HIV virologically controlled on HAART. Eleven patients (65%) achieved biochemical and virological response at 4 weeks (defined as transaminase normalisation and negative HCV RNA respectively) and 15 (88%) had negative HCV RNA levels at 12 weeks. The same number had an undetectable HCV RNA at the end of therapy, and of the nine who were followed-up to 48 weeks, all remained undetectable. Only 2 (15%) discontinued therapy prior to 24 weeks. The genotypes were not specified.

In order to assess the impact of adverse events (AEs) on rates of treatment success in HIV/HCV coinfection, Sulkowski et al analysed data from APRICOT. [12]

This trial compared three therapeutic strategies, pegylated interferon alfa-2a (PEGASYS) with ribavirin, peginterferon alone and standard interferon with ribavirin, all for 48 weeks duration. 'Safety events' included treatment-related serious adverse events (AEs), premature withdrawal secondary to AEs, laboratory abnormalities (neutropenia, thrombocytopenia and anaemia) and depression; Sustained viral response (SVR) was defined as HCV RNA < 50 IU/mL at the end of follow-up (week 72).

Among patients treated with peginterferon/ribavirin, treatment-related AEs and AEs leading to withdrawal of therapy were associated with the greatest reductions in SVR rates; laboratory abnormalities and depression had minimal impact on SVR in this group. These results suggest that the prevention or treatment of AEs may improve rates of SVR to HCV treatment.

Another analysis of APRICOT was presented by Lissen et al. Following the superior SVR rates achieved with peginterferon/ribavirin compared with peginterferon monotherapy and conventional interferon plus ribavirin, they analysed the histology of individuals with baseline bridging fibrosis or cirrhosis. All individuals fulfilling these histological criteria at baseline, with paired biopsy samples (15 months or less prior to randomisation and 56 or more days after treatment) were included in the analysis. Biopsies were rated using the Ishak-modified system to assess changes in histological activity index (HAI) or fibrosis score. [13]

Overall, peginterferon/ribavirin was shown to have the greatest impact on fibrosis and HAI scores with a mean reduction of 0.2 (SD 1.5) and 2.5 (SD 2.7) respectively. The greatest improvements were achieved in cirrhotic patients, with a mean reduction in HAI of 3.3 (SD 3.5) and in fibrosis score of 0.6 (SD 1.3). Histological response (HR) was shown to be independent of SVR; HR was seen in 80% of individuals with SVR but also in 58% of those who failed to achieve SVR. The lowest HR was observed in the peginterferon monotherapy arm.

This study supports the use of therapy even in patients with advanced HCV infection as improvements in HAI and fibrosis can be expected. The lack of association between histological response and SVR may support full treatment courses even in individuals who experience a suboptimal viral response at 12 weeks.

Also extracted from the APRICOT database, Soriano et al analysed the rates of SVR achieved with peginterferon/ribavirin in subjects infected with HCV genotype 4. In HCV mono-infection similar, relatively poor SVR rates are seen in genotype 1 and 4 infection. In APRICOT only 7% (60/860) of individuals had genotype 4 and 38% of this group experienced SVR; SVR rates were influenced by baseline viral titre (27% SVR if $> 800,000$ IU/ml and 60% if $< 800,000$ IU/ml). [14]

Overall, the SVR rate in those with genotype 4 was similar to the overall rate seen in APRICOT (40%), suggesting slightly higher SVR rates for genotype 4 than genotype 1.

Interferon and HIV replication

Neumann et al studied HIV kinetics in 23 HIV-infected patients coinfecting with genotype 1 HCV (mean CD4 cell count 612 cells/mm³) receiving peginterferon alfa-2b and ribavirin for 48 weeks. In the nine subjects with a detectable HIV RNA there was a steady decline in HIV viral load during the first week of HCV therapy and the authors suggest that this is indicative of interferon suppressing de-novo HIV infection; in vitro studies are ongoing. [15]

Liver biopsy in patients with normal ALT

The question of whether liver biopsy is useful in individuals with normal liver function tests remains controversial. Sanchez-Conde et al performed liver biopsy in 256 HIV/HCV coinfecting subjects over a 5-year period. 9.4% had a persistently normal ALT (PNALT) defined as two or more normal measurements within 6 months and their biopsy results were compared with those in individuals with elevated ALTs. PNALT was found to correlate with lower fibrosis scores ($p<0.001$) but approximately 1 in 4 had significant fibrosis (F2), supporting the use of liver biopsy in patients with PNALT. [16]

Treatment of acute HCV

Increasing detection of acute HCV infection has raised interest in early treatment. HIV negative individuals have very high rates of HCV clearance, approaching 100%, when treated with standard interferon alone.

A group of 50 gay men attending the Chelsea & Westminster hospital were diagnosed with acute HCV infection (44 during investigation for liver enzyme abnormalities, 4 following sexual contact with an HCV-infected partner and 2 during screening at HIV seroconversion). Sequential HCV RNA measurement was performed at 0, 4, 12, 24, 32 and 48 weeks; 24 weeks therapy with 1.5mcg/kg/week Peg-IFN (alpha-2b) and weight-adjusted ribavirin was offered to subjects who after 12 weeks had a positive HCV-RNA or earlier in the face of a rising RNA level. [17]

12 individuals became HCV-RNA negative spontaneously; this was significantly associated with a higher median CD4 count ($p=0.029$), CD4 count >500 ($p=0.017$) and lower HCV RNA level at diagnosis ($p=0.017$). Of those offered treatment, 27 accepted and 16 (59%) experienced SVR; SVR was associated with a higher peak mean ALT ($p<0.001$) but not with genotype.

This study demonstrated a high level of spontaneous HCV seroconversion but lower rates of SVR compared to the results achieved in HIV-negative subjects. The factors associated with spontaneous clearance of HCV-RNA have not been clearly elucidated.

Grebely et al analysed data from the CHASE Project, a prospective cohort study in Vancouver in an area with high rates of injecting drug use. 523/1202 HCV antibody positive subjects underwent HCV-RNA testing between 1991 and 2004. [18]

Excluding individuals who had undergone HCV treatment previously, the analysis revealed a negative correlation between HIV infection and spontaneous HCV clearance (adjusted OR 0.41; $p=0.007$). Reinfection was observed in 5.7% of those achieving spontaneous HCV clearance.

Response to HAART in HCV-infected subjects

Although HIV has been shown to accelerate the progression of HCV, a number of previous studies assessing the impact of HCV coinfection on HIV disease have yielded conflicting results. Sullivan et al performed a retrospective, multicentre analysis of patients commencing HAART between 1998 and 2003. They analysed changes in viral load and CD4 cell count to test the hypothesis that viral load reduction during the first 30 days of HAART and CD4 rise during the first year differ in HIV-positive individuals with and without HCV. [19]

Eighteen per cent of the 1531 subjects included were coinfecting with HCV but this was not associated with attenuation of virological or immunological response to HAART; the only patients to experience inferior response to ARVs were those with coinfection and previously diagnosed alcoholism.

The difficulties in assessing the impact of HCV on response to HAART were highlighted by the CASCADE collaboration. Pre-HAART (i.e. pre-1996) data from 22 HIV-seroconverter cohorts were pooled to assess the effect of HCV on time from seroconversion to death and on virological response to HAART. [20]

6053 seroconverters were included, 1405 of whom died. 22%, 25% and 53% were HCV-positive, negative and untested respectively. After adjustment for known prognostic factors, previous ARVs and baseline HIV viral load, a positive HCV antibody was associated with a significantly lower risk of death compared with the untested population (RR=0.18; $p<0.001$).

2322 individuals subsequently commenced HAART of who 22%, 42% and 36% were HCV-positive, negative and untested. $>90\%$ of IDUs were coinfecting compared with $<16\%$ in other groups, and after adjusting for IDU status there was no effect of HCV on likelihood of achieving an undetectable viral load ($p=0.69$).

The authors conclude that HCV positivity may contribute to the inferior virological responses seen in IDUs but the high prevalence of HCV in this group makes it difficult to assess accurately.

In another study, Moore et al performed a survival analysis on 721 HIV mono-infected and 673 HIV/HCV coinfecting patients initiating HAART between 1999 and 2003. Crude mortality rates were 8.6% and 18.1% in the mono and coinfecting groups respectively ($p<0.001$). After adjustment for age, VL, IDU status and adherence to HAART the baseline CD4 associated with increased mortality were similar for HIV/HCV coinfecting individuals compared with those infected with HIV alone. This was interpreted as suggesting no benefit to earlier HAART for HCV coinfecting subjects. [21]

Impact of HCV on HIV

A number of cohort analyses have suggested an increased risk of non-Hodgkin's lymphoma (NHL) in HCV monoinfected populations. NHL is greatly increased in HIV-infection and a UK cohort analysis examined the relationship between HCV and NHL in HIV-infected individuals. 102 cases of NHL occurred in 5832 HIV-infected subjects but the incidence of NHL did not differ between those with HIV/HCV coinfection and those with HCV alone. [22]

HAART pharmacokinetics in coinfecting patients

In the cross-sectional HEPADOSE Study the C_{min} of various ARVs were compared between 66 HIV monoinfected and 73 HIV/HCV coinfecting patients. The coinfecting group had all undergone liver biopsy within the last 2 years and the groups were matched for sex and antiretroviral agents. [23]

The median C_{min} for protease inhibitors were similar in the coinfecting and monoinfected individuals except for Lopinavir (LPV) which was found to be significantly lower in the coinfecting group ($p=0.04$). For NNRTIs, efavirenz/EFV (Sustiva) and nevirapine/NVP (Viramune) concentrations were both higher in the presence of coinfection and these elevations correlated significantly with hepatic fibrosis score; stage F4 fibrosis was correlated with an 86% increase above the expected concentration in NNRTI C_{min} and stage F0-3 with a 56% elevation ($p=0.01$).

In summary, lopinavir levels were unexpectedly decreased and NNRTI levels increased in HIV/HCV coinfecting patients; the authors recommend the use of TDM in this population.

However, another analysis of lopinavir/ritonavir (LPV/r; Kaletra) pharmacokinetics, presented by Dickinson et al, quantified LPV concentrations in 39 patients: 13 HIV monoinfected, 26 HBV or HCV coinfecting of whom 7 were cirrhotic. The area under the curve (AUC) for both total and unbound LPV levels was unchanged in the coinfecting group. [24]

Safety of ARVs in coinfecting patients

Coinfection with HIV and HBV or HCV may increase the risk of ARV-related hepatotoxicity and a number of studies addressed this issue.

The impact of single PI, boosted PI and NNRTI based therapy on liver enzymes in HIV/HCV coinfection was assessed Torti et al. Prospectively collected data from an Italian cohort of 1038 HIV/HCV coinfecting individuals was used to construct a multivariate model including ARV history, HBV status, CD4 and VL. [25]

In naïve patients ($n=155$) the risk of grade 3/4 transaminase elevation was 17.1% per patient year; baseline ALT (HR=1.118; $p=0.029$) and CD4 increment (HR=1.112; $p=0.045$) were the only factors significantly associated with hepatotoxicity.

Hepatotoxicity incidence and risk factors differed in experienced patients ($n=883$). 8.22% per patient year developed grade 3/4 AST/ALT rise; baseline ALT (HR=1.137 per 10 IU/l; $p<0.001$), previous hepatotoxicity (HR=3.051; $p<0.001$) and NNRTI use (HR=2.752; $p<0.001$) were significant risk factors; nevirapine was associated with a greater risk of hepatotoxicity than efavirenz.

The authors advised strict monitoring in ARV-experienced patients with elevated ALT, previous hepatotoxicity or on NNRTI-containing regimens.

In contrast, Konopnicki et al found that PI and NRTI agents but not NNRTIs were associated with hepatotoxicity in HIV-infected individuals with chronic hepatitis. Of the 293, 770 and 488 subjects starting a triple NRTI, PI-based or NNRTI-based regimen respectively, 13% were HCV and 5% HBV coinfecting. A >2 grade increase of at least one liver enzyme was more frequent in the coinfecting than monoinfected group on a PI (24% vs 12%; $p=0.0004$) or triple-NRTI (14% vs 4%; $p=0.02$). [26]

Multivariate analysis of the PI group revealed chronic hepatitis to be an independent risk factor for hepatotoxicity (OR 1.87; $p=0.02$) while female sex (OR 0.42; $p=0.002$) and CD4 >250 cells/mm³ (OR 0.47; $p=0.004$) were protective. Single or ritonavir-boosted PI based therapies were not associated with hepatotoxicity in naïve or experienced coinfecting subjects.

DeJesus et al presented data confirming the safety of ritonavir-boosted fosamprenavir/ FPV/r (Lexiva) in therapy naïve individuals coinfecting with HBV or HCV. Subjects coinfecting with HBV or HCV could be enrolled into the SOLO study if hepatic transaminase levels were not in excess of 5 x ULN within 28 days of randomisation. [27]

322 patients enrolled in the SOLO study were randomised to receive fosamprenavir/r and 211 continued into APV30005 (the SOLO rollover); a subanalysis assessed liver enzymes and adverse events. 45/211 (21%) were hepatitis coinfecting at study entry, 20 (9%) with HBV (surface antigen positive) and 26 (12%) with HCV (HCV antibody positive).

Median baseline ALT and AST were higher in the coinfecting patients but there was a median decrease in liver transaminase levels by week 120 in both patient groups; by week 120 5/164 (3%) of monoinfected and 13/45 (29%) had experienced a grade 3/4 ALT rise; however, only 3 new cases developed in each group after week 48.

Of note, there were two new cases of grade 3/4 AST elevation in the monoinfected subjects but none in the coinfecting group. Over 120 weeks the numbers experiencing drug-related AEs overall were similar in the two groups. Forty-four per cent of

the coinfecting individuals experienced a grade 2-4 drug-related AE compared with 43% of those infected with HIV alone; the rates of serious drug-related adverse events were 11% and 10% respectively.

Overall the authors concluded that ritonavir-boosted fosamprenavir administered once daily had similar rates of side-effects in HIV monoinfected and coinfecting subjects; at 120 weeks there was a median decrease in transaminase levels in both groups.

The safety of abacavir (ABC) plus lamivudine (3TC) based HAART in naive subjects was assessed by Zhao et al in an analysis of 4 randomised trials using ABC/3TC once or twice daily in combination with efavirenz (EFV) or a PI. [28]

Safety data were compared between individuals coinfecting with HBV (positive s-antigen) or HCV and those with HIV monoinfection. Twenty per cent of the 1985 subjects included were coinfecting with HBV and/or HCV. Baseline characteristics in the two groups (coinfecting vs monoinfected) were similar, as was the overall incidence of AEs with 71% in each group reporting grade 2-4 AEs over 48 weeks. In addition, the incidence of specific AEs was also comparable.

Atazanavir (Reyataz) safety was assessed by Perez-Elias et al by comparing 180 coinfecting ('Hep') and 124 monoinfected ('noHep') prospectively recruited into an early access study of ritonavir-boosted atazanavir (ATV/r) based HAART. 67% Hep and 73% noHep individuals reached at least 6 months of follow-up. [29]

Similar rates of virological success (<500 copies/mL) were achieved in both groups (approximately 75%) with 9.4% Hep and 5.6% of noHep patients discontinuing treatment secondary to AEs. Only three individuals (1.7%) were withdrawn for elevated liver enzymes.

With respect to scleral icterus and jaundice, 4.4% of the Hep group and 3.2% the noHep group discontinued therapy for this reason. Overall ATV/r-based HAART was concluded to be a safe treatment option for those coinfecting with HBV or HCV.

Ammassari et al prospectively monitored transaminase and plasma drug levels in 251 patients commencing HAART. Overall, liver enzyme elevations were more frequent in patients reporting poor adherence and those with suboptimal or undetectable drug levels. No particular group of ARVs was associated with raised ALT though in multivariate analysis, HCV coinfection and duration of ARV exposure were (RR=2.71; p=0.04 for HCV, RR=1.44 per year of ARV exposure; p=0.001). [30]

The same study showed no difference in hepatotoxicity in patients receiving NNRTIs or lopinavir/r, there was also no relationship between liver enzyme elevations and trough NNRTI levels.

To specifically address the issue of HAART-related hepatotoxicity in HIV/HCV coinfecting individuals with advanced liver disease, Aranzabal et al prospectively followed 195 individuals undergoing liver biopsy between 2000 and 2004. [31]

They found HAART-associated hepatotoxicity to be closely related to HCV-related histological liver damage.

The presence of HBV surface antigen (p=0.01), increased baseline ALT (p=0.04) and longer duration of HCV infection (p<0.01) were associated with more advanced (grade 3-4) fibrosis. Forty-seven per cent of patients developed hepatotoxicity, which, after adjusting for alcohol abuse, was more frequent in those with grade 3-4 than 1-2 fibrosis (5 vs 2.3 cases/100 person years; p=0.02). HIV viral load, CD4, HCV RNA and HCV genotype were not associated with the risk of hepatotoxicity.

In the HEPATOX study presented by Aranzabal et al 246 individuals who started HAART in 2004 were prospectively monitored for hepatotoxicity. No associations with age, sex, risk group, baseline CD4 or CD4 increment were detected and only HCV was found to be independently associated with liver enzyme elevations (RR=3.3; p<0.01). The overall rate of hepatotoxicity was 4% over 100 days. [32]

Finally, in contrast to the above study, liver disease but not HCV was shown to be predictive of HAART discontinuation by Uberti-Foppa et al. A multivariate analysis of 526 patients commencing HAART found liver disease (low albumin), but not HCV per se, to be associated with an increased risk of stopping therapy. [33]

Neuropsychological function (NF) in HIV/HCV coinfection

The suggestion that HIV/HCV coinfection may be associated with greater impairment in NF than HIV alone was explored by Munoz-Moreno et al. In a descriptive, observational study of 50 patients (10 coinfecting) NF, anxiety and depression scores, premorbid intelligence and contributing HIV-related factors were assessed. A number of differences were elicited between the two groups and HIV/HCV coinfecting subjects showed significant impairment in a number of functions compared with their monoinfected counterparts. [34]

ARVs and HCV RNA

In order to determine the effect of ARVs on HCV replication Braitstein et al performed HCV RNA tests on 118 HCV antibody-positive/RNA-negative individuals 6-12 months after commencing ARVs. 20% (24/118) became RNA-positive suggesting that HIV therapy may affect HCV replication with increased replication occurring as part of immune restoration disease. This finding which is difficult to explain needs to be assessed in other cohorts. [35]

HBV epidemiology

The afore-mentioned study by Benea et al also calculated the prevalence of HBV infection in their HIV cohort. Nearly 40% had at least one marker of HBV infection and 13.53% were surface antigen positive.

Similar rates of active HBV infection (14.8%) were found in a Nigerian clinic by Agbaji et al. This is an important issue in countries where agents active against HBV may not be routinely available. [36]

A Brazilian HBV/HCV prevalence study found that almost 28% of HIV-infected individuals had not been screened for serological markers of HBV. 45.9% remained susceptible to HBV emphasising the importance of screening for, and vaccinating against, HBV. Likewise, a retrospective analysis in Venezuela found 70% of the 733 screened for HBV to be in need of vaccination.

HBV prevention

Vaccination against HBV is established as a safe and efficacious method to protect against acquisition of HBV in high-risk groups. Health care workers are amongst those for whom routine vaccination is usually recommended. A study of health care workers (HCWs) in Uganda found that 74% had not been tested for, or vaccinated against, HBV. A survey of HCWs in Pakistan reported that 60% had experienced one needle stick injury over an average of 5 years but only 50% were HBV vaccinated.

Sud et al confirmed previous analyses showing the success of HBV vaccination in HIV-infected individuals depends on CD4 cell count at time of vaccination. Subjects with a CD4 count <200 (n=13) produced lower titres of sAb than those with a CD4 count >200 (n=27); p<0.05. However, even those with a CD4 count >200 achieved lower titres than HIV negative controls (n=20; p=0.05). [37]

Impact of HAART on liver-related death

Liver disease has emerged as the most frequent cause of mortality in the HAART-era in a number of studies and a common cause of morbidity in HIV-infected individuals.

Sanchez-Somolinos et al (abstract TuPe1.1C32) performed a retrospective review of hospital admissions in 2514 patients between 1996 and 2004, the majority of whom were IDUs (82%). Decompensated chronic viral liver disease (CVLD) was either the cause of or developed during admission in 14% overall and increased significantly between 1996 and 2001 (9.1% vs 15%) but decreased significantly between 2001 and 2004 (11%). The same was found to be true for liver-related deaths, accounting for 9%, 53% and 23% of mortality in 1996, 2001 and 2004 respectively. Admissions secondary to HAART-related hepatotoxicity increased after 2000. [38]

Puoti et al performed an analysis of 13 cohorts of HIV/HBV coinfecting patients who commenced HAART with liver related death (LRD) as the study end-point. The investigators defined LRD as death with concomitant decompensated liver disease (DLD) or hepatocellular carcinoma (HCC) in the absence of other causes, and calculated the impact of lamivudine (3TC) on LRD. 2041 individuals were included in the analysis amounting to 7648 patient years of follow-up on HAART, 5569 of those years 3TC-containing. [39]

There were 217 deaths during the study period and 57 of these were defined as LRD; 38/57 had information available on previous liver morbidity and 21 (55.3%) of these had experienced DLD or HCC. A model was constructed including the 57 subjects with LRD. The relative risk of LRD per year of 3TC use was calculated to be 0.73 (95% CI 0.59-0.90; p=0.004).

Other factors significantly associated with LRD were age with significantly greater LRD per 10 years (p=0.003) and low CD4 cell count (per 100 cell reduction; p=0.0001). The impacts of other nucleoside analogues (AZT, d4T, ddI and ddC) were analysed and none were found to be associated with the rate of LRD (p-values 0.1, 0.84, 0.97 and 0.28 respectively).

The authors concluded that the use of 3TC within HAART is associated with a reduction in LRD in HIV-infected subjects coinfecting with HBV or HCV over a 4 year period but acknowledge that longer-term data are needed to verify this benefit despite the development of the YMDD mutation.

In another presentation, Puoti et al prospectively followed 812 individuals from 1997/1998 amounting to over 4000 patient years of follow-up. 46/129 deaths were liver related and a number of factors were associated including HCV infection (HR=9.2; p=0.0024), HBV infection (HR=2.7; p=0.0025), alcohol abuse (HR=2.7; p=0.0017), occurrence of life-threatening HAART-related hepatotoxicity (HR=5.8; p<0.0001) and HAART initiation at a CD4 <350 cells/mm³. [40]

Use of HAART was found to be independently protective against liver related death (HR=0.31; p<0.0001).

HBV therapy

The use of 3TC (Epiriv-HBV) monotherapy for the treatment of HBV is associated with high rates of 3TC resistance, particularly in HIV/HBV coinfecting individuals. In contrast, HBV resistance to the nucleotide analogue tenofovir/ TDF) is uncommon. Whether initial combination therapy with 3TC and TDF is superior to sequential therapy with 3TC then TDF

has not been determined.

Mauss et al undertook a multicentre 1:2 matched pair study comparing HIV/HBV coinfecting subjects commencing TFV/3TC-containing HAART with patients who had highly replicative, genotypic 3TC-resistant HBV who commenced TFV-based therapy in the absence of other active anti-HBV agents. [41]

Baseline HBV-DNA was similar in the two groups, 56 million copies/mL and 89 million copies/mL in the TFV/3TC (n=21) and TFV-only (n=42) groups respectively (p=0.96). Both groups experienced similar and strong HBV-DNA suppression at 3 and 12 months. Sustained suppression of HBV-DNA (<1000 copies/mL) was achieved in 18/21 (86%) on TFV/3TC and 33/42 (78%) on TFV alone (p=0.74). HBV e-antigen seroconversion occurred in 6/19 on TFV/3TC and 12/38 on TFV (p=0.77) and loss of s-antigen was seen in 1/21 and 4/42 patients respectively (p=0.66).

The investigators concluded that in coinfecting individuals the use of TFV after the development of 3TC resistance was as effective as TFV/3TC in terms of HBV-DNA suppression and e-antigen/s-antigen loss. The durability of these responses will be assessed in continued follow-up.

Occult HBV

Ten to eighteen per cent of individuals with HIV/HBV coinfection develop anti-core antibody (HBVcAb) in the absence of neutralising surface antibody (HBVsAb). 955 patients were screened for HBV markers, including HBV DNA in cAb+/sAb- patients, by Marino et al. 19.9% tested positive for cAb alone; 6.9% had detectable HBV DNA (between 102 and 103 copies/mL). Further follow-up showed HBV DNA positivity to be intermittent and to occur in 14.3% of cAb+/sAb- patients over a 6-12 month period. These individuals did not demonstrate clinical or laboratory abnormalities. The authors advise that longitudinal HBV DNA detectability is required to form a diagnosis of occult HBV infection. [42]

Decompensated liver cirrhosis in HIV-infected patients

A Spanish cohort analysis studied 110 HIV-infected patients who developed Decompensated Liver Disease between 1990 and 2003. Subjects were sub-divided according to date of first decompensation; group A (pre-HAART) 1990-1996 and group B (HAART) 1997-2003 contained 48 and 62 individuals respectively. [43]

Of the 110, 81% were coinfecting with HCV and 34.5% with active HBV. The four commonest initial events were ascites (89%), hepatic encephalopathy (19%), gastrointestinal bleeding (7%) and spontaneous bacterial peritonitis (6%).

Comparison between groups A and B revealed those in group A to be younger (32 vs 38 years; p<0.01), less frequently on ARVs (29% vs 56%; p=0.012) and with lower mean CD4 counts (134 vs 197; p=0.09).

HIV risk factor, cause of cirrhosis, Child-Pugh classification at first decompensation and subsequent complications did not differ significantly between group A and B. Median survival after decompensation was 6 months and significantly associated with Child-Pugh classification.

The cumulative 12-month survival after decompensation was the same for the two time periods, 35% for group A and 34% for B (p=0.85). However, death secondary to liver disease was commoner in the HAART era (81.8% of deaths compared to 60% pre-HAART; p=0.024).

This study confirms the poor survival associated with decompensated liver cirrhosis and highlights the need for rapid consideration of transplant in these patients.

Cicconi et al evaluated the incidence, risk factors and outcomes for decompensated cirrhosis (DC) in the I.Co.N.A cohort. The incidence of DC was 1.85/1000 person years in the 5138 individuals included and not influenced by calendar year after adjustment for other variables. [44]

Factors associated with an increased risk of DC were IDU (RR=17.31 vs heterosexuals; p=0.0005) and increased age (RR=1.66 per 10 years; p=0.06); different ARVs were not found to influence DC risk. DC was shown to be an independent risk factor for death (RR=8.5; p=p<0.0001) with a median survival of 126 days after diagnosis of DC and a 2-year survival rate of 10.8%.

Hepatocellular carcinoma in HIV/HCV coinfection

Since the huge reductions in HIV-related mortality in the HAART-era, longer-term consequences of coinfection have emerged. HCV is associated with a marked increase in the risk of developing hepatocellular carcinoma (HCC).

A European study previously suggested shorter survival in HIV/HCV infection than HCV alone leading Brau et al to perform a retrospective chart review of HCV-infected individuals with HCC with and without HIV co-infection. Forty-one coinfecting HCC cases from 15 US and Canadian centres between 1992 and 2004 were identified and compared with 119 HCV-monoinfected cases during the same period. [45]

Looking at baseline demographics, 99% of the subjects were male. The median CD4 cell count and HIV viral load at time of HCC diagnosis were 273 cells/mm³ and 529 copies/mL respectively.

The results demonstrated a number of differences between the two groups. Mean age at HCC diagnosis was significantly lower in coinfecting than mono-infected subjects (52.4 vs 61.1 years; $p < 0.001$) despite similar ages at HCV infection (25.5 and 23.9 years respectively; $p = 0.46$).

This was mirrored by the duration of HCV infection prior to the development of HCC, 26.4 years in the coinfecting group and 35.2 years in mono-infected subjects ($p < 0.001$).

In addition, amongst coinfecting individuals, median alpha-fetoprotein (AFP) levels were significantly higher (1274ng/ml vs 192ng/ml; $p = 0.02$), rates of portal vein thrombosis were lower (10% vs 26%; $p = 0.03$) and the incidence of multifocal HCC was higher (58% vs 36%; $p = 0.011$).

The study also found that HIV-coinfecting patients were more likely to receive HCC treatment than those with HCV alone (56% vs 36%; $p = 0.025$).

In terms of prognosis the presence of symptoms at diagnosis, HCC therapy and AST/ALT ratio were all predictive of survival in a multivariate analysis.

Elevated AFP levels were only predictive in HCV-mono-infected patients and CD4 cell count and HIV viral load were not associated with survival rates in HIV-coinfecting individuals. There was no difference in survival between mono-infected and coinfecting individuals (83.2% vs 80.5% mortality respectively).

Blood transfusion

The risks of viral blood-borne infections from transfusion of contaminated blood are inarguable. Erhabot et al tested 1500 blood donors in Nigeria for HIV, HBVAg and HCV antibody demonstrating prevalence of 1%, 1.1% and 0.5% respectively; these were higher in remunerated donors (1.45, 1.7 and 0.8%). The authors called for immediate implementation of mandatory and universal donor screening. [46]

Conclusions

Coinfection with hepatitis viruses in the HIV-infected individual continues to be of concern. Although there has been a rapid increase in epidemiological research on this subject, the practicing physician is still hampered by the lack of choice of agents to treat hepatitis infections and whether the results of clinical trials on the mono-infected patient can be translated into the dually infected population.

As new drugs are developed it is important that they are studied in the coinfecting population.

Source: HIVandHepatitis.com 09/09/05

http://hivandhepatitis.com/hiv_hcv_co_inf/2005/ads/090905_feat.html

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Highlights of HIV Drug Resistance Studies Presented at the 3rd IAS Conference

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Issues concerning HIV drug resistance are a growing concern in the treatment and management of HIV infection. In the review that follows, Dr. Ian Frank summarizes selected studies on resistance presented at the 3rd IAS meeting in Rio de Janeiro, Brazil.

Unless otherwise stated, all references in this review article are to the Program and Abstracts of the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment. July 24-27, 2005. Rio de Janeiro, Brazil.

Epidemiology: contacts of the New York City “superinfection” case identified

Early in 2005 a New York City man was identified as an individual with apparent recent HIV infection who had multiple class resistant virus, dual-tropic virus, and experienced rapid disease progression. [1] Two possible contacts, who were sexual partners of this NYC case, were identified independently by Quest Diagnostics and LabCorp after searching their genotyping databases for matches to the unusual mutational pattern of the virus from the NYC case, and traced to an HIV practice in Connecticut. [2]

These two contacts had a history of unprotected insertive intercourse among themselves (phylogenetic analyses of isolates suggests that one individual may have acquired the particular resistance profile of the other by superinfection), and admitted to unprotected intercourse with the New York City case at a sex club.

Although neither of these individuals experienced rapid disease progression and both had R5, rather than mixtures of R5 and X4 phenotypes or dual tropic virus, the epidemiologic evidence for transmission of this uniquely resistant virus is strong.

The authors take-home messages were that: the community must continue to be educated that safer sex practices are important among infected individuals; that the HIV uninfected community should not misconstrue the benefits of today's antiretroviral therapy to believe that becoming HIV infected means just taking a few pills a day, and that your genotype may be able to identify you as easily as your social security number.

Infection with resistant virus is not associated with more rapid disease progression

Motivated by the New York City case, a group of European investigators evaluated whether infection with resistant virus was associated with more rapid disease progression. [3]

A case control study was performed using a prospective, multicenter cohort of 1415 individuals diagnosed in 2003. Seventy-eight individuals were identified at presentation with at least one primary resistance associated mutation, based upon the IAS-USA resistance algorithm. These cases were compared to 77 randomly selected controls matched by baseline viral load and CD4+ count with sensitive virus.

Median baseline viral loads and CD4+ counts were 4.8 log copies/mL and 359 cells/mm³ in the cases (resistant virus) and 4.7 log copies/mL and 365 cells/mm³ in the controls. Subjects were followed for a median of 16 months for the development of one of three endpoints; fall in CD4+ count to <200 cells/mm³, new AIDS-defining clinical illness, or initiation of therapy.

During follow-up, 17 subjects with resistant virus started therapy, two experienced CD4+ cell count declines to <200 and one developed an AIDS-defining event, compared to 28 subjects with sensitive virus who started therapy, one had a CD4+ count decline to <200, and two developed an AIDS-defining event. There are no statistically significant differences in immunologic or clinical disease progression between the two groups. These data suggest that individuals who get infected with resistant virus have similar disease progression as those who get infected with sensitive virus.

New mechanisms for NRTI resistance: mutations in the RNase H encoding region

As reverse transcriptase (RT) constructs a DNA strand, the RNase portion of the enzyme is simultaneously degrading the RNA template. New data suggests that mutations in the portion of the RT genome that encodes the RNase H domain influence susceptibility to the thymidine analogs zidovudine (ZDV; Retrovir) and stavudine (d4T; Zerit). [4]

To date the number of RNase H sequences available in the GenBank database are relatively few, and the commercially available genotyping resistance assays do not amplify the RNase H domain (amino acids 441 – 560). For this reason, the influence of RNase H on susceptibility to NRTIs has not been carefully evaluated.

In vitro, site directed mutants in RNase H increased the IC₅₀ value of wild type virus to ZDV and d4T by 10- to 100-fold. These mutations conferred synergistic levels of resistance when combined with thymidine analog mutations (TAMs).

To evaluate whether mutations in RNase H contribute to RT resistance in patients, RNase H sequences from NRTI-experienced and naïve subjects were cloned and sequenced, and then inserted into a wild RT genome, replacing the WT RNase, which could be used to test the phenotypic susceptibility of recombinant isolates.

Among patients with RT sequences that were wild type for RT mutations in the pol gene associated with resistance, treatment

experienced patients had RNase sequences that were associated with 2.4- to 5.7-fold resistance to ZDV and 1.0- to 1.8-fold resistance to d4T, in some cases, clinically significant levels of resistant.

In contrast, the RNase sequences from treatment naïve patients had no impact on phenotypic susceptibility, suggesting that treatment may have selected for virus with RNase sequences that impart some phenotypic resistance independent of that associated with mutations in other areas of the pol gene.

The level of phenotypic resistance was amplified in treatment-experienced patients with TAMs. The RNase H sequence from one subject with TAMs conferred 1839-fold resistance, compared to 11-fold resistance with a wild type RNase sequence.

The mechanism by which RNase H mutations cause RT resistance is not known, but is hypothesised to occur by delaying RT processivity, thereby increasing the time that excision of the terminal nucleotide could occur. More studies need to be done to investigate whether RNase mutations may be associated with resistance to non-thymidine analogs and what mutations in RNase H may be clinically significant, to ultimately determine whether genotyping and phenotyping assays need to be designed to include an evaluation of RNase H.

NRTI resistance: absence of K65R in subjects failing tenofovir in GS934

GS934 was an open-label comparison of tenofovir (Viread), emtricitabine (Emtriva), and efavirenz (Sustiva) versus fixed dose zidovudine/lamivudine and efavirenz in antiretroviral naïve subjects. Subjects who received tenofovir + emtricitabine had better virologic outcomes in the intent to treat analysis. In Rio, data on the mutational analysis in subjects with virologic failure were presented and are summarised in the accompanying table. [5]

Table 1: Resistance in GS934*

	TDF + FTC + EFV (n = 244)	ZDV/3TC + EFV (n = 243)
Resistance analysis	12 (5%)	23 (10%)
Resistant virus	n	n
Any mutations	9	17
EFV-R	9	16
M184V/I	2	7
Any TAM	0	1
K65R	0	0
WT or as baseline	3	5

*Excluding subjects with resistant virus at baseline

Mutations were not identified in every subject, some of whom rebounded with wild type virus. As expected, the majority of subjects with resistant virus had NNRTI resistance. A greater proportion of subjects developed I84V/I on 3TC than FTC, though those numbers are not statistically significant. In contrast to GS903, a comparison of TDF, 3TC (Epivir), and EFV versus d4T, 3TC, and EFV, in which 8 subjects of 47 subjects (17%) with virologic failure in the TDF arm had virus with a K65R mutation (one subject in the d4T arm developed K65R) [6] no subjects in GS934 failing on tenofovir developed K65R. Whether the long half-life of FTC can “protect” against the selection of K65R will be determined with data from larger studies currently underway.

PI resistance: establishing the clinical cutoffs for atazanavir and tipranavir

Rick Pesano from ViroLogic provided data describing the establishment of the clinical cutoffs for the protease inhibitors (PI) atazanavir (Reyataz) and tipranavir (Aptivus) relevant to their Phenosense assay. [7]

The clinical cutoff for unboosted atazanavir was derived from specimens available from the BMS 043 trial, a comparison of unboosted atazanavir versus fixed dose lopinavir/ritonavir in patients with previous virologic failure on a PI-containing regimen. The clinical cutoff for boosted atazanavir was derived from specimens available from BMS 045, a comparison of boosted atazanavir versus fixed-dose lopinavir/ritonavir.

The clinical cutoff for unboosted atazanavir is 2.2 (corresponding to approximately 3 mutations), and for boosted atazanavir, it is 5.2 (corresponding to approximately 5 mutations). The clinical cutoff for boosted tipranavir is 4.0, corresponding to approximately five mutations.

Source: HIVandHepatitis.com
http://hivandhepatitis.com/recent/ad/090905_b.html

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ANTIRETROVIRALS

GSK stops trials of CCR5 entry inhibitor GW873140 in naïve patients

September 15, 2005 - GlaxoSmithKline (GSK) is informing you that we are making changes to the development program for the investigational CCR5 entry inhibitor, aplaviroc (GW873140), due to safety data observed in Phase IIb studies. GSK has received reports of severe hepatotoxicity with elevated liver enzymes (AST, ALT) and total bilirubin in clinical trials involving treatment-naïve patients. GSK has taken immediate steps to protect the welfare of patients in clinical studies of aplaviroc.

After review of these liver toxicity findings with the US Food and Drug Administration, GSK has terminated the aplaviroc clinical trials in treatment-naïve patients. In addition, GSK is amending its ongoing Phase III studies in treatment-experienced patients to implement additional safety monitoring requirements and changes to patient inclusion/exclusion criteria. Treatment-experienced patients already enrolled in the Phase III studies may elect, in discussion with their physician-investigator, to continue on their study medication, but will be monitored closely for signs or symptoms of hepatotoxicity and/or elevations in liver function tests.

Clinical trial investigators and their review boards have been notified of the situation and how to handle the treatment of the patients involved. A protocol amendment for Phase III studies involving treatment-experienced patients will be forthcoming in the next week and will include a revised informed consent form.

"GSK is committed to excellence in the care of individuals with HIV infection, and we are taking all necessary steps to protect the safety and health of these clinical trial participants," said Lynn Marks, MD, Senior Vice President, GSK Medicine Development Centre, Infectious Diseases. "While we are stopping our work in treatment-naïve patients, we are proceeding cautiously with treatment-experienced HIV patients who need new treatment options. We are working closely with regulatory authorities, the clinical trial sites and the patients involved in these studies. Patient safety remains our major focus."

Source: GSK statement to HIV patient community: Information from GlaxoSmithKline on Changes to Studies of Investigational CCR5 Entry Inhibitor Aplaviroc (GW873140).

AZT comes off patent: generic versions approved for US market

On 17 September 2005, AZT, the first approved antiretroviral drug, manufactured and marketed by GSK, came off patent. On 19 September, the FDA approved several generic formulations of AZT for the US market.

Previously, the products had been only tentatively approved and were not available in the United States because patent or market exclusivity blocked their approval for domestic marketing. With the expiration of those patents, the following products from two Indian and one US manufacturer have received full marketing authorisation for the United States:

- i) zidovudine tablets, 300 mg, manufactured by Ranbaxy Laboratories
- ii) zidovudine tablets, 300 mg and oral solution, 50 mg/5mL, manufactured by Aurobindo Pharma
- iii) zidovudine tablets, 300 mg, manufactured by Roxane Laboratories

These are the first generic versions of the already-approved Retrovir brand manufactured by GlaxoSmithKline to be approved for marketing in the U.S. FDA previously determined, as part of a tentative approval action, that these products meet all U.S. manufacturing quality and clinical safety and efficacy standards.

C O M M E N T

The European patent for AZT ends in March 2006. When this occurs, it is unclear how the availability of generic AZT will affect ARV drug costs in the UK. BHIVA guidelines already highlight cost of drugs in the UK. The increasing pressure on ARV and related drug budgets is likely to restrict choice in the future. The guidelines also recommend not using AZT in first-line therapy because of the association with lipoatrophy.

The cost versus benefit argument over use of AZT could easily become more important next year.

Patient awareness of the issue of cost of treatment and the implications for future costs is currently low, but inclusion of a cost comparison table in the BHIVA guidelines should send a clear signal that cost may become an increasing factor in deciding Trust and hospital purchasing and prescribing policy.

Source: FDA listserve:

<http://www.fda.gov/oashi/aids/listserve/archive.html>

VIRAL RESERVOIRS

Depletion of latent HIV-1 reservoir with valproic acid: interesting data but not a cure

Gareth Hardy, HIV i-Base

In the 13 August edition of the Lancet, Ginger Lehrman of University of Texas South Western Medical Centre, USA, reported a small study investigating the effects of the drug, valproic acid (an anticonvulsant) on depletion HIV-1 reservoirs. This proof of concept study was conducted in four patients who had been treated with fully virally suppressive HAART (<50 copies/mL) for at least two years and who then were initiated on an intensified HAART regimen which included their original regimens with the addition of 90_g T-20 (enfuvirtide) twice-daily. Following a further 4-6 weeks of stable T-20, patients were initiated on three months of 500-700mg twice-daily oral valproic acid.

The authors explained that valproic acid has been previously described to inhibit the enzyme Histone deacetylase 1 (HDAC1). Histone deacetylase 1 mediates chromatin remodeling, viral gene expression and virion production, since histone deacetylation is important in maintaining latency of HIV provirus and repression of HIV-1 gene expression. Valproic acid has, therefore been demonstrated in vitro to induce the expression of latent HIV from resting CD4 T cells in patients on HAART maintaining undetectable viraemia. Such induction of latent expression by Valproic acid is as efficient as that induced by mitogen, but in contrast does not give rise to cellular activation. Approaches designed to achieve activation of latent integrated virus without cellular activation are likely to be considerably more successful than previous strategies which have involved global T cell activation in the patient, presenting both an abundance of new host cells for induced virus to replicate in and significant, potentially life-threatening toxicity.

Leukopheresis was conducted on each patient at baseline (before T-20) and following 16-18 weeks treatment with T-20-intensified HAART and valproic acid. 200-1200 million resting CD4+ T cells were obtained from the resting leukocytes and were purified for recovery and quantification of replication-competent virus in CD8+ T cell-depleted PBMC outgrowth assays. Real-time PCR for integrated HIV DNA was also carried out on purified resting CD4+ T cells. The number of infected units of resting CD4+ T cells per billion (IUPB) was estimated using a maximum likelihood method. In addition, plasma viral RNA was quantified by a real-time RT-PCR assay capable of quantifying and detecting HIV-1 RNA down to 1 copy/mL and immunophenotypic analysis was carried out for cell surface activation and differentiation markers by flow cytometry.

The authors report that the treatment regimen was well tolerated and all patients adhered well to therapy. Patient 1 had a single episode of transient viraemia (71 copies/mL), which was self limiting and associated with an upper respiratory tract infection, and which resolved without intervention. No significant changes were noted in the proportion or level of expression of cell surface activation markers of naive and memory CD4+ or CD8+ T cells. Three of the four patients were culture negative for viral outgrowth culture at baseline and remained negative throughout the study period. The fourth patient was culture positive at baseline and at initiation of valproic acid therapy (after 6 weeks HAART intensification). Following 11 weeks of valproic acid, this patient became culture negative. One of the patients who maintained culture negativity throughout had detectable levels of viral RNA at various time points during the study, though always below 10 copies/mL. Thus replication competent viral DNA was not always demonstrable despite the occasional presence of plasma viral RNA and the persistent presence of integrated viral DNA.

Most interestingly, there was a substantial decline of integrated viral DNA during the study. This decline in resting CD4+ T cell infection was much greater than predicted by the half-life estimates previously reported (44.2 months on normal HAART, 10.3 months on some intensified regimens). The minimum decline seen in IUPB was 29%, with a decline of more than 50% in the other three patients. Declines were: Patient 2 - >84%, patient 3 - 68% and patient 4 - 72% (patient 2's result was

estimated on a single macroculture as outgrown virus could not be recovered at week 18 – end of valproic acid therapy). Based on these figures the authors suggest that valproic acid decreases the half-life of HIV latently-infected resting CD4+ T cells to 2-3 months. This is however based on a single time point determination of IUPBs following 3 months treatment, although multiple determinations were made prior to valproate therapy, which confirmed the stability of the latent reservoir on normal HAART regimens. Taken together with the substantial decline in the frequency of replication-competent HIV recovered from peripheral resting CD4+ T cells in these patients, the authors suggest that this data argues in favour of the use of HDAC inhibitors in long-term HAART treated patients with stable undetectable viral RNA levels. They go on to suggest that the eradication of established HIV infection might be achieved by such an approach, with the concomitant intensification of HAART.

C O M M E N T

It is unclear whether the mechanism for maintaining HIV latency targeted by valproic acid is responsible for maintaining all latent HIV in the body. In addition, although in theory T-20 should not be able to impact the resting CD4+ T cell reservoir, as there is no data on this, the impact of valproic acid vs additional of T-20 in this study is not known. At least one previous study has reported that intensification of anti-HIV therapy decreases the half-life latently infected CD4+ T cells [2]. However, as two patients had residual viremia after addition of T-20, it is unclear whether this intensification is either necessary or particularly beneficial.

In addition, the assays used to quantify the resting CD4 T cell reservoir are complex, cumbersome and the intra-person variability from day to day is uncertain. Even defining and isolating resting CD4 T cells is complicated and the samples aren't 100% pure. Absolute CD4 counts vary on a daily basis in patients on stable therapy and this may impact on the latent pool of infected cells.

This is interesting work, but it presented tentative data on a potential mechanism in four patients, none of whom show any evidence that eradication is possible, and with no control group. The possibility of a cure should never be forgotten or abandoned, but the way the Lancet presented this data, using a quote on their front cover to suggest that a cure is suddenly more likely, and generating subsequent 'cure' reports in the lay press, was just exploitative.

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FATIGUE

Fatigue among HIV-infected patients in the era of highly active antiretroviral therapy

Simon Collins, HIV i-Base

A study published in the September issue of *HIV Medicine* showed a high level of fatigue in patients attending a specialist HIV clinic in South London in the post-HAART era.

The cross-sectional study covered a five-month period in 2002. Participants completed four self-administered questionnaires measuring fatigue, functional status, anxiety and depression, and illness perception.

Of the 205 patients approached, 148 agreed to participate, 65% of who were defined by the questionnaires as fatigued (95% CI 57-73%). Significant psychological distress (86% vs 34%, $p < 0.001$) and functional impairment were both significantly associated with fatigue, but there was no association with HAART use or demographics.

There was a trend for patients reporting fatigue to have higher CD4 counts - which was not explained by use of HAART - and neither HAART use, nor particular regimens were strongly associated with fatigue. There was also a trend towards fatigued patients perceiving the impact of their illness more seriously than non-fatigued patients. This also registered as a poorer quality of life, and suggested that fatigued patients feel they have little control over their condition.

The figure of 65% is at the higher end of prevalence reported in previous HIV studies, but is similar to levels seen in other chronic illnesses including heart disease, lupus and rheumatoid arthritis. Sixty-eight per cent of the participants were identified as psychologically distressed and this was strongly associated with fatigue.

The study volunteers compared to the clinic population were more likely to be male (78% vs 68%), gay or bisexual (60% vs 38%) or on HAART (81% vs 68%), and less likely to be black African or black Caribbean (35% vs 43%).

The authors commented that 'the strong association between psychological distress and markers of quality of life has implications for the clinical management of fatigue in HIV-infected patients. Firstly, it suggests that the symptom of fatigue should elicit not only a search for physical mechanisms, but also detailed questioning about depression and anxiety. Secondly,

the high rates of psychological distress described here suggest that a proportion of patients have significant depression or anxiety that may benefit from specific interventions, such as antidepressant medication, which may also improve fatigue. Thirdly, there is growing evidence that non-pharmacological treatments such as cognitive behaviour therapy and graded exercise therapy are effective in the treatment of medically unexplained fatigue occurring in chronic fatigue syndrome [50-52]. Such treatments aim to help improve functioning by giving patients strategies for managing fatigue. Given the high prevalence, and apparently serious consequences for functional capacity, of fatigue in individuals with HIV infection, there is a need for further evaluation of these interventions in the HIV-infected patient population.'

C O M M E N T

Selection bias could have influenced these findings either way - with fatigued patients being more inclined to participate or conversely, and perhaps indicated by these results, feeling less motivated in their general healthcare. Patient management and outcome would ideally need to be reported in a prospective study following patients over time, that this cross-sectional study could not access. Fatigue is additionally a symptom of hepatitis C disease and hepatitis coinfection was not recorded in this study.

Ref: Henderson M, Safa F, Easterbrook P et al. Fatigue among HIV-infected patients in the era of highly active antiretroviral therapy. HIV Medicine Volume 6 Issue 5 Page 347, September 2005. Text available:

http://www.natap.org/2005/HIV/091505_03.htm

PREGNANCY AND PMTCT

Breast milk HIV suppression and decreased mother to child transmission

Polly Clayden, HIV I-Base

Breast milk HIV-1 transmission contributes to 30-50% of infant infections in Africa. Recently published findings suggest that breast milk HIV suppression can decrease post partum mother to child transmission risk in this setting.

A study published in the September edition of The Journal of Infectious Diseases conducted by Shapiro and colleagues as a sub study of the Mashi trial in Botswana compared breast milk HIV-1 RNA and DNA in breast milk of women receiving and not receiving HAART (nevirapine, 3TC and AZT). [1, 2]

Women in the HAART group received treatment for a median of 98 days at the time of sampling; 23/26 (88%) had whole breast milk HIV-1 RNA <50 copies/mL, compared with 9/25 (36%) women in the comparator group who did not receive HAART ($p=0.0001$).

The authors report that in a multivariate analysis this finding remained significant ($p = 0.0006$). However they found that the whole milk HIV-1 DNA was not affected by HAART. Of the group of women receiving HAART, 13/26 (50%) had HIV-1 DNA loads <10 copies/10⁶ cells, compared with 15/23 (65%) who did not receive HAART ($p= 0.39$).

The authors also noted that among the 21 women receiving HAART before delivery through the breastfeeding period (median duration 5.9 months), whose infants received AZT no transmissions occurred at 7 months after delivery.

They found that HAART suppressed cell-free HIV-1 RNA in breast milk and so may therefore reduce mother-to-child transmission (MTCT) of HIV-1 via breast-feeding. However, HAART initiated during pregnancy or early after delivery had no apparent effect on cell-associated HIV-1 DNA loads in breast milk. They wrote: "Clinical trial data is needed to directly measure MTCT rates in women receiving HAART. As the cost of HAART decreases and simplified regimens become available, maternal HAART may be a realistic strategy to maximise MTCT prevention in areas of the developing world where formula feeding is neither safe nor feasible."

The investigators also report findings from a Mashi PK substudy to measure concentrations of nevirapine, 3TC and AZT in serum and whole breast milk from HIV positive mothers and serum from their uninfected breast feeding infants. [3]

Twenty mother-infant pairs were enrolled. The mothers had been receiving HAART (18 nevirapine/3TC/AZT and 2 nevirapine/3TC/d4T) for at least six weeks and the infants were receiving prophylaxis AZT and had received single dose nevirapine at birth.

The authors report that maternal serum concentrations of nevirapine were high (median, 9534 ng/mL at a median of 4 hours after nevirapine dose). Median breast milk concentrations of nevirapine, 3TC and AZT were 0.67, 3.34, and 3.21 times, respectively, those in maternal serum.

The median infant serum concentration of nevirapine was 971 ng/mL, at least 40 times the IC₅₀ and although lower than

therapeutic concentrations similar to peak concentrations after a single 2 mg/kg dose of nevirapine at birth. The median infant serum concentration of 3TC was 28 ng/mL, which is 5% of the IC50, and the median infant serum concentration of AZT was 123 ng/mL, which is 25 times the IC50. Infant serum concentrations of AZT were a median of 2.5 times higher than the maternal concentrations but infants were also receiving AZT prophylaxis. The authors made no comment about the breastfeeding infants of mothers receiving d4T that also received AZT prophylaxis.

The authors report that HIV-1 inhibitory concentrations of nevirapine are achieved in breast-feeding infants of mothers receiving this regimen, exposing infants to the potential risks and benefits including selection of resistant viruses should an infant become infected while breastfeeding. There were no transmissions during the study period.

They conclude that infant antiretroviral exposure to breastfeeding infants may be protective against mother to child transmission. They write: "Further study is needed to better understand the pharmacokinetics of these drugs in both the serum and breast milk of women in the developing world."

Findings from Chung and colleagues published in the September edition of AIDS compared the effects of single dose nevirapine (HIVNET 012) and short course AZT (Thai-CDC) MTCT prophylaxis regimens on breast milk viral shedding and transmission at 6 weeks in a randomised controlled trial conducted in Nairobi. [4]

From March to October 2003, 76 women electing to breast feed were enrolled. A total of 795 breast milk samples were collected from 60 women over the first 6 weeks postpartum: 391 samples from 30 women in the AZT arm and 404 samples from 30 women in the nevirapine arm. The median number of breast milk samples collected per woman was 14. Breast milk was collected between 1 and 49 days postpartum with half of the total number of samples collected within the first 14 days after delivery.

Between days 3 and 7, mothers receiving nevirapine tended to have lower HIV-1 RNA viral loads in breast milk compared to those receiving AZT (median log₁₀ HIV-1 RNA, 1.98 versus 2.42, $p = 0.1$). The effects of nevirapine compared to AZT became statistically significant in the second week postpartum (median log₁₀ HIV-1 RNA, 1.78 vs 2.48, $p = 0.005$), and continued through the third week (median log₁₀ HIV-1 RNA, 1.90 vs 2.97, $p = 0.003$). After four weeks, there was no statistically significant difference between the two arms.

At week two there were two infants infected in the AZT arm and one infant infected in the nevirapine arm. At 6 weeks, there were eight infants infected in the AZT arm and two infants infected in the nevirapine arm. The cumulative MTCT rate at 6 weeks was 6.8% [95% CI, 0.0-15.9%] in the nevirapine arm vs 30.3% (95% CI, 12.7-47.9%) in the AZT ($p = 0.02$).

The authors write: "Compared to a peripartum zidovudine regimen, nevirapine was significantly more likely to decrease HIV-1 RNA in breast milk during the first week and through the third week postpartum following single-dose administration, and corresponded with decreased transmission risk at 6 weeks. Sustained breast milk HIV-1 suppression may contribute to the ability of nevirapine to decrease perinatal transmission of HIV-1."

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Single dose nevirapine infant prophylaxis to reduce mother to child transmission may have similar efficacy to maternal and infant doses

Polly Clayden, HIV i-Base

Administration of single-dose nevirapine for mother to child transmission prophylaxis is associated with rapid emergence of nevirapine resistance in both the mother and HIV-infected infants.

This is likely to increase risk of treatment failure in women who subsequently receive nevirapine-containing HAART, which despite limited coverage is an important consideration as treatment programmes roll out. Single-dose nevirapine prophylaxis given only to the infant would avoid the risk of nevirapine resistance in the mothers.

A study conducted by Glenda Gray and co-workers published in the August 12 edition of AIDS compared HIV infection rates at 12 weeks in a group of infants born to HIV positive mothers, uninfected at birth and randomised to receive either single dose nevirapine (10 mg/ml oral suspension at a dose of 2 mg/kg) or 6 weeks AZT (10 mg/ml at a dose of 4 mg/kg every 12 hours) [1]. The effect of breastfeeding on the efficacy of the regimens was a secondary objective of the study.

Women delivering with unknown HIV status at three South African clinics were offered voluntary counselling and rapid

testing. Women testing HIV positive were offered enrolment into the trial.

Pre term infants were excluded from the study if they weighed < 1200g, needed ventilation, were unable to take oral medication or had congenital abnormalities. Informed consent and randomisation took place within 24 hours of delivery. Formula was provided for women who opted not to breastfeed and those opting to breastfeed were advised to do so exclusively.

From October 2000 to September 2002 1051 infants were randomised into the study: 533 in the AZT arm and 518 in the nevirapine arm. At 12 weeks, 718 infants had evaluable results.

Overall 12-week mother to child transmission probability was 16.3% (95% CI: 13.4-19.2%). Among infants not infected at birth, 24 (7.9%) new infections were in the nevirapine arm and 41 (13.1%) in the AZT arm ($p=0.06$).

There was no statistical significance in the incidence of serious adverse events between the two arms.

The additional infection rate in the breastfed infants in the AZT arm was 20.6% compared with 11.1% in those infants who were not breastfed ($p=0.004$). The additional infection rate in the breastfed infants in the nevirapine arm was 9.9% compared with 7.3% ($p=0.3$) in the non-breastfed arm.

The authors report that in multivariate analysis, maternal viral load, CD4 count, breastfeeding and infant AZT were independently associated with an increased risk of infection between day 10 and day 100. Maternal CD4 count < 500 cells/mm³ was associated with a twofold increase in transmission (multivariate OR, 2.5; 95% CI, 1.3-5.0); a maternal viral load of > 50 000 copies/mL led to a more than threefold increased risk of infection (multivariate OR, 3.6; 95% CI, 2.0-6.2). Breastfeeding (multivariate OR, 2.2; 95% CI, 1.3-3.8) was also a significant risk for transmission at week 12.

They found that compared with 6 weeks of AZT, "single-dose nevirapine is easier to implement, is likely to be more cost-effective and adherence would be easier to ensure." Additionally, in multivariate analysis, the AZT regimen did not appear to be as effective as single-dose NVP in reducing postnatal transmission.

They reported a comparable transmission rate seen in the single-dose single dose arm at 6 weeks (11.9%; 95% CI, 8.8-15.0) to the transmission rate seen in HIVNET 012 (11.8%; 95% CI, 8.2-15.5), where both mother and infant received nevirapine [2]. It was also comparable to the transmission rate at 6-8 weeks (15.3%) seen in infants who received single-dose nevirapine in addition to one week AZT in the Malawi study [3]. Additionally at 12 weeks, the transmission rate seen in the single-dose nevirapine arm (14.3%) was similar to the transmission rate (13.1%) seen in HIVNET 012 at 14-16 weeks.

They note that a limitation of this study is that 20% of infants were lost to follow-up, although the baseline characteristics of the lost to follow up group were similar to those of the infants overall. The authors suggest: "In countries with a high HIV burden, universal nevirapine therapy to all newborns could be considered, particularly where HIV testing and counselling is not available. This could be viewed as analogous to the universal use of tetracycline eye ointment in newborns for preventing ophthalmia neonatorum."

They conclude: "As access to antiretroviral therapy becomes a reality in countries heavily affected by HIV, attempts should be made to preserve the efficacy of nevirapine for the treatment and care of women. Post exposure prophylaxis to infants provides a valuable alternative."

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PAEDIATRICS

Pharmacokinetics of nevirapine in HIV positive children receiving Thai fixed dose combination

Polly Clayden, HIV i-Base

Due to cost restraints and lack of available paediatric formulations, it is common practice in Thailand and other resource limited countries to use cut up adult fixed dose combinations (FDCs) for treating HIV positive children. Although dividing tablets is considered by most, to be a "transitional option" in paediatric scale up, dosing in children is notoriously variable, and pharmacokinetic data are lacking to support the implementation of this strategy.

A study from Chokephaibukit and co-workers published in the September 23rd edition of *AIDS* evaluated the steady state PK of nevirapine in HIV-positive children receiving GPO-VIR S30 (30mg d4T, 150mg 3TC, 200mg nevirapine) which is the

Thai Government Pharmaceutical Organisation (GPO) produced generic FDC. GPO-VIR is the first line regimen provided by the Ministry of Public Health in Thailand.

This cross-sectional study enrolled 34 children (18 girls, 16 boys) with a median age of 8.4 years (range 3-15 years), a median CD4 count of 576 cells/mm³ (range 35-1443 cells/mm³) and a median CD4 percentage of 20.2% (range 1.7-30.2%), who had received GPO-VIR for at least 8 weeks.

The dose was based on a nevirapine dose of 120-200mg/m² every 12 hours and tablets were divided where necessary to 1/4, 1/2, 3/4 or 1 tablet. Blood samples were taken at three time points, pre-dose and at 2 and 6 hours post dose.

CD4 was measured at baseline and then every 6 months; viral load was measured in children receiving GPO-VIR as their first line treatment.

One child was excluded for non-adherence. The nevirapine dose averaged 164+/- 27mg/m² every 12 hours. Twenty-four children (71%) received broken tablets as part of their dose; 32 children swallowed tablets without crushing. Four children also received indinavir boosted with ritonavir with GPO-VIR as salvage regimens.

The median pharmacokinetics parameters were area under the curve (AUC) at 12 hours, 78.4 h ug/ml; minimum plasma drug concentration, 5.98 ug/ml; plasma half-life, 25.5 h; apparent oral clearance, 0.079 l/kg/h; and volume of distribution, 2.95 l/kg.

Only one child (receiving 190mg/m² every 12 hours) had less than the target drug concentration of 3.4 ug/ml (2.57 ug/ml) however, at 2 and 6 hours after nevirapine drug intake the drug levels were 4.93 and 4.64 ug/ml, respectively, and a good virological, immunological and clinical response was observed.

Nevirapine plasma levels were similar in the four children who also received indinavir boosted with ritonavir, except for one child who had a very high minimum nevirapine concentration of 24.37 ug/ml.

Of the 13 children who received GPO-VIR as their first-line treatment, 12 had plasma HIV-1 RNA < 400 copies/mL at 6-18 months, with a median CD4 increase of 216 and 433 cells/mm³ at 6 and 12 months of treatment, respectively.

The authors write: "The pharmacokinetics parameters in our study were in the ranges reported in studies performed in adults. The therapeutic adequacy of nevirapine could be considered by using a minimum concentration of > 3.4 ug/ml or by comparison of AUC values; however, there is no clear defined AUC threshold that correlates with virological response for nevirapine. In our study, all the children apart from one had trough concentrations > 3.4 ug/ml despite a higher clearance than adults. Pill cutting may alter drug absorption and cause inaccuracy of drug dosing, but in this study we demonstrated that this practice gave satisfactory plasma concentrations of nevirapine".

They note that the study was limited as the nevirapine concentrations were only obtained at three time points in each child; therefore, some of the pharmacokinetics parameter estimates, particularly volume of distribution and half-life, have limited accuracy.

They conclude: "It is reassuring that dividing the adult fixed-dose combination tablet GPO-VIR does not adversely affect nevirapine bioavailability and can be used to generate paediatric doses between 120 and 200 mg/m² to achieve therapeutic levels of exposure. This study encourages the use of adult fixed-dose combination as a transitional measure to support scaling-up antiretroviral therapy in children where the paediatric formulations are not available."

Ref: Chokeyphaibulkit K, Plipat, N, Cressey T et al. Pharmacokinetics of nevirapine in HIV-infected children receiving an adult fixed-dose combination of stavudine, lamivudine and nevirapine. AIDS: Vol 19(14) 23 September p1495-1499.

OTHER NEWS

WHO - Patients for Patient Safety: Call for Participants

As part of the Patients for Patient Safety action area of the World Alliance for Patient Safety launched by the World Health Organization (WHO) in 2004, a Patients for Patient Safety Workshop is to be held from 27 November – 1 December 2005 in London, UK.

The event will develop a core team of proactive patient and consumer partners who are, or wish to become, champions in advancing patient safety in their region. Selected participants will have their accommodation and travel expenses covered.

http://www.who.int/patientsafety/patients_for_patient/p4ps_workshop/en/print.html

Does buprenorphine have a role in preventing HIV transmission and treating HIV-infected IDUs?

Chris Gadd, aidsmap.com

A review article published in the 15 September edition of *Clinical Infectious Diseases* has outlined the benefits of buprenorphine (Subutex) in the treatment of intravenous drug use. The drug, which was added to the World Health Organization's (WHO's) list of essential drugs in July 2005, may be beneficial in reducing HIV transmission through injecting practices, as well as treating HIV-infected drug users.

Injecting drug use is a major factor in the transmission of HIV internationally, and is linked to the majority of HIV transmissions in central and Eastern Europe and Southeast Asia.

The most commonly used treatment for addiction to opioids, such as heroin and morphine, is replacement therapy with methadone. This drug mimics the effects of opioids by binding to the same receptor molecules as these drugs. These receptors, called mu-opioid receptors, are found on the surface of cells in the brain and spinal cord and trigger the drugs' sedating, euphoric and pain-killing effects.

Methadone works by preventing the withdrawal symptoms and craving brought about when an addict stops injecting drugs. By reducing the frequency of drug injection, it has been shown to reduce the incidence of HIV infection. However, the use of methadone has a number of problems, including being itself addictive, and its risk of causing breathing problems and overdose. It also interacts with many HIV drugs.

Buprenorphine, in contrast to methadone, is a partial agonist of the mu-opioid receptor. This means that it activates mu-opioid receptors less strongly than methadone, which, the authors argue, may reduce the likelihood of it being abused, particularly in regions where it is supplied in combination with naloxone, a drug that blocks mu-opioid receptors. It is also very difficult to overdose on buprenorphine as its effects plateau at high doses, and it has fewer interactions with HIV drugs, so is easier to use in patients taking antiretroviral therapy.

"The introduction of buprenorphine, a new medication to treat opioid dependence that has fewer restrictions than methadone, holds promise for reducing HIV transmission and improving the care of patients with opioid dependence and HIV disease," write the review's authors, Lynn Sullivan and David Fiellin from Yale University School of Medicine. "Methadone has a long history of proven efficacy and benefits in treating opioid dependence, and the addition of buprenorphine serves to expand the treatment options".

Buprenorphine has become more widely available over the last ten years. It is taken as a tablet dissolved under the tongue daily or three times a week, and was recently added to the WHO's list of essential drugs. This lists all medicines that should be available in adequate amounts and at an affordable price within all health systems, and are selected according to public health relevance, efficacy, safety and cost-effectiveness.

In their review, the authors summarise the results of cost-effectiveness studies comparing buprenorphine to methadone. They have concluded that buprenorphine treatment programmes may be preferable, both in the treatment of opioid dependence itself, and in its effects on reducing new HIV infections.

However, despite the drug's benefits, the authors point out that few studies have examined its effects on HIV risk behaviour, such as needle sharing and unsafe sex, although larger scale studies are planned.

In injection drug users (IDUs) who are already HIV-positive, there is evidence from the French Manif 2000 cohort study that use of buprenorphine improves adherence to antiretroviral drugs. Although this was not associated with a better response to HIV therapy, and over half of the patients reverted to IV drug use during the study, they pointed out that, despite limited evidence, buprenorphine is less likely to interact with HIV drugs than methadone.

AZT (zidovudine, Retrovir) and some protease inhibitors may increase buprenorphine levels, but the pharmacological properties of buprenorphine mean that its effects are not increased above a 'ceiling' level, so increased buprenorphine levels are unlikely to cause dangerous side-effects. However, the authors write, "as efforts continue with the goal to integrate use of buprenorphine into HIV care, further studies will need to be undertaken to make more than theoretical statements about these interactions."

In conclusion, there is room for substantial optimism about the inclusion of buprenorphine in the treatment of IDUs for the prevention of HIV transmission and the treatment of IDUs who are already HIV-positive. Although the practicalities of treatment programmes remain to be fully evaluated, many of the questions surrounding the drug's role will be answered in ongoing and future studies. "In the meantime, office-based clinicians, for the first time in nearly 100 years, have the opportunity to provide a unique treatment to minimise the adverse impact of opioid dependence," the authors conclude.

Source: www.aidsmap.com

Ref: Sullivan LE et al. Buprenorphine: its role in preventing HIV transmission and improving the care of HIV-infected patients with opioid dependence. *Clin Infect Dis* 41: 891-896, 2005.

ON THE WEB

Conference reports:

3rd IAS Conference on HIV Pathogenesis and Treatment, July 2005, Rio de Janeiro, Brazil.

Original conference reports, news, and web casts.

<http://hivinsite.ucsf.edu/InSite?page=cfaids-05-00>

<http://www.thebody.org>

<http://www.natap.org>

Medscape articles and online papers:

The following journal articles are available online in full. Medscape requires a simple one-time free online registration.

JAIDS: Journal of Acquired Immune Deficiency Syndromes

http://www.medscape.com/viewprogram/4516_pnt

Redefining Lipodystrophy Syndrome: Risks and Impact on Clinical Decision Making - Kenneth A. Lichtenstein, MD

Neurological complications of HIV infection

McArthur JC et al.

<http://www.thelancet.com/journals/laneur/article/PIIS1474442205701654/fulltext>

Summary

Cognitive disorders, vacuolar myelopathy, and sensory neuropathies associated with HIV are the most common disorders in patients with HIV AIDS, and are the focus of this review. These disorders are treatable and of those associated with HIV AIDS the pathogenic mechanisms are the most understood. Although triggered by productive HIV macrophage infections, aberrant immune activation plays a major role in inducing the CNS disorders. Novel therapies aimed at these inflammatory mechanisms can be effective. The sensory neuropathies associated with HIV infection are a major cause of morbidity; incidence may be increased by the toxic effects of specific antiretroviral drugs within the peripheral nervous system.

Online Medical Resources

HIV inSite Knowledge Base

Ophthalmic Manifestations of HIV

Irma Ahmed, MD, Everett Ai, MD, Eugene Chang, MD, Alan Luckie, MB, ChB, updated August 2005.

<http://hivinsite.ucsf.edu/InSite?page=kb-04-01-12>

Other resources:

WHO list of essential medicines

The WHO Expert Committee on the Selection and Use of Essential Medicines met in Geneva earlier this year. The revised, 14th WHO Model List of Essential Medicines (in English) was posted on their web site shortly after.

French, Spanish, Russian, Arabic and Chinese versions of the 14th Model List are available now at:

<http://www.who.int/medicines/organization/par/edl/eml.shtml>

Launch of a new WHO Medicines web site

The Department of Technical Cooperation for Essential Drugs and Traditional Medicine and the Department of Medicines Policy and Standards are pleased to announce the launch of a new Medicines web site

<http://www.who.int/medicines/>

The site was developed following a User Survey conducted recently and we have benefited from the active input of colleagues within WHO and from partner organizations. It offers fresh content and includes a number of additional features

and information resources. The site is structured according to WHO's activities in the area of medicines, facilitating navigation and generally making it more user-friendly. Key features include:

- Advanced Medicines and WHO Google site search
- An expanded medicines "News and Events" section; and
- Integrated web databases and on-line information retrieval.

Other important resources available on the site are:

- Antimicrobial Drug resistance

<http://www.who.int/drugresistance/>

- Essential Medicines Library

<http://mednet3.who.int/emEMLib/>

- Prequalification of Medicines

<http://mednet3.who.int/prequal/>

MEETING ANNOUNCEMENTS

Conference on Retroviruses and Opportunistic Infections (CROI) 2006

The 13th CROI will be held February 5-9, 2006 at the Colorado Convention Center in Denver, Colorado. Please visit the updated 2006 website, for information regarding dates and deadlines, travel grants, international scholarships and the community educator programme:

<http://www.retroconference.org>

PUBLICATIONS AND SERVICES FROM i-BASE

i-Base website redesigned

<http://www.i-Base.info>

The website has been redesigned to be faster, easier to use, and more accessible for those with impaired sight. For those who understand these matters, all pages conform to at least the W3C-WAI Level A and most to level AAA.

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.

There is a new section on Education and Training with treatment training for advocates. This includes our training manual with eight 2-hour modules that include questions and evaluation. Training modules start with basics, including CD4, viral load and other monitoring tests, combination therapy and side effects, and include brief overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment

All i-Base publications are available at our website, including 2005 editions of the treatment guides. 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).

A new page has been added on how to adapt and translate treatment resources, and included examples from projects we have worked with outside the UK.

An average of 2000 pages a day are served from the site.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting for three years. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

Reading material, reports and presentations from these meetings (the 15th meeting is on 25 November this year) are posted to the i-Base website and are available in printed format.

The August meeting included reports back from the IAS conference and a meeting with Roche about European and UK

access to the Biojector needle-free delivery system for T-20.

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

World CAB - reports on international drug pricing

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

The latest report focusses on a meeting held in January 2005 with four Indian generic manufacturers. An earlier report is from a meeting in February 2004 with three major brand manufacturers. Both are available to download as a pdf file from the i-Base website.

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

Introduction to Combination Therapy

June 2004 edition

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/or pdf versions of earlier versions of this booklet are available in Bulgarian, Chinese, English, French, Georgian, Italian, Latvian, Macedonian, Portuguese, Russian, Slovak, and Spanish. Please see the 'translations' page or the website for more details.

Introduction to Combination Therapy - New Portuguese edition

The June 2004 edition of this i-Base guide is now available in Portuguese as a pdf file posted to the website.

Guide to HIV, pregnancy & women's health

Spring 2005 edition

Updated and revised in April 2005, this patient guide helps women get the most out of HIV treatment and care before, during and after pregnancy. It should help whether on therapy or not and includes information for the mothers health and for the health of the baby. The guide gives information on medication, Caesarean section and breastfeeding, as well as details of other sources of help. It is aimed at people in a wide range of circumstances including positive women thinking about having children and pregnant women who have recently been diagnosed HIV-positive.

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

April 2005 edition

Also updated and revised in April 2005, this is a non-technical patient guide to changing treatment and what to do if treatment fails. This booklet helps patients in discussions with doctors, and covers what can be done if viral load starts to rise, and the importance of considering or finding out why the current combination failed, treatment strategies and new pipeline treatments.

Guide to avoiding & managing side effects

February 2005 edition

This is a comprehensive 44-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.

New sections are included on heart disease, lipodystrophy, and information relating to newer drugs including T-20, atazanavir, tenofovir, FTC and fosamprenavir.

Chinese, French, Italian and Spanish translations of the previous edition are still available.

Treatment 'Passports'

These popular booklets are for HIV-positive people – whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Like all i-Base publications, they are available free as single copies, or in bulk.

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published 10 times a year in a printed version, in a pdf file that we can email to you, and on our website.

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

Treatment information request service – 0808 800 6013

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

We can provide information and advice over the phone, and we can mail or email copies of the latest research studies relevant to the caller. For further details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm. All calls are in confidence and are free within the UK. This service is available in English and French.

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/2004>

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

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

Copies of publications can also be ordered by post or fax using the form on the back page of HTB. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), 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 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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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.

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Earlier versions 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
This 44-page comprehensive report is now only available in pdf format and on the i-Base website.

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