ISSN 1472-4863

HIV treatment bulletin

h-tb e

Volume 5 Number 9/10

The e-mailed (pdf version) of HTB is fully hyperlinked, including contents page and referenced websites

October/November 2004

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(hyperlinked)

CONFERENCE REPORT

10th BHIVA Autumn Conference

8-9 October 2004, London

BHIVA audit on management of HIV/Hepatitis coinfection

Simon Collins, HIV i-Base

Each year BHIVA audit an aspect of HIV management and the degree to which recommendations included in UK guidelines are being followed in practice. The 2004 audit assessed the impact of last years BHIVA guidelines for management of patients coinfected HIV and hepatitis B (HBV) or hepatitis C (HCV). Preliminary results were presented at the 10th BHIVA Autumn Conference on Friday 8th October by Dr Shamela de Silva from St Mary's Hospital, London.

The format for the audit is a questionnaire survey of 100 UK clinics, this year conducted from October 2003 - January 2004. Nineteen clinics were in the London NHS region and eight centres were exclusively haemophilia centres.

Eight clinics had >500 patients, 20 centres had 201-500 patients, 101-200 patients and 51-100 patients and 30 centres had less than 50 patients.

Increasing UK caseload

Increasing numbers of new HIV diagnoses bring direct financial pressure and limitations to service providers, as central budgets are not increased proportionally. This is the wider context for any HIV management survey and was clearly highlighted at the start of this presentation.

Over 60% centres had seen their caseload increase by over 15% in the previous year and 25% centres reported an increase of 5-15%. Only 2 centres (other than the six clinics dealing exclusively with haemophilia care) reported no increase in caseload.

Prevalence underestimated

BHIVA's guidelines for both HBV and HCV were published last year and had been used by 87% clinics. Among those who'd read the respective guidelines around half found them "very" useful and a third "quite" useful.

Five centres said that none of their HCV coinfected patients HIV patients had so far required treatment for HCV, and 11 said they would refer HCV coinfected patients elsewhere. 21 centres had referred at least one patient to be assessed for liver transplantation, including five of six exclusive haemophilia centres.

Estimated prevalence of both HBV and HCV coinfection was largely underestimated by the majority of centres. 44 centres estimated HBV prevalence among their HIV patients as 0-3% and 32 estimated 4-6%. Five did not know or did not answer.

HCV prevalence was estimated by 48 centres as 0-3% and by 23 centres as 4-6%. Ten centres estimated 7-9% and 13 estimated >10%, including all 6 exclusively haemophilia centres. Six did not know or did not answer.

Access to viral load testing

Over 15% centres reported restrictions on access to HCV RNA and HBV DNA testing respectively, largely due to local availability and/or financial restrictions. 24 centres weren't sure or didn't answer (for HCV RNA).

HBV management

HBV management was provided by the HIV unit in around 25% centres, and a further 15% in consultation with the HIV unit. 35% patients had HBV treated in a regional or local hepatitis unit. Just under 20% were not sure or didn't answer.

Only fifteen clinics said they would offer liver biopsy to most HIV/HBV patients, (unless it was contra-indicated). Just over 25% would biopsy those considering HBV therapy, and around 20% only in cases of severe liver disease. More than a quarter of clinics were not sure or did not answer.

Choice of HBV therapy in patients whose HIV does not require treatment also varied considerably:

37 centres would start HAART early and include 3TC/tenofovir; 20 centres would use interferon; 15 centres use adefovir. Of concern, one centre chose lamivudine as their only option, and three centres chose lamivudine but not early ART with a lamivudine/tenofovir combination.

Antiretroviral treatment in patients not requiring HBV treatment showed broad choice of ARVs with HBV activity: half of the clinics in the survey would use dual 3TC/tenofovir. Twelve clinics selected lamivudine as their only choice, not in combination

with tenofovir, apparently unconcerned about the long-term risk of HBV resistance. One selected tenofovir as their only choice.

The audit highlighted a range of vaccination schedules currently used in coinfected patients (44% using 0, 1, 6 months inc. 6/7 exclusive haemophilia centres; 23% 0, 1, 2, 12 months; 23% using 0,1, 3 weeks, 12 months). The 0, 1, 3 week, 12 month schedule which is the schedule recommended in DoH and CEG guidelines for GU clinic attendees, has not been tested in people with HIV.

HCV management

Routine screening for HCV is now widespread although six clinics still do not routinely screen all adult HIV patients for HCV but all screen injecting drug users.

Although HCV genotype testing is recommended in the BHIVA guidelines only 38% clinics routinely genotype patients, and 40% only genotype people who are being assessed for HCV treatment. Genotype is such a major factor in treatment outcome, that it is difficult to understand how treatment could be considered or delayed without this baseline information. This is certainly an important area of patient concern. One centre selected "other" and 21 did not know or did not answer.

Liver biopsy in HCV Co-Infection is offered routinely in 27% centres, unless contra-indicated. A further 41 would offer biopsy to those being considered for HCV therapy. Thirteen selected other options and 19 weren't sure or didn't answer.

Restrictions on the availability of HCV treatment for co-infected patients were reported by 20% clinics – 10 for most therapies, 10 for some – relating to funding restrictions (n=16), lack of expertise (n=6) and two mentioned restrictions related to HIV status.

Overall, 40 respondents reported waiting times for HCV therapy for HIV patients of less than 3 months. 23 reported 3-6 months, eight reported 6-12 months, two longer than 12 months. 27 did not answer. Waiting times were longer in centres reporting restrictions on treatment access – of these, six (30%) reported waits of 6-12 months and two (10%) of more than 12 months.

Conclusions

Survey has shown support for BHIVA guidelines and yielded information about current practice regarding HIV/HBV and HIV/HCV co-infection.

The main areas of concern include:

- an underestimation of the prevalence of both HBV and HCV coinfection,
- that a small minority of clinics (six centres) still are not routinely screening for HCV.
- restrictions on access to HBV DNA and HCV RNA tests have a direct impact on the management of coinfection
- HCV therapy at the time of the survey was still not routinely available to all centres.
- Inappropriate choice of drugs are routinely made in some centres for treating patients with HBV coinfection

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C O M M E N T

BHIVA coinfection guidelines are available on the BHIVA website: http://www.bhiva.org

The guidelines for management of coinfection with HBV and/or HCV are currently updated and will be presented in draft format for comment in early 2005. Results from this audit will be available on the BHIVA website and more detailed information of the BHIVA national clinical audit process is available on a website managed by the audit co-ordinator, Dr Hilary Curtis, at:

http://www.bhiva-clinical-audit.org.uk

CONFERENCE REPORTS

Further reports from the XV International AIDS Conference

11-16 July 2004, Bangkok

Main reports from this conference appeared in the last issue of HTB.

Unless otherwise stated, all references in the following conference reports are to the programme and abstracts of the XV International AIDS Conference 11-16 July 2004, Bangkok.

Abstracts are available at:

http://www.aids2004.org/

The X4 files: sampling the science on HIV co-receptors in Bangkok

Bob Huff, for GMHC

It has become conventional wisdom that the International AIDS Conference (IAC) is no longer the place to find cutting-edge research on HIV science. And although Track A, the basic science track at the conference, had fewer posters and presentations than the tracks for clinical research, prevention, social issues and policy, a respectable 618 basic science presentations were submitted and 439 accepted to the 2004 IAC in Bangkok. Here's a selection of abstracts covering one aspect of HIV basic research of emerging importance.

As most people who follow HIV therapies have learned by now, HIV infects a new target cell through the process of entry, which can be described as having three basic stages. First, a protein on the surface of HIV attaches to a CD4 protein on the surface of a target cell. This step, attachment, allows the viral protein to change its shape so that it can bind with a different kind of protein on the cell's surface, called a co-receptor. Then, after co-receptor binding and a few more intermediate steps have been accomplished, the virus can finally pull itself into contact with the cell's surface, where the two merge in a process called fusion. After fusion is complete, the viral payload can be delivered and the process of hijacking the cell and turning it into an HIV factory is well on the way.

Fuzeon, the only approved entry inhibitor, acts to block the fusion process at the point when the virus is pulled into contact with the cell. As for the other steps, several experimental drugs are in development to block attachment and co-receptor binding. As a number of orally available entry inhibitor candidates move through the drug development pipeline (injectable Fuzeon was approved in 2003), concerns are being raised about a subset of the class, known as CCR5 blockers. Because there are two basic types of cellular co-receptors that HIV can use, drugs are being developed that block both kinds. The most common co-receptor protein that HIV uses for entry is called CCR5 or R5, for short. In someone who is newly infected, R5 is often the only kind of virus that can be found. But in about half of the people who develop advanced HIV disease, the virus begins to use another co-receptor called CXCR4, or X4. The shift to using X4 is considered a bad sign because it is often accompanied by a dramatic increase in the rate of T-cell depletion. It is not entirely clear if HIV with the X4 phenotype causes accelerated T-cell loss or if it is only a symptom of some other shift in the T-cell ecology, but everyone agrees: you want to avoid developing an X4-using virus.

This means there is a critical open question about using the new R5 blocking drugs: will they cause HIV to start using X4? And will that be worse than letting the R5-using virus chug along at its own, slower, but no less dangerous pace? So far there's no solid evidence that blocking R5 will lead to HIV mutations that prefer using X4. But there is increasing evidence that some people may have small amounts of X4 virus in their bodies that could be given a green light to take over if their R5-using cousins are shut down. Again, it's not clear if these were acquired at the time of infection or if HIV can mutate step-by-step from exclusively using R5, to using both R5/X4, to using only X4. While there is now an experimental phenotype assay that can detect R5, X4 and dual R5/X4-using virus in a person's blood, it may not be sensitive enough in all cases to identify X4-using variants that are hiding in tissues or are only present in very small numbers. Now, as several pharmaceutical companies are getting ready to start large phase III trials for their R5 blocking drugs, discussion of the X4 problem is heating up.

A better blocker?

One attractive feature of blocking CCR5 is that there may be little or no toxicity penalty to pay, since some people are born without CCR5 proteins on their cells and seem to suffer no ill effects. (Yes, it is rare for these people to become HIV infected, and when they do — via other co-receptors, no doubt — they tend to have a very slow course of progression.) But blocking CXCR4 may not be as trouble-free, since a lack of the protein has been shown to lethally prevent infant mice from developing normally. Nevertheless, a couple of X4-blockers have been used in human safety studies with no disastrous results. Ideally, it seems, one would want to use an X4-blocker in tandem with an R5-blocker to prevent the possibility of an X4-using HIV

variant escaping and causing accelerated immune damage. But, in the first few upcoming trials, at least, the R5 blockers may have to work without a safety net as researchers rely on the imperfect assay to screen out those at risk for switching to an X4-using virus. If all goes according to schedule and no unforeseen problems with toxicity arise (and there is no guarantee that they won't), the first oral entry inhibitors could possibly appear in expanded access studies by late 2006 and be approved for sale in 2007.

Bangkok rocks

Here's a look at some of what we learned about the R5 and X4 co-receptors at the International AIDS Conference in Bangkok.

It is recognised that HIV with the X4 phenotype is rarely, if ever, transmitted — even when the donor predominantly carries X4 virus. In sexually transmitted infections, it is thought, dendritic cells (DC) patrolling the body's mucosal frontier are the first immune cells to contact HIV. However, instead of infecting the DC, HIV is internalised into a bubble-like vesicle and eventually carried to a lymph node, where it is introduced to circulating T-cells, normally the next line of defence in the immune response to foreign viruses. Unfortunately, these T-cells are the very cells that HIV prefers to infect. This is where HIV actually takes root in a new host.

So, why do R5 viruses seem to be favoured for starting new infections? In a laboratory-based study by J. Alcami and colleagues in Madrid, infections of T-cells by X4-using HIV were observed to be greatly reduced in the presence of dendritic cells, while infections by R5 strains were enhanced. This, the authors say, suggests that dendritic cells may produce a chemokine, or signaling factor, that effectively prevents X4 HIV from establishing a new infection — while having the opposite effect on R5 virus. In other words, if dendritic cells are the gatekeepers to HIV infection, they may routinely filter out X4 virus, which allows R5 viruses to initially become the dominant strain. [1]

Epi snaps

Although most people's HIV infections start out using the R5 co-receptor, in about half the X4 strain will eventually appear at some point during their lives. But how quickly does this happen, and to whom? In Bangkok, two studies presented retrospective analyses of co-receptor usage in a large number of samples and correlated the R5 phenotype with viral load, CD4 count and other variables. A study by Harrigan retroactively evaluated samples and records from 806 participants in a cohort of treatment naive-adults in British Columbia, and a study by Moyle evaluated data and co-receptor phenotype in a collection of 169 stored samples from treatment-naive individuals. In general, both studies confirm that, within a given sample population, as the duration of HIV infection increases and CD4 counts decline, the prevalence of the exclusive R5 phenotype decreases and X4 and dual R5/X4 phenotypes become more common.

In the Harrigan cohort, detection of the R5/X4 or X4 phenotype increased from 6% in people with CD4 counts above 500 cells/mm3 to over 50% in those with CD4 counts below 25 cells/mm3. There was only one exclusively X4 phenotype sample in the cohort. The odds of having an X4-using virus increased by about 1.5-fold in those with CD4 counts between 200 and 500 compared to those above 500 cells/mm3; the odds were 5- to 7-fold greater in those with CD4 counts between 25 and 200 cells/mm3; and jumped to 17-fold greater in those with fewer than 25 CD4 cells/mm3. [2]

In the Moyle study, detection of the R5/X4 phenotype ranged from about 7% in samples with CD4 counts above 300 cells/mm3 to 46% in those with CD4 counts below 100 cells/mm3. There were no exclusively X4 phenotype samples. The mean CD4 count for the R5 samples was 307 versus 117 cells/mm3 for the R5/X4 samples. [3]

In neither study was viral load a significant predictor of co-receptor usage phenotype. In the Harrigan cohort, injection drug use was not correlated with having R5 or X4 HIV; in the Moyle study there was no difference between B and non-B HIV subtypes.

Crowd control

A study by Ito and colleagues of the National Institutes of Health in Bethesda, Maryland, investigated how competing "swarms" of HIV with different co-receptor usage phenotypes might interact within lymphoid tissue. They found that X4-using HIV variants — including R5/X4-using strains — were able to suppress replication of their R5-using competitors. Meanwhile, the R5 viruses had no effect on the X4 interlopers. The researchers identified several chemokines stimulated by X4 HIV that seemed to be responsible for suppressing the R5 variants. When a cocktail of these chemokines was added to lymphoid tissue with only R5-using HIV present, the same suppressive effects were observed. The authors suggest that a better understanding of these chemokine-induced effects could possibly lead to the development of a new approach to anti-HIV therapy. [4]

Max factor

Early in the history of the epidemic one of the first distinguishing phenotypes of HIV described by scientists was the ability of some strains to cause groups of infected cells to fuse into clumps called syncytia. Syncytium inducing (SI) HIV was recognised as a highly virulent form and it became associated with rapid progression to terminal AIDS. At one point it was thought that syncytium formation was HIV's main mechanism for killing T-cells; to this day it is not entirely clear what is responsible for T-cell death in AIDS and multiple effects are suspected, ranging from apoptosis (cell suicide), to immune exhaustion through

overstimulation to direct killing. Eventually, SI and non-syncytium-inducing (NSI) HIV were correlated with the X4- and R5-using phenotypes and the SI and NSI nomenclature was generally put on the shelf.

Researchers from the lab of Jay Levy in San Francisco investigated the patterns of gene expression in T-cells stimulated by infection with two different phenotypes of HIV, the old-school SI and NSI variants. The quantities of various RNA gene products from the test cells were analysed using microarrays that can detect thousands of known gene products to see which were upregulated and which were downregulated when compared to uninfected cells. They found that SI HIV tends to upregulate genes involved with production of a cellular factor called tumor necrosis factor (TNF), which is associated with immune hyperstimulation, a state often implicated in T-cell depletion. [5]

The observation that people with AIDS have high levels of TNF in the blood was also made very early in the epidemic. At Bangkok, a group led by A. Valentin of the National Cancer Institute in Maryland reported on their recent studies of TNF levels in 63 patients (30 controls) and the impact that TNF has on virus production and co-receptor availability. They found that TNF inhibited replication of R5-using HIV strains while having no effect on X4 HIV. TNF was also observed to downregulate the number of CCR5 co-receptors that appear on the surface of T-cells, which could explain why R5-using viruses have such a hard time of it when TNF levels are increased. [6]

Couple this with Bonneau's finding that X4 HIV stimulates TNF production, and you have one possible explanation for how the shift from R5 to X4 predominance occurs. Of course, these shifts may be happening all the time on a small scale in isolated tissue compartments. What causes the overall population of HIV to shift? And why does the appearance of X4 virus signal the demise of so many T-cells?

From cradle to grave

Choudhary and colleagues from the University of California, Irvine, investigated the effect of HIV infection with an X4 strain on thymocytes, precursors to T-cells that reside in the thymus, a kind of incubator for immature immune cells. [7]

One theory for the accelerated CD4 cell depletion associated with X4 HIV maintains that the virus is capable of killing T-cells while they are still in their thymic cradle. In the experiment, thymocytes were infected with HIV and microarray technology was used to monitor changes in the expression of 22,000 gene products. They also assayed for various indicators of apoptosis. The most significant finding was that HIV infection induced apoptosis through a pathway involving a protein called caspase. This was confirmed by artificially inhibiting caspase, which had the effect of blocking apoptosis in infected cells. These results suggest that if the war between R5- and X4-using HIV comes to the thymus, the impact on CD4 cell production could be very dramatic indeed. There is still much to be learned about how and where HIV causes all the harm it does. Fortunately, we don't need to understand every detail of HIV pathogenesis to continue developing newer and better therapies.

In vivo studies at Bangkok

At Bangkok, Pfizer presented five posters on its CCR5 blocker, UK-427,857, including results from a 10-day proof-of-concept study. Patients with CD4 counts above 250 cells/mm^3 (currently off treatment or treatment-naïve) were randomised to a series of escalating doses or to placebo. Dosing began at 25mg once-a-day (QD) and increased to 300mg twice-a-day (BID), including one arm at 150mg BID taken with food. Monitoring continued for 30 days after treatment was stopped at day 10.

All doses from 100mg QD onward produced mean viral load reductions better than -1.0 log copies/mL. At the 150mg BID dose, food reduced the peak concentration and total exposure (AUC) to the drug by about half, although there was no difference in viral load reduction at that dose whether taken with food or not. This may be because blood concentrations of CCR5 blockers are not as important as how many R5 receptors become occupied by drug molecules and how long they stay. It seems that these drugs tend to stick to their targets and not let go, a quality that could extend the effective potency of a dose by several days. In this study, high levels of receptor saturation were achieved at every dose except 25mg QD.

All persons enrolled were assayed for HIV co-receptor usage phenotype and were required to have an exclusively R5-using strain at time of enrollment.

Of the 66 patients exposed to the drug, 2 experienced an emergence of a dual R5/X4 strain by day 11 of the study. One of these individuals reverted to R5 phenotype by day 40, but the other's dual phenotype HIV persisted throughout the first 6 months of follow-up. Because the assay cannot pick up sequestered or very small populations of X4-using HIV, the risk of forcing a population shift is evident in this small, initial study. However, in the person whose X4 phenotype persisted, no evidence of accelerated immunological or clinical deterioration has yet been reported. A more detailed presentation of this individual's case is anticipated at an upcoming conference. Adverse events were mild to moderate and included headache and dizziness. A separate report found no impact on QT interval, the cardiac rhythmic parameter that was perturbed by Schering's first R5 blocker. [8]

Source: GMHC Treatment Issues, July/September 2004
http://www.gmhc.org/health/treatment/ti/ti1807.html#2

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7. Choudhary SK, Powell D, Walker R et al. HIV-1 induces apoptosis in infected thymocytes. XV Intl AIDS Conference, Bangkok. Abstract MoPeA3008
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Women and HIV: research directions

Forum for Collaborative HIV Research

The symposium, a follow-up to the 2002 "Sex & Gender in the Management of HIV Disease Care, Prevention and Research workshop was designed to focus attention on *research needs* specific to women and HIV. Three themes from the frontlines of HIV care and prevention research were chosen for discussion: new approaches to prevention, addressing underlying social needs, and special needs of women in conflict and post-conflict settings. These were addressed from the researchers' as well as the community perspective. A third objective was to stimulate increased funding opportunities to address these research needs.

The symposium was co-chaired by Judy Auerbach, Vice-President for Public Policy for the American Foundation for AIDS Research (amfAR) and Kathleen Squires from the Keck School of Medicine, University of Southern California. Veronica Miller, Director of the Forum for Collaborative HIV Research introduced the Forum, the symposium objectives and the research themes to the participants. A specific research example illustrated each research theme, ranging from ongoing and funded research projects to research concept ideas in search for funding.

New approaches to prevention: use of ARVs in pre-exposure prophylaxis

Use of antiretrovirals to prevent HIV infection is neither a novel nor unfamiliar concept: its efficacy in prevention of mother-to-child transmission is well established and widely accepted. As an intervention in high-risk but HIV-negative adult populations however, it certainly is novel. Kimberly Page-Shafer, from the Centre of AIDS Prevention Studies, University of California, San Francisco reviewed the current thinking on, and rationale for, the use of antiretrovirals to prevent HIV infection by sexual transmission. If successful, this approach may be of significant benefit to women who are frequently especially vulnerable due to social, economic and biological factors. Potential benefits include prevention of HIV infection, prevention of secondary cases, and availability of a personal and private prevention method that women can control. Dr Page-Shafer is the principal investigator for the Cambodian HIV Prevention Study, "Kdey Sonkum Roboh Satrei" – *Hope of Women*, sponsored by the US National Institutes of Health (NIH) and Family Health International, with collaborators in Cambodia, University of New South Wales and at the University of California, San Francisco. This placebo-controlled, double blind trial plans to recruit 960 female HIV-negative sex workers over the age of 18 to be randomised to placebo or once-daily tenofovir.

During a brief discussion period following Dr Page-Shafer's presentation, researchers and community members alike deliberated risks and benefits. While representing hope for prevention of HIV/AIDS in the absence of effective vaccines, treatment of HIV-negative, at-risk for infection individuals with antiretrovirals raises ethical as well as scientific questions. What are the appropriate care and treatment provisions for trial participants who acquire HIV? What are the risks for development of drug resistance? Will toxicity be a problem? What is the impact on risk behavior and vulnerability? How can informed consent be assured in a research naïve population? [Post Bangkok note: the relevance of these questions is illustrated by the recent decision by the Cambodian government to stop the trial in Cambodia, see WSJ August 12. The study investigator team is discussing with the Cambodian government to resolve their concerns and hope to open the study in the near future.] The efficacy of tenofovir in pre-exposure prophylaxis is also being tested in clinical trials in Western Africa, Thailand, and the USA.

Addressing underlying social needs

Prevention research has focused primarily on individual risk, behavioral change models and technical interventions. There has been a growing recognition of the importance of structural factors, such as poverty and economic inequalities, gender inequalities and mobility and migration and their impact on individual behavior. Interventions targeting structural factors are those that alter the context in which health is produced, including laws and policies, cultural norms, and interventions that affect the physical environment and socio-economic conditions. Although the importance of structural factors in health matters is

recognised, few examples of studies designed to address these exist. Julia Kim reviewed the issues associated with research of structural interventions to address underlying social/structural vulnerability of women to HIV. Barriers to structural intervention research include lack of tools to conceptualise and mount broader social and economic interventions, as well as the requirement for new partnerships across multiple sectors and disciplines, for a shift in emphasis towards concepts of community participation, and for innovative and complex experimental methods. Not least, structural interventions may challenge firmly rooted political, economic and social interests. The disease-focused and vertical funding mechanisms in place make obtaining funding for this research a challenge.

Dr Kim runs the RADAR (Rural AIDS and Development Action Research) Programme, a partner in the IMAGE (Intervention with Microfinance for AIDS and Gender Equity) study. The IMAGE is a multi-faceted research programme, representing an attempt to integrate structural interventions and HIV/AIDS prevention research. The study is a prospective, community randomised intervention trial among 8 villages designed to develop and test interventions addressing poverty, gender and inequalities. The interventions include microfinancing, gender and HIV training, and community mobilisation. It is funded by the Ford Foundation, Department for International Development (DFID), UK and Kaiser Family Foundation. Evaluation will include the impact of these interventions on a range of outcomes, including HIV incidence, at the individual, household and community level.

Women in conflict and post-conflict settings

Women in conflict situations frequently experience the worst that violence and gender inequality have to offer. Dr Agnès Binagwaho, Executive Secretary of the National AIDS Commission Control of Rwanda used the Rwandan experience of genocide and massive rape of Tutsi women as an example to illustrate the impact of such experience on women and society during and after the conflict period. Women were raped with the intent to infect them with HIV, and many women were left alone, after other family members were killed, and forced into high-risk behaviour for survival.

With 64% of the population living in poverty, 27% of children having lost one or both parents and destruction of much of the infrastructure, the national government launched a response with no prioritisation for women traumatised by the war, although the promotion of women is a primary goal of the Rwandan government. Community action was the real driver of the emergency response for women, organising as communities to provide support and care. At the moment, women survivors have access to care but not separate from the general populations; plans for special programmes designed for women survivors are being planned. Special programmes are necessary because of the double-stigma faced by these women: sexual violence and HIV/AIDS. Dr Binagwaho finished by listing special areas of research for women, including social research to increase women's access to treatment and treatment success and behavioral research on acceptance of equality and rights for women before, during and after war. Community ownership and participation are essential cornerstones for these research activities.

Dr Kathryn Anastos, from the Bronx Women's Interagency Study and a member of the Women's Equity in Access to Care & Treatment (WE-ACTx) presented a framework for research including Rwandan women survivors of rape and genocide. The research framework is built on the maxim "treatment always trumps research in importance". Dr Anastos stressed the need to seek and incorporate community and research participants' opinions and the need to develop local infrastructure that will allow sharing and transfer of control to an in-country team. Dr Anastos has worked with the Rwandan Women's Treatment Access Initiative, a collaboration of three partners: five survivor organisations, the Rwandan government through their Treatment and Research in AIDS Care (TRAC) programme within the Ministry of Health, and WE-ACTx. The goal is to provide comprehensive HIV care, including antiretrovirals and prophylaxis for opportunistic infections. The group expects to achieve this goal for 30,000 Rwandans. Plans are underway to establish the Rwandan Women's Cohort Study, a collaboration between the three partners listed above and the Women's Interagency HIV Study of the US. The collaborators will help define the research agenda, and will involve such issues as the influence of trauma on response to treatment, through biological mediators (eg cytokines), behavioral mediators (eg adherence) and bio-behavioral mediators (eg depression and post-traumatic stress syndrome).

The short panel discussion that followed the presentation of these three research themes included Judith Auerbach (amfAR), Anne-Christine D'Adesky (WEACTx), Catherine Hankins (UNAIDS), Sandra Lehrman (NIH/DAIDS), Glennis Mabuza (HIVSA), James Rooney (Gilead Sciences), and Dawn Smith (CDC) and was moderated by Veronica Miller (Forum for Collaborative HIV Research). Glennis Mabuza started the discussion by reiterating the positive effect of including women participants and communities in the planning of the research studies, and the importance of the studies such as the IMAGE study in her community in Soweto. The three research projects covered in this symposium – examples of three different approaches to addressing women's needs - underlined the interdisciplinary and cross-disciplinary aspects of research in the context of women's lives. More opportunities for performing research within such a framework are urgently needed.

The Planning Group for this symposium members were Judy Auerbach, Polly Clayden, Judy Currier, Anne-christine D'Adesky, Veronica Miller, Kathleen Squires and Fulvia Veronese. The speakers' presentation slides are available on the Forum for Collaborative HIV Research's website at:

http://www.hivforum.org

Source: Forum News, Forum for Collaborative HIV Research; part of their report of their activities at the International AIDS Conference, which is also available at the same website.

TREATMENT ACCESS

A round-up of news about access to treatments with links to sources: Britain, Ukraine, Thailand, Europe, South Africa

Graham McKerrow, HIV i-Base

UK gives £3m to Global Fund to help secure US donation

The UK is giving US$ 5.3 million (£ 3 million) to the Global Fund to Fight AIDS, Tuberculosis and Malaria - money that has been brought forward from the UK pledge for 2005.

The announcement helps the Global Fund obtain money from the United States, which was promised on condition that every $1 was matched by $2 from other donors by September 30, 2004, The United States pledged $547 million for 2004 on this condition.

Even if full payment of outstanding pledges from non-US donors were to be received by the Global Fund, $53 million was needed to maximise the US contribution, before taking into account the new UK donation.

The new pledge from the UK follows the announcement by Prime Minister Tony Blair in July of £154 million over the next three years, which effectively doubled the UK contribution for 2005-2007.

Britain has been a key donor to the Global Fund since making one of the first pledges to the organisation in 2001, and has also been a strong supporter through advocacy at the highest political level and this will take on a fresh importance next year when the UK assumes the presidency of the G8.

The original letter sent to Tony Blair:
http://www.theglobalfund.org/en/media_center/press/pr_040923.asp

Status of pledges and contributions to the Global Fund:
http://www.theglobalfund.org/en/files/pledges&contributions.xls

Information on the work of the Global Fund:
http://www.theglobalfund.org/

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Ukraine joins Clinton Initiative to expand treatment and care

Ukraine has joined the Clinton HIV/AIDS Initiative Procurement Consortium, a move that will let the country purchase ARVs and diagnostics at the lowest prices in the world and so scale up its national care and treatment programme. Ukraine has the highest incidence of HIV/AIDS of all Eastern European countries; about 1% of the population of 48 million is HIV-positive.

Elena Franchuk, the founder of Ukraine's ANTI-AIDS Foundation, said: "The high cost of ARV's is the main obstacle to expanding national prevention and treatment programmes for people living with HIV/AIDS. According to Ministry of Health data, at least 4000 people currently need treatment."

The prices for ARVs negotiated by the Clinton HIV/AIDS Initiative are between a third and a half of the next lowest prices; training, reagents and maintenance and are up to 80% cheaper than otherwise available. More than 20 countries purchase drugs or diagnostics at the Clinton Initiative reduced prices.

Volodymyr Zhovtyak, the Head of the Coordinating Council of All-Ukrainian Network of PLWH said: "The All-Ukrainian Network of PLWH, of course, welcomes Ukraine's joining the Clinton HIV/AIDS Initiative Procurement Consortium because any opportunity to procure cheaper ARV drugs and diagnostics for Ukraine is vitally necessary."

Full story:

http://www.aegis.org/news/pr/2004/PR040931.html

Clinton Foundation:

http://www.clintonfoundation.org

Thailand to give ARVs and condoms to Myanmar to combat HIV on frontier

Thailand will give Myanmar (formerly Burma) anti-Aids drugs and condoms, worth 10 million baht (£135,000), to help combat the spread of HIV along their mutual border.
The gift includes supplies of a fixed dose combination of nevirapine, d4T and 3TC, called GPO-Vir, which is produced by the Thai Government Pharmaceutical Organisation, to treat 200 people, mostly hill tribe villagers, for three years. Thailand will also give a million condoms.

Cooperation between the two countries includes a health care programme to combat elephantiasis, malaria, meningococcal meningitis and tuberculosis. Thai health authorities believe Burmese immigrants have spread infections to Thai villagers along the border.
Thailand will renew efforts to gain financial support from the Global Fund and the World Health Organisation to provide generic ARVs and to develop infrastructure in Burma. The Global Fund had declined to give billions of baht to Thailand because of its failure to work with the Burmese government and to curb Aids along the border.

Full story:

http://www.aegis.org/news/bp/2004/BP040905.html

Activists outline detailed demands for action by EU

Health ministers, industry and civil society representatives from across Europe met in Vilnius in September to pledge action to counter the growing HIV/AIDS epidemic. The Conference adopted a declaration 'expressing willingness' to coordinate a continent-wide effort to fight the disease with all involved working together in partnership. The European AIDS Treatment Group, together with civil society representatives urged the European Ministers and the EU to commit to fighting the HIV epidemic rather than just 'express their willingness'.

They said there should be measurable outcomes, specified deadlines and monitoring and allocated resources.

Among their demands, they called for:

- Secure access to prevention, treatment and care for all people living in Europe, regardless of their legal status.
- Guaranteed respect, protection and promotion of human rights as a fundamental tool to effectively prevent and combat the epidemic.
- The meaningful involvement of people living with HIV/AIDS in policymaking, monitoring and evaluation.
- Safe housing, safe work places and safe parenthood for People with HIV/AIDS.
- Guaranteed European wide access to opiate substitution therapy, de-penalisation of drug use, and availability of sterile injecting equipment and its safe disposal.

Full EATG press release is at:
http://www.eatg.org/

Agenda, press releases, working paper and key document:

http://europa.eu.int/comm/health/ph_threats/com/aids/ev_20040916_en.htm

Only 8,000 on ARVs in South Africa

Fewer than 8,000 people are receiving antiretroviral treatment at public facilities in South Africa despite the government promising a new chapter in tackling the country's HIV disaster, according to a report of the inaugural meeting of the Joint Civil Society Monitoring and Evaluation Forum of the Operational Plan for Comprehensive HIV and AIDS Care, management and Treatment for South Africa in September.

The Forum comprises 10 leading organisations including the Treatment Action Campaign and Médecins Sans Frontières and the report of the meeting at Polokwane, Limpopo, said the Forum welcomed the progress made in scaling up treatment in some provinces and is encouraged by the efforts and determination of some healthcare workers and some provincial governments in accelerating the implementation of the government's Operational Plan.

The report goes on to say that delays in most provinces in systematically expanding access to ARVs have caused several public health problems: patients are starting treatment very late, and people are dying waiting to be clinically assessed. About 5.6 million South Africans were estimated to be living with HIV last year.

For full text of the summary of the discussion, Google the keyword "forum" at:

http://www.tac.org.za/

Body Mass Index at diagnosis is independent predictor of survival

HIVandHepatits.com

Identification of basic prognostic indicators of HIV infection is essential before widespread antiretroviral therapy can be implemented in low-technology settings. This study assessed how well body mass index (BMI:kg/m2) predicts survival.

BMI within 3 months of HIV diagnosis was obtained from 1657 patients aged >/=15 years, recruited in a seroprevalent clinical cohort in The Gambia, West Africa, since 1992 and followed up at least once.

Baseline CD4+ counts and clinical assessment at time of diagnosis were done. The mortality hazard ratio (HR) of those with a baseline BMI <18 compared with those with a baseline BMI >/=18 was 3.4.

The median survival time of those presenting with a BMI <16 was 0.8 years, in contrast to a median survival of 8.9 years for those with a baseline BMI >/=22.

Baseline BMI <18 remained a highly significant independent predictor of mortality after adjustment for age, sex, co-trimoxazole prophylaxis, tuberculosis, reported wasting at diagnosis, and baseline CD4+ cell count.

Sensitivity and specificity of baseline BMI <18 was comparable to that of a CD4+ count <200 in predicting mortality within 6 months of diagnosis

The authors conclude: "BMI at diagnosis is a strong, independent predictor of survival in HIV-infected patients in West Africa … In the absence of sophisticated clinical and laboratory support, BMI may also prove a useful guide for deciding when to initiate antiretroviral therapy."

The investigators also note that these study results have significant implications for drug treatment in developing countries. They conclude, "BMI at diagnosis is a low-technology, affordable, prognostic indicator, independent of age, sex, CD4 cell count, or HIV type."

Source: HIVandHepatits.com

Ref: van der Sande M et al. Body Mass Index at time of HIV diagnosis: a strong and independent predictor of survival. Journal of Acquired Immune Deficiency Syndromes. 37(2): 1288-1294, 1 October 2004.

http://www.hivandhepatitis.com/recent/developing/100404_a.html

ANTIRETROVIRALS

Six generics compare well with US-made ARVs

Graham McKerrow, HIV i-Base

A comparison between several generic antiretrovirals and the brand name formulations, carried out by researchers in Channai, India, and Boston, USA, shows that the drug content of the generics compared well. All the formulations were within the 5% range of the stated contents compared with the proprietary drugs, except for two.

Researchers at the Tuberculosis Research Centre in Chennai and Tufts University School of Medicine in Boston, analysed six widely used nucleoside and non-nucleoside reverse transcriptase inhibitors alone and in combination, from three Indian manufacturers: Aurobindo Pharma, Ranbaxy and Cipla.

They looked at efavirenz (600mg), nevirapine (200mg), AZT (300mg), ddI (250mg) d4T (30mg), 3TC (150mg), and a combination pill containing nevirapine, d4T and 3TC in those dosages and compared them to drugs manufactured in the USA. The samples analysed were physicians' samples provided for patient use during July and August 2003.

Six tablets or capsules of each drug were crushed to a fine powder and analysed in duplicate by high performance liquid chromatography. In total, 12 chromatographic analyses were performed for each medication.

The researchers report that all the formulations were within the 5% range of the stated contents compared with the American products, except for stavudine and lamivudine "which were slightly higher but within the 10% range". The authors add that their analyses "indicate that the amount of active drug is very similar to those medications manufactured in the USA".

Ref: Ramachandran G, Perloff E, von Moltke L et al. Analysis of generic antiretroviral formulations manufactured in India. AIDS 2004, Vol 18, No 10, 1482-3.

Viral load response at 4 weeks predicts treatment success

Laurence Gibson, HIV i-Base

To prevent the development of drug resistance, it is useful to be able to predict at an early stage whether or not a treatment-naïve patient's viral load will become undetectable (VL <50) after 24 weeks.

The possibility that results taken at week 4 of a given new treatment regimen could predict the outcome after 24 weeks was discussed by British and German researchers in the September 2004 issue of AIDS.

Previous studies have pointed toward a correlation between results at week 4, and those of week 24 – but the viral load lower limit was measured at 500 copies/mL, not using the ultra-sensitive assay.

This study looked at 656 anti-retroviral naïve patients attending three centres - Chelsea & Westminster and Royal Free hospitals in London, and the JW Goethe University Hospital in Frankfurt – who had had baseline viral loads measured before starting treatment and had subsequent viral load measurements recorded at close to 4 (range 2-6) and 24 (range 16-32) weeks. The majority (73%) of patients showed viral load suppressed to below 50 copies/mL and 51 patients (8%) had undetectable loads after just 4 weeks.

The association between viral load at week 4 and week 24 was statistically significant – with those patients who had the lowest viral load after 4 weeks being more likely to attain undetectable levels at week 24 (P<0.0001).

Indeed, for every 1-log higher viral load at week 4, the odds of having a viral load of <50 copies at week 24 decreased about 3-fold (odds ratio 0.35; 95% CI, 0.27 – 0.45). The researchers also found that patients with the lowest baseline viral loads were most likely to achieve virologic suppression at 24 weeks (P=0.0001).

Three hundred and sixty (84%) patients with viral load <1000 copies/mL at 4 weeks went on to experience viral suppression <50 copies/mL by week 24 – but only 61% of those with viral loads between 1001 and 10,000 copies/ml at 4 weeks did so.

Explanations for why the viral loads of some did not fall to below 1000 copies at week 4 include: inadequate adherence, poor absorption, pre-existing drug resistance, or a very high initial viral load.

In their discussion, the authors write: "Although we have shown that the week 4 viral load is associated with subsequent virologic outcome, it is unclear whether acting on this information will improve outcome. If there is suboptimal adherence, simplification of the regimen or some other intervention to improve adherence may be appropriate, although awareness of the possible implications of a high viral load at week 4 for future virologic response may in itself act as an intervention to improve adherence."

They point out that they did not consider clinical outcomes or immune response to HAART, although viral response has been shown to be a good predictor of long-term clinical outcome.

Ref: Smith C, Staszewski S, Sabin C et al. Use of viral load measured after 4 weeks of highly active antiretroviral therapy to predict virologic outcome at 24 weeks for HIV-1-positive individuals. JAIDS, 37 (1) 1155-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15319675

Resistance mutations in patients with persistent viraemia show need to improve clinical assays

Graham McKerrow, HIV i-Base

Richard Nettles and colleagues at Johns Hopkins University and the Howard Hughes Medical centre, Maryland, USA, conclude from a study of 21 patients who had persistent, detectable, low level viraemia while on highly active antiretroviral therapy, that there is a need to improve the sensitivity of clinical assays for the detection of drug resistance.

The researchers were concerned that technical limitations in the sensitivity of commercial genotyping methods might prevent clinicians from determining whether drug-resistant HIV-1 was present in patients with low-level viraemia. They performed ultra sensitive HIV-1 genotyping for 21 patients with persistent plasma virus loads of 50–400 copies/mL to better define the prevalence of drug resistance and the most common resistance mutations during persistently detectable low-level viraemia. They studied the 21 patients for a median of 11 months and found that nine (43%) had HIV-1 isolates with significant resistance mutations. The most common mutations were M184V, K65R, and M41L/T215Y.

They report that for isolates in some patients, the resistance was both diverse (ie there was resistance to all classes of antiretroviral drugs) and significant (ie there was resistance to a median of 3 of 5 antiretroviral drugs received by the patients during the study). In certain cases, the resistance mutations appeared to have been selected for by the study regimen and may have arisen during the period of low-level viraemia. The researchers write: "In such cases, we cannot exclude transmission or superinfection with resistant virus."

All the patients in whom resistance mutations were detected had mutations that could compromise the efficacy of the regimen they were on. The availability of genotypic information at this level of viraemia has the clear potential to guide the choice of an alternative regimen before overt failure occurs.

They also write that for the 43% of patients with isolates that were resistant to at least 1 antiretroviral agent in the HAART regimen they were on during the study, persistent, low-level viraemia was "particularly concerning because sequential accumulation of additional mutations conferring resistance to the remaining antiretroviral drugs in the regimen may lead to virologic failure and may limit future treatment options". It may be necessary to intensify or modify the HAART regimes for these patients.

The authors conclude: "Because persistent, detectable, low-level viraemia has been associated with the development of resistance and the failure of HAART regimens, and because of the technological limitations of commercial genotyping laboratories, clinicians currently have to make educated guesses as to the presence of resistance in HIV-1 isolates from patients with low-level viraemia. This study used novel ultra sensitive genotype assays at the clonal level to confirm that detectable, low-level viraemia is frequently, but not always, associated with resistance. We have found that previous nonsuppressive HAART, exposure to antiretroviral drugs before the current HAART regimen, and longer duration of protease inhibitor exposure were associated with the presence of resistance. The findings of this study point to the importance of improving genotype technology and demonstrate multiple clinical applications for such ultra sensitive genotypes when available."

C O M M E N T

Importance of assuming resistance at low levels from treatment history. This has previously most clearly been shown with NNRTI exposure (Mellors et al).

Ref: Nettles R et al. Genotypic resistance in HIV-1–infected patients with persistently detectable low-level viraemia while receiving highly active antiretroviral therapy. Clinical Infectious Diseases 39(7): 1030-1037. 1 October 2004.
http://www.hivandhepatitis.com/recent/test/genotype/092904_a.html

Researchers call for new approach to assessing pipeline drugs for salvage patients

Graham McKerrow, HIV i-Base

Researchers from four countries have written to the Lancet calling on the pharmaceutical industry, the US Food and Drug Administration (FDA), researchers and the patient community to work together to assess the use of more than one new drug simultaneously to provide more effective so-called salvage therapy.

This growing patient group encompasses those at greatest risk of clinical disease but the pathophysiology of HIV and the available clinical data suggest that the successful outcome of future therapy will be determined by the number of new drugs used as well as the retained susceptibility to previous agents, argue the researchers from Britain, USA, France and Canada.

"Assessment of the use of more than one new drug simultaneously in the subsets of patients who are at greatest risk of clinical disease would, therefore, seem logical," they write. "For instance, within the TORO (T-20 vs Optimised Regimen Only) studies there was a direct correlation between the success of virological suppression and immunological benefit with the number of active agents within the optimised background therapy used to support enfuvirtide. Unfortunately, to date, planned codevelopment of investigational agents has not occurred, and patients continue to be offered serial monotherapy along with potentially weakening regimens."

The authors speculate that pharmaceutical companies might be concerned about compromising the clarity of single agent development and a "perceived fear" that the FDA would consider this action inappropriate. However, they say it has been publicly stated that few barriers exist to combining experimental agents in prelicensing studies in such a patient population.

The letter is signed by Mike Youle of the Royal Free Hospital, London, Cal Cohen of the Community Research Initiative, Boston, Massachusetts, USA, Christine Katlama of the Hopital de la Pitie Salpetriere, Paris, France, Dan Kuritzkes of Harvard Medical School, Cambridge, Massachusetts, USA, and Sharon Walmsley of the Toronto General Hospital, Toronto, Canada.

Ref: Codevelopment of new antiretrovirals in very treatment-experienced HIV-infected individuals. Lancet. 2004 Sep 18;364(9439):1036-7.

METABOLIC CHANGES

Vancouver researchers urge caution with combinations of lipid drugs

Sean R. Hosein, catie.org

As people age there is a trend to gradually develop abnormal levels of sugar and lipids (cholesterol, triglycerides) in their blood. People with HIV/AIDS (PHAs) who use highly active antiretroviral therapy (HAART) can also develop high levels of these substances. If left untreated, this increases the risk of developing diabetes and cardiovascular disease.

Sometimes a combination of changes to diet and lifestyle (such as exercising and quitting smoking) can help improve blood sugar and cholesterol levels. However, for some HAART users, these changes to diet and lifestyle may not be enough. In such cases, doctors may prescribe drugs, including the following:

* Fibrates: These drugs help lower triglycerides and raise levels of good cholesterol (HDL-c). Examples of fibrates include fenofibrate (Lipidil, Tricor) and gemfibrozil (Lopid).

* Glitazones: These drugs can make cells more sensitive to the effects of the hormone insulin, helping to reduce high sugar levels in the blood. Glitazones can also raise levels of good cholesterol. Examples of glitazones include pioglitazone (Actos) and rosiglitazone (Avandia).

Because increased lipid levels may also be associated with higher-than-normal blood sugar, sometimes doctors prescribe both fibrates and glitazones. In theory, a combination of both drugs should maintain or even enhance the decrease in triglycerides seen with either drug alone.

A team of researchers in Vancouver, British Columbia, from the Canadian HIV Trials Network, the Centre for Excellence in HIV/AIDS, and the Healthy Heart Programme at St Paul's Hospital recently reported an unexpected result with combinations of both classes of drugs. They found that HDL-c levels decreased significantly in both HIV positive (33%) and HIV negative (20%) people. Moreover, among HIV positive people, triglycerides rose on average by almost 50% in those taking combination therapy with lipid drugs.

Study details

Researchers reviewed the medical records of three groups of people:

* Group A: PHAs taking fenofibrate – 12 participants

* Group B: PHAs taking fenofibrate and rosiglitazone – 9 participants

* Group C: HIV negative diabetics taking fenofibrate and rosiglitazone – 12 participants

The profile of PHAs at the start of the study were: 1 female, 20 males; average age – 50 years; most had been taking the study drugs for between six and seven months; and PHAs did not change their HAART regimens while the study took place

Results

Changes in HDL-cholesterol levels were +19%, -33% and –20% in Groups A, B and C respectively. These differences were statistically significant.

Changes in triglyceride levels were – 27%, + 48% and - 9% in Groups A, B and C respectively.

When participants on combination lipid therapy stopped taking either drug, HDL-c concentrations rose to pre-study levels.

Note that PHAs taking fenofibrate alone (group A) had the expected increase in HDL-c and decrease in triglycerides.

The research team is not certain why HDL-c levels fell with combination lipid therapy, and they think an interaction between the two drugs is not likely. They hope that their report will stimulate other researchers to study the issue and find an explanation. Until this happens, the Vancouver researchers suggest that the combinations of fenofibrate and rosiglitazone be used with caution.

References

1. Normen L, Frohlich J, Montaner J, et al. Combination therapy with fenofibrate and rosiglitazone paradoxically lowers serum HDL cholesterol. Diabetes Care 2004;27(9):2241-2242.
2. Davidson MH and Toth PP. Combination therapy in the management of complex dyslipidaemias. Current Opinion in Lipidology 2004;15:423-243.

http://www.catie.ca

HEPATITIS COINFECTION

3TC-resistance leads to hepatitis B flare

Graham McKerrow, HIV i-Base

Doctors in Melbourne, Australia, report a severe and prolonged flare of hepatitis B in an HIV-HBV co-infected patient, which they believe was caused by the emergence of 3TC-resistant HBV together with a strong and prolonged HBV-specific CD8 T cell response.

The patient was a 40-year-old man diagnosed with HIV and HBV in 1998; treatment with d4T, 3TC and nevirapine was commenced. However, after three months the HIV load remained high and the regimen was changed to AZT, ddI and nelfinavir. The viral load then fell to less than 50 copies/ml. Eighteen months after the initial diagnosis, the man was referred for management of severe hepatitis.

Sequencing of the HBV genome isolated from the patient's serum did not identify compensatory mutations in the HBV polymerase that may have restored viral replication. "However, a strong HBV-specific CD8 T-cell response was identified and may have resulted in the severe hepatitis," write Theo Gouskos and colleagues in the journal AIDS.

C O M M E N T

This case report adds to the increasing body of literature on the dangers of lamivudine montherapy for the treatment of HBV in HBV/HIV co-infection. Other studies have reported around 90% lamivudine resistance by four years in HBV/HIV co-infected patients. Although not all 'YMDD' mutants have increased replicative capacity, this may occur in some cases where further compensatory mutations develop.

As demonstrated here, the mechanism of the flare is multifactorial, and an immune restoration phenomenon resulting from the HAART in the presence of replicating HBV (even at low levels) may be enough.

Current BHIVA guidelines suggest considering a HAART regimen that includes tenofovir and lamivudine for patients with viraemic HBV/HIV co-infection. This should prevent the emergence of lamivudine-resistance mutations in HBV.

Ref: Gouskos T, Wightman, F, Chang J et al. Severe hepatitis and prolonged hepatitis B virus-specific CD8 T-cell response after selection of hepatitis B virus YMDD variant in an HIV/hepatitis B virus coinfected patient. AIDS 2004, Vol 18 No 12, 1734-7.

Sight changes reported with PEG-interferon

Sean Hosein, CATIE News

Hepatitis C virus (HCV) infects the liver and over the long-term can cause serious damage to this vital organ. Some people with HIV/AIDS (PHAs) are co-infected with hepatitis C. Treatment for HCV infection is a combination of a long-lasting form of interferon, peginterferon (Pegetron, Pegasys), together with the drug ribavirin.

Like all treatments, peginterferon can cause side effects, including tiredness, lack of energy and depression. Now, researchers at the US National Institutes of Health (NIH) have reported that peginterferon treatment may be linked to temporary eye complications in as many as 35% of co-infected PHAs in one study.

Researchers monitored 23 co-infected participants who had the following baseline characteristics at the start of the study, before they began to receive HCV treatment: CD4+ T cell count – 533 cells/mm^3; HIV viral load – less than 50 copies/mL; HCV viral load – 3.3 million copies; all but four of the participants were taking anti-HIV drugs.

Before receiving HCV treatment, all participants had eye examinations and doctors found no problems. During the study, eye examinations were scheduled regularly (at least every three months). Standard doses of peginterferon and ribavirin were given for up to one year.

A total of eight participants (35%) of the group developed temporary eye complications including cataracts, decreased colour vision and cotton wool spots.

Five months after beginning therapy with peginterferon, cataracts — clouding of the lens of the eye — occurred in two people. The cataracts did not become worse while the people continued therapy but they did not resolve.

Two participants had changes to their ability to see red and green colours. In one case this was so severe that doctors stopped further use of peginterferon; two and a half months later colour vision returned to pre-study levels. In the other case, colour vision returned to normal despite continued use of peginterferon.

Cotton wool spots (CWS) are small white patches on the retina, the light sensitive area at the back of the eye. CWS occur when the nerves that make up the retina are damaged because their blood supply has been reduced. This can occur in people with diabetes and high blood pressure. Sometimes CWS can be associated with blurred vision but usually they are not linked to any particular symptom and are only seen on examination by an ophthalmologist. In the time before HAART, CWS were a common finding in studies of PHAs. In the present study, all seven participants with CWS had them clear despite continued use of peginterferon.

The three types of eye complications occurred in participants who had relatively high CD4 counts (around 533 cells/mm^3). The research team is not sure why the eye complications occurred in some PHAs and not others. Clearly, further study is needed with a larger number of co-infected PHAs to begin to gain a better understanding of these interferon-related (and possibly ribavirin-related) problems. Such studies, it is hoped, will include a careful evaluation of pre-existing complications—diabetes, high triglycerides, high blood pressure — as well as potential drug interactions.

Other studies of eye complications

The rate of vision complications in the NIH trial appears to be high (35%). But another study by researchers in Japan, using regular interferon in HIV negative people with HCV infection, has found similar rates of eye complications — mostly cotton wool spots. In that study, researchers gave some participants vitamin C 600 mg/day to see if this would prevent the development of CWS but it did not. The Japanese research team speculates that because CWS can disappear two to three weeks after first appearing, they may not be noticed between visits to an ophthalmologist and may therefore be under-reported.

A study of regular interferon and ribavirin, also in HIV negative people with HCV, by American ophthalmologists found a high rate of eye complications (64%) — again, mostly CWS. A Canadian study in a similar population found that CWS were the most common eye complication, but they faded despite continued therapy. An unusual finding from the Canadian study was that patients whose HCV levels were not falling significantly or who were at risk of having HCV infection relapse were at increased risk of eye complications.

Studies in co-infected PHAs

Reports from two other clinical trials (Apricot and ACTG A5071) do not appear to have noted high rates of changes in vision in HCV-co-infected PHAs receiving either regular or peginterferon and ribavirin.

In ending their report, published in the 3 September issue of the journal AIDS, the NIH team suggests that regular eye examinations by an ophthalmologist may be needed in co-infected PHAs who take peginterferon and ribavirin.

C O M M E N T

Eye complications with interferon therapy have been reported previously, and include retinal vascular proliferation and heamorrhages, cataracts, changes in colour vision and cotton wool spots (CWS).

CWS are the commonest and benign, and have also been reported in HIV patients without interferon therapy.

Most clinicians now recommend a pre-treatment ophthalmology review and ask patients to report any changes in vision immediately.

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BMS submits marketing applications for entecavir to treat HBV in US and Europe

Bristol-Myers Squibb Company has announced the submission of a New Drug Application to the US Food and Drug Administration for entecavir, an investigational antiviral agent under development for the treatment of chronic Hepatitis B. The company also submitted a marketing authorisation application for entecavir to the European Medicines Evaluation Agency.

Entecavir is an investigational oral antiviral discovered at Bristol-Myers Squibb that is designed to selectively inhibit the Hepatitis B virus, blocking all three steps in the replication process.

Source: BMS press release

http://www.bms.com/news/press/data/fg_press_release_5036.html

PREGNANCY AND MTCT

Study raises questions about cost effectiveness of nevirapine regimen

Polly Clayden, HIV i-Base

A cost effectiveness analysis published in the 20 August 2004 edition of AIDS reports that the efficacy of the nevirapine regimen for reducing mother-to child transmission in a field setting is much lower than desired and despite the low cost of the drug itself requires significant financial resources to implement successfully.

Four-component strategy

The authors explain that the United Nations (UN) agencies recommend a four-component strategy for reducing HIV-infection in children:

- HIV prevention particularly in young women;
- Prevention of unintended pregnancy in HIV-infected women;
- Reduction of MTCT through interventions with antiretroviral drugs, safer delivery and infant feeding;
- Care, treatment and support to HIV-infected women, their infants and their families.

However, the third component, particularly the use of antiretroviral drugs, has dominated the focus of donors and researchers in the MTCT field. Although in the developed world, use of effective interventions has meant that MTCT has been virtually eliminated, in developing countries interventions have been difficult to implement due to high costs and lack of healthcare infrastructure. Single-dose nevirapine to the mother and a single dose to the infant - according to the HIVNET 012 results published in 1999 - have been the most widely discussed strategy. The authors also emphasise that although in a trial setting this intervention has been shown to reduce MTCT by approximately 47%, for very little cost, in a field setting clinics frequently need additional financial and technical resources to implement the protocol. “Thus, the benefits of low cost and simplicity of the intervention may not always be realised in practice,” they write.

Additionally they explain that less attention has been given to the other components of the UN strategy and funds are primarily being dedicated to this single intervention. The study examines these issues by modeling the cost-effectiveness of single-dose nevirapine interventions for HIV-infected women and their infants using field data from eight sub-Saharan African countries. National programme costs and impact on infant infections, and reductions in adult HIV prevalence and unplanned pregnancies among HIV-infected women that would have equivalent impact on infant infections prevented by the nevirapine are analysed. The model outcomes include total national programme costs, the number of infant infections averted, the cost per HIV infection averted, and the cost per disability adjusted life year (DALY) saved by the intervention.

The primary research question was: “What are the health benefits for national health care systems to invest in a short-course nevirapine intervention for HIV infected pregnant women, and what reduction in adult HIV prevalence and reduction in the number of HIV-infected women who become pregnant, would yield equivalent reductions in infant HIV transmission as the nevirapine intervention.”

Data from antenatal clinics from Botswana, Cote D’Ivoire, Kenya, Rwanda, Tanzania, Uganda, Zambia and Zimbabwe were used. These countries were selected because they have high HIV prevalence among pregnant women and great differences in uptake of the various stages involved in accessing the nevirapine intervention. The investigators report wide variation in cost outcomes across countries.

Base-case cost effectiveness results

In this analysis the average national programme costs for the intervention were $3,646,703, this ranged from $439,537 in Botswana to $6,679,675 in Uganda. The average cost per HIV infection averted was $3,813, ranging from $1,808 in Botswana

to $9,258 in Cote d'Ivoire. The cost per DALY saved ranged from $58 in Botswana to $310 in Cote d'Ivoire. They noted that healthcare systems accounted for most programme expenses, followed by HIV testing and counselling but drug costs accounted for a very small proportion of the overall costs. Besides the very low cost of the drug, this also reflected the low numbers of eligible women taking up all the interventions and in turn receiving the nevirapine.

Impact of HIV prevalence and unplanned pregnancy

They report that lowering HIV prevalence by just a small amount among women of childbearing age would have an equivalent impact to the nevirapine intervention in reducing infant infection. In Cote d'Ivoire, prevalence would only need to be reduced by 1% from 10% to 9% and in Botswana – where the most cost effective nevirapine intervention was found – a reduction from 43% to 39% would be necessary to produce an equivalent reduction.

Similarly, a minimal reduction in unplanned pregnancies in HIV-positive women would lower the rate of infant infection by the same rate as the nevirapine intervention. The authors cite Kenya and Zambia, lowering the pregnancy rate by 5.6% and 6.6% respectively would have the equivalent impact. In countries where the nevirapine intervention was more cost effective such as Rwanda a greater reduction would be needed, in this case by 35% to achieve the same reduction in infant infection.

Cost effectiveness of more effective regimens

In this study, a sensitivity analysis determined that cost-effectiveness of the nevirapine intervention was highly sensitive to the effectiveness of the regimen. The amount of money that would be equivalent to the nevirapine intervention was calculated as cost per DALY saved, this could then be spent on alternative peri or postnatal regimens or strategies. The model uses a drug cost of $0.27 for the nevirapine and an effectiveness rate of 47% in reduction of mother to child transmission.

The authors explain that it has been suggested that more costly antiretroviral regimens are either unaffordable or not cost effective in most developing countries. Compared to the across country base-case analysis in this evaluation, however, they report that $152 could be spent per pregnant woman to maintain an equivalently cost effective programme to the nevirapine intervention if the efficacy of that intervention were 70%.

The greatest expense

Overall, this analysis found that the greatest expense in scaling up antiretroviral programmes to reduce mother to child transmission will be the cost of building up the healthcare system to implement them successfully. The authors believe that earlier analysis of the cost-effectiveness of these programmes have either not accounted for or underestimated the limitations of current healthcare systems in Africa. The estimated cost per DALY saved of a mean of $127 across all eight African counties evaluated far exceeds earlier published estimates of $11.29.

They point out though that overall this intervention should be considered cost effective, although variable across countries and less so than previously reported. The finding that programmes could spend up to $152 per woman on an antiretroviral drug that had 70% efficacy and achieve the same cost effectiveness as the current nevirapine programmes is important, and the authors add: "Therefore spending more on the eligible women who actually make it through the system and receive the antiretroviral drug would be more efficient and effective."

Ref: Sweat M, O'Reilly KR, Schmid GP et al. Cost-effectiveness of nevirapine to prevent mother-to-child HIV transmission in eight African countries. AIDS: Volume 18(12) 20 August 2004 pp 1661-1671.

Low effectiveness of nevirapine to reduce MTCT in real life situation

Polly Clayden, HIV i-Base

A research letter in the 3 September edition of AIDS discusses the effectiveness of nevirapine in reducing mother to child transmission in a field setting in Mombasa, in which mother to child transmission rates were similar to those found using no intervention. The authors point out that although the HIVNET012 regimen has been widely recommended, data to validate the effectiveness of this strategy outside a research setting are lacking.

In the study - conducted between April 2001 and October 2003 - HIV-positive women received nevirapine and instructions to use it at the onset of labour, and were invited to participate in the follow up study. Infant blood was taken at 6 and 14 weeks and DNA PCR were performed. When no sample was available at 6 weeks, the result of the 14-week sample was used to calculate transmission rates, when there was no 14 week result and the 6-week sample was negative, the results were not included in the calculation of the overall perinatal transmission rate. A child was considered HIV positive when the 6-week sample was positive and the 14-week sample missing.

The programme enrolled 482 women, and 172 presented for follow up at 6 or 14 weeks. The investigators report, over 58% of the women delivered at the hospital, 19% delivered at home, and 22% delivered in another hospital. More than 85% of the women (147/172) reported taking the maternal dose, 86.0% of babies (148/172) received the nevirapine suspension, and 82% (141/172) reported the administration of both the maternal and neonatal dose.

Samples were available for 127 babies, and the authors report a transmission rate of 18.1% at 14–16 weeks. They write that there was no correlation between the maternal dose intake only, intake by the baby only, or the intake of nevirapine by both mother and baby, and the transmission rates at 14 weeks (p= 0.887, p=0.336 and p= 0.529, respectively).

The authors write that this transmission rate is similar to a perinatal transmission rate at 14 weeks of 21.7% using no intervention in this Mombasa setting, and does not compare well to the HIVNET012 reported rate of 13.1% at 14 weeks.

The authors add: "These data, suggesting a rather limited effect of the widely recommended HIVNET012 intervention, call for further research on the long-term efficacy of the HIVNET012 regimen in a field setting. Taking into account the low coverage of the nevirapine regimen, the lack of benefit for maternal health, the concerns about resistance, the enormous deployment of resources needed to provide nevirapine within the current voluntary counselling and testing paradigm, and the reported lack of efficacy in real life conditions, the true health gains of the intervention should be reconsidered."

Ref: Quaghebeura A, Mutungab L, Mwanyumbac F et al. Low efficacy of nevirapine (HIVNET012) in preventing perinatal HIV-1 transmission in a real life situation. AIDS: Vol 18(13), 3 September. Research Letters 1855.

C O M M E N T

Two articles are presented with data and analysis which result in assessments of the potential financial cost and clinical effectiveness of single dose maternal plus single dose infant nevirapine for the prevention of mother-to-child transmission of HIV-1 that differ from earlier studies. The findings are not particularly surprising and will continue the swing of the pendulum away from this approach which might have begun when the first reports of nevirapine resistance in mothers following single dose exposure were reported - by Eshleman et al - from HIVNET012 but certainly gained momentum in February 2004 when Jourdain et al reported the negative impact of these mutations on maternal treatment at six months.

It is clear to most that single dose nevirapine is not the panacea of MTCT. The trick now is not to throw the baby out with the bathwater. Nevirapine is a highly effective HIV RT inhibitor which efficiently crosses the placenta and which has a long plasma half-life that can be used to advantage. Lallemant et al showed that used in combination with zidovudine monotherapy from 28 weeks single dose nevirapine contributes significantly to reducing pre/intrapartum transmission to 2%. While McIntyre et al demonstrated the addition of Combivir for 4 – 7 days post-partum dramatically limits the development of detectable nevirapine resistance mutations in plasma at 12 days. Whether these two approaches can be successfully combined and the determination of the optimal duration and components of therapy to preserve the use of nevirapine is the next priority.

Meanwhile we should not forget that the prevention of paediatric HIV infection as well as the survival of HIV uninfected children starts with prevention of HIV infection in their parents and with treating those mothers already infected if this is indicated for their own HIV. The point is already implicit in the cost effectiveness analysis but could stand a little more emphasis, some have speculated that all the infrastructure needed for 012 is just about what is needed for treatment. The study also reminds us: "The goal in the *Declaration on HIV/AIDS* of the UN General Assembly Special Session is bold in its mandate, 'reduce the proportion of infants infected with HIV by 20% by 2005, and by 50% by 2010'. We are very unlikely to reach this goal if we concentrate on MTCT single dose nevirapine interventions in isolation.

Use of T-20 at the end of pregnancy to a multi-treated HIV-infected woman with virological breakthrough

Polly Clayden, HIV i-Base

A research letter in the 24 September edition of AIDS describes a French case of a treatment experienced pregnant woman with virological breakthrough treated with enfuvirtide during the last three weeks of her pregnancy.

The 38 year old HIV positive woman became pregnant in January 2003 while receiving an antiretroviral regimen of 3TC, tenofovir and lopinavir/ritonavir (Kaletra). Her CD4 count was 365cells/mm^3 and she had a viral load of 40,522 copies/mL.

The patient was diagnosed in 1990 and treated with zidovudine monotherapy in 1994 (her lowest CD4 cell count of 25 cells/mm^3 was recorded in May 1995) to which 3TC was added in 1995, and indinavir in 1996.

Her CD4 cell count was stable at 300 cells/mm^3 on this regimen, but her viral load remained detectable. Her treatment was changed to d4T, ddI, ritonavir, and saquinavir (Invirase) in 1997 and switched again to d4T, 3TC and efavirenz in 1999 due to lipodystrophy. In August 2001, after virological breakthrough she was again switched to another regimen of 3TC, tenofovir and lopinavir/ritonavir. She became pregnant on this regimen.

She received a genotype resistance test in August 2003, at which time her viral load was 32,961 copies/mL. The test results found her to be resistant to both nucleoside reverse transcriptase inhibitors and protease inhibitors but sensitive to non nucleoside reverse transcriptase inhibitors. Mutations were found at M41L, E44D, D67N, M184V, L210W and T215Y,

indicating resistance to AZT, 3TC, ddI, d4T and abacavir and possible resistance to tenofovir. And at L10F, K20R, M36I, M46L, I54V, L63P, A71V, V82A, I84V and L90M, conferring resistance to all protease inhibitors.

Enfuvirtide and nevirapine were added to her regimen of 3TC, tenofovir and lopinavir/ritonavir three weeks before an elective Caesarean section was performed, and on 10 September 2003 she gave birth to a healthy baby girl.

The neonate was treated at birth with AZT, 3TC and nevirapine, and was PCR negative at day 3, and 1, 3 and 6 months. At the time of delivery, the mother's viral load was 57 copies/mL and her CD4 cell count was 549 cells/mm^3 (16.8%).

The investigators write: "This is the first reported use of enfuvirtide during pregnancy in a patient with virological breakthrough. The HIV viral load was reduced to less than 400 copies/mL at the time of delivery, with no adverse effects in the mother or in the child (up to age 6 months). Despite the very limited experience with enfuvirtide in pregnancy, this case shows the potential value of this fusion inhibitor in preventing maternofoetal HIV transmission."

C O M M E N T

The first report of T-20 in pregnancy confirms that the introduction of two classes of therapy to which HIV is sensitive effectively reduces viral load. This is known to be associated with a reduced risk of transmission.

Treatment appears to have been deferred to late in pregnancy to minimise the risk of further virological rebound before delivery. Little comment can be made on the safety of T-20 in this setting.

Ref: Meyohasa MC, Lacombea K, Carbonneb, B, et al. Enfuvitide prescription at the end of pregnancy to a multi-treated HIV-infected woman with virological breakthrough. AIDS 2004, Vol 18 No 14. Research letters 1966.

PAEDIATRIC CARE

CHIPS data finds response to HAART varies with age in children

Polly Clayden, HIV i-Base

The Collaborative HIV Paediatric Study (CHIPS) is a multicentre cohort of children in the UK and Ireland participating in PENTA trials since 1996. A study reported in the 24 September issue of AIDS evaluates the effect of age, pre-HAART CD4 percentage (CD4%) and plasma HIV-1 RNA on response to highly active antiretroviral therapy (HAART) in treatment naïve children.

The investigators reported that on 1 June 2003, 692 children had enrolled in CHIPS and 462 had received HAART. Of these 324 were drug naïve when initiating HAART regimens and 265 (82%) had both CD4 and viral load values pre-HAART and therefore eligible for this evaluation.

Seventy-seven (29%) children were less than 2 years old. 39 (17%) under one year, 49 (18%) were over 9 years. One hundred and thirty-eight children (52%) had CD4% of 15% or lower at HAART initiation.

The investigators reported that at 6 months, 181 (86%) of children had higher CD4% than at baseline. In univariate and multivariate analyses, adjusted for confounding factors, 10% CD4% increase was more likely at younger age [OR 0.84 per year, p=0.001] and lower pre-HAART CD4% [OR, 0.67 per 5% higher, p=0.001), but was not related to pre-HAART viral load. Effects of AIDS stage, calendar year of HAART initiation or HAART regimen were not significant

Younger age was also associated with a higher chance of achieving CD4% of >30% at 6 months. Children starting with a four drug regimen were more likely to achieve CD4% >30% at 6 months at all ages (OR, 5.48; 95% CI, 1.18-25.5; p=0.03).

Conversely older children were more likely to achieve HIV-1 RNA suppression, <400 copies/ml at 6 months (p= 0.03), and this was unrelated to pre-HAART HIV-1 RNA or CD4%. Children initiating HAART with 4 drugs had a greater likelihood of suppression (adjusted OR, 3.07; 95% CI, 1.04-9.08; p=0.04). Only 57 (27%) children achieved HIV-1 RNA <50 copies at 6 months and the likelihood was also greater in older children (OR, 1.09 per year of age; 95% CI, 1.01-1.18; p=0.02).

CD4% and HIV-1 RNA results were available for 149 children at 24 months and the investigators report that predictors were similar to 6 months results for CD4% increases over 10% at 24 months (overall rate 62% vs 38% at 6 months): initiation of HAART at younger age (OR, 0.87 per year, p=0.02) or with lower CD4% (OR, 0.60 per 5% higher baseline, p=0.0001). There were no predicting factors for viral load suppression <400 copies/ml at 24 months (overall rate 54% vs 60% at 6 months).

The authors write: "The findings from our study suggest that there are critical differences in the predictors of immunological and virological responses to HAART in previously untreated children and adults. Specifically, in children there are substantial

and opposed effects of age on immunological and virological response, and a lack of association between response and pre-HAART HIV-1 RNA…. these results may help inform the timing of initiation of HAART in children: this is likely to be a compromise between improved immunological and poorer virological response (potentially driving the development of resistance) at younger ages, versus the need to avoid clinical disease progression before starting HAART at older ages with poorer immunological and improved virological response." They add "Longer follow up is required to determine whether children with low CD4% prior to HAART are able to normalise CD4 values and improve the quality of immune response."

Ref: Walker SA, Doerholt K, Sharland M et al. Response to highly active antiretroviral therapy varies with age: the UK and Ireland Collaborative HIV Paediatric Study. AIDS 2004, 18:1915–1924.

HAART is effective in African children in a resource-limited setting

Graham McKerrow, HIV i-Base

Researchers in Abidjan, Cote D'Ivoire, and in Paris, France, conclude from a study of the effects ofHAART in an observational cohort of 159 HIV-1-infected children in Cote d'Ivoire, that it is possible to treat African children in a resource-limited setting and that this treatment appears to be as effective as in developed countries.

Cote d'Ivoire is the West African country with the highest prevalence of HIV and 80,000 children under 15 years are infected with the virus, most undiagnosed. This was one of the first studies to analyse the feasibility and results of ARV multitherapy in African children.

The researchers followed 78 (49%) children receiving HAART for a mean duration of 21 months. Mean age of treatment initiation was 7.2 years (median 6.5; range 0.7-15.2). All were from families with limited resources and 29 were from very poor families (income less than 30 euros a month). The children were given trademark drugs with the exception of d4T (30mg) which was replaced for a few months by a generic made by Cipla in India. Due to a shortage of ddI and 3TC, treatment was totally interrupted in eight children for a total of 204 days (median and mean 25.5). Two NRTIs were given with either a PI or an NNRTI. Thirteen of the youngest children received the drugs as syrup, the rest received adult formulations, doses calculated according to weight.

Z-score, CD4 count and viral load were measured before starting HAART and every six months thereafter. Probability of survival and incidences of pneumonia and acute diarrhoea were calculated.

Mean weight-for-age Z scores before treatment were –2.02 and after 620 days were -1.39 (P<0.01). Mean height-for-age Z scores were –2.03 before and –1.83 after (P=0.51). Incidence of pneumonia was 0.07/child-month before and 0.025 after (P=0.002). Incidence of acute diarrhoea was 0.12/child-month before and 0.048 (P<0.001) (incidence changes statistically significant only in children <6.5 years).

Overall the probability of survival under HAART was 72.8% at 24 months for children with <5% CD4+ T cells versus 97.8% in children with >/=5% (P=0.01).

At start of treatment, median viral load was 5.41 $\log_{10}$ copies/mL and CD4 percentage was 7.7%. After an average of 756 days on treatment, 50% of patients had viral load below detection and 10% had 2.4-3.0 $\log_{10}$ copies/mL. The median CD4 percentage was 22.5%.

In their Discussion, the authors write that under HAART, HIV RNA viral load was below the detection limit in about 50% of children, and 60% had <1000 copies/mL (3 $\log_{10}$ copies/mL). This is similar to what is generally observed in Europe and the United States.

They point out: "It will be a long time before antiretroviral treatment becomes generally available for children in Africa. Nevertheless, treatment for HIV should cover the whole family, including children. We hope that our study will help to eliminate the feeling of inevitability that surrounds this disease in children in Africa."

C O M M E N T

These results are clearly impressive. They demonstrate that children in the developing world can be successfully treated. This group deserves congratulations.

Ref: Fassinou P, Elenga N, Rouet F et al. Highly active antiretroviral therapies among HIV-1-infected children in Abidjan, Cote d'Ivoire. AIDS 2004, 18 (14) 1905-13.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15353976

Predictive factors of virologic success in HIV positive children treated with lopinavir/ritonavir

HIVandHepatitis.com

Predictive factors of the virologic success of the use of the protease inhibitor lopinavir/r (Kaletra) in HIV-infected children are unknown, especially in children who have been pretreated with protease inhibitors (PIs).

This longitudinal, single-centre, observational study included 69 children (21 PI-naive and 48 PI-experienced) who had received LPV/r for at least 3 months. The mean (+/-SD) age was 10.3 +/- 4.8 years, and the mean baseline of CD4+ T cell percentage and HIV-1 RNA was 14.9% +/- 9.8% and 4.8 +/- 1.05 log10 copies/mL, respectively.

The mean duration of follow-up was 16.5 +/- 8.3 months.

At 6, 12, and 18 months, 52%, 57%, and 49% of all children, respectively, had a viral load less than 50 copies/mL. The risk of virologic failure, defined as two consecutive viral loads greater than 1000 copies/mL, was significantly higher when the children were previously treated with PIs and when the baseline LPV mutation score exceeded 3 mutations.

In the pretreated children, the ratio of the plasma LPV maximal concentration to the baseline LPV score mutation was also associated with failure, independently of resistance score.

Finally, in children failing an LPV-containing regimen, accumulation of additional PI-associated resistance mutations was evidenced in viral isolates from children with prior PI treatment, even with viral replication levels less than 10,000 copies/mL.

The authors conclude: “In pretreated children, LPV plasma levels should be optimised in an attempt to achieve sufficient drug concentrations to overcome the resistance level.”

Source: HIVandHepatitis.com

Ref: Delaugerre C et al. Predictive factors of virologic success in HIV-1-infected children treated with lopinavir/ritonavir. Journal of Acquired Immune Deficiency Syndromes 37(2): 1269-1275. 1 October 2004.
http://www.hivandhepatitis.com/recent/children/100404_a.html

OPPORTUNISTIC INFECTIONS

Clinical features and predictors of survival in patients with AIDS-related non-Hodgkin’s lymphoma

HIVandHepatits.com

In this study, Australian researchers analysed the clinical features and predictors of survival for AIDS-related non-Hodgkin’s lymphoma (NHL) in the era of HAART, compared to earlier in the HIV epidemic.

All AIDS-NHL cases diagnosed at three inner Sydney hospitals caring for people with AIDS during 1985-2001 were identified through medical record searches. Demographic, clinical, immunological and histopathological information was recorded. Year of NHL diagnosis was grouped into three periods, corresponding to whether monotherapy (1985-1991), dual therapy (1992-1995) or HAART (1996-2001) was the main treatment for HIV infection. Statistical comparisons were made between the pre-HAART and post-HAART eras.

Three hundred cases of AIDS-NHL were identified. Divergent trends were identified for systemic and primary central nervous system (CNS) NHL. For systemic NHL, the CD4+ T cells count at NHL diagnosis increased markedly to 208 cells/mm3 in the post-HAART era (P=0.014) and there was a trend towards presentation as the first AIDS-defining illness (69%, P=0.053), and as earlier stage NHL disease (42%, P=0.048). Median survival time increased from 4.2 months in 1985-1991 to 19 months in the post-HAART era (P<0.001).

In a multivariate model, predictors of poor survival from systemic NHL included: NHL diagnosis after another AIDS-defining illness (P<0.001), stage 4 NHL (P<0.001), presentation at extra lymphatic sites (P=0.001), and non-receipt of chemotherapy (P=0.002).

After adjusting for the factors, those diagnosed in the era of HAART had a significant 56% reduction in rate of death (P<0.001). In contrast, for CNS NHL, clinical features were little changed and survival did not improve in the era of HAART.

The study concluded that systemic NHL is presenting earlier in the course of HIV disease, and at a less advanced NHL stage. There has been a marked improvement in survival in the era of HAART even after adjustment for other prognostic variables. In contrast, primary CNS NHL remains a disease that presents late in the course of HIV infection and is associated with a very poor prognosis.

Source: HIVandHepatitis.com

http://www.hivandhepatitis.com/recent/malignancies/092404_f.html

Ref: Robotin MC et al. Clinical features and predictors of survival of AIDS-related non-Hodgkin's lymphoma in a population-based case series in Sydney, Australia. HIV Medicine 5(5): 377-384. September 2004.

OTHER NEWS

Dispersal of HIV-positive asylum seekers: national survey of UK healthcare providers

Beginning April 2000, the UK National Asylum Support Service initiated a policy of dispersing asylum seekers from London and southeast England to locations around the United Kingdom in an effort to diffuse health care costs. More than 100,000 asylum seekers to date have been dispersed, many of whom are from regions with HIV epidemics. It is not known how many HIV- positive seekers have been affected by the policy. Asylum seekers may receive only 48 hours notice, and they face immediate cessation of income, housing and legal benefits if they decline dispersal.

In the current study, the authors surveyed lead clinicians working in genitourinary medicine clinics about their experiences and opinions of the dispersal of HIV-positive asylum seekers. Centres that do not treat HIV-positive patients were excluded. In December 2003, anonymous questionnaires were sent to doctors asking about the appropriateness of dispersal in 10 clinical scenarios and about perceived barriers to effective dispersal.

Fifty-six of 75 eligible centres returned questionnaires; 34 of these were outside London, and 20 had had an HIV-positive asylum seeker dispersed to them. A total of 13 centres reported patients dispersed both to and from them.

Of the 56 returned questionnaires, frequently cited barriers to successful dispersal were dispersal at short notice (37) or with no prior arrangement (43). Just three centres had experienced appropriate transfer of care. Additional barriers cited included lack of community support (41), low staffing levels in the receiving centre (40), and lack of facilities to support vulnerable asylum seekers with psychological problems (43).

Some doctors spontaneously listed negative consequences attributed to dispersal, although the questionnaire did not inquire about such. Problems relating to unintentional interruption of antiretroviral therapy (4), mother-to-child HIV transmission (3), and HIV-related death (2) were reported. Many of the 56 returned questionnaires said dispersal of HIV-infected asylum seekers was inappropriate in certain situations - during initiation of HIV therapy (47), in patients receiving salvage treatment (43), in those currently undergoing medical investigations (50), where care involved multiple medical specialties (52), and when patients had progressed to AIDS (45).

Of the potential barriers to safe dispersal of HIV-infected asylum seekers, it is of particular concern that dispersal is done at short notice and frequently without appropriate transfer of medical information, the researchers noted. "Inappropriate dispersal of an HIV infected patient could lead to HIV resistance, onward transmission of HIV infection and avoidable morbidity and mortality for the asylum seeker," the researchers noted. "Before the decision to disperse, the National Asylum Support Service should seek specialist advice and consider the impact on the infrastructure and staffing of the receiving centre," they concluded.

Source: CDC HIV/STD/TB Prevention News Update, via AEGiS

http://www.aegis.com/channel/s/AD041664.html

Full article available online at bmj.com (free registration required):

Ref: Creighton S, Sethi G, Edwards SG et al. British Medical Journal (08.07.04) Vol. 29; No. 7461: P. 322- 323 - Monday, August 16, 2004.

http://bmj.bmjjournals.com/cgi/content/full/329/7461/322?ecoll

Medical journals require pre-trial registration in public database as criteria for submission for publication

A statement form the International Committee of Medical Journal Editors, whose members include The Lancet, New England Journal of Medicine, JAMA and Medline (US National Library of Medicine) committed these and other member publications to new criteria for any study reports submitted for publication.

The move is an attempt to maintain a record of trials that find either negative or inconclusive results and which are less likely to be submitted for publication.

All studies need to be registered at or before patient enrollment on a 'free-to-view' accessible electronically searchable database that is managed by a not-for-profit organisation.

An acceptable registry must include at minimum the following information: a unique identifying number, a statement of the intervention (or interventions) and comparison (or comparisons) studied, a statement of the study hypothesis, definitions of the primary and secondary outcome measures, eligibility criteria, key trial dates (registration date, anticipated or actual start date, anticipated or actual date of last follow-up, planned or actual date of closure to data entry, and date trial data considered complete), target number of subjects, funding source, and contact information for the principal investigator.

The statement only mentions one currently available database that meets these criteria:

http://www.clinicaltrials.gov

Source: Editorial, NEJM, September 2004

ON THE WEB

Conference abstracts and reports:

13th International HIV Drug Resistance Workshop

8-12 June 2004, Tenerife Sur-Costa Adeje, Canary Islands, Spain

The 13th International HIV Drug Resistance Workshop abstracts have been loaded to the AEGiS conference database. They are available in both PDF and XHTML files. The HTML files are fully indexed, cross-referenced, and keyword searchable.

HTML files are located at:

http://www.aegis.org/conferences/13thHIVDrugResWkshop/

Second Salvage Therapy Think Tank

On 16 and 17 April 2004, the "Salvage Therapy II Think Tank" was held at the Baylor College of Medicine in Houston at the Texas Medical Centre. This meeting was co-sponsored by The Centre for AIDS (CFA) and the Forum for Collaborative HIV Research. The Centre for AIDS Research (CFAR) at Baylor College of Medicine and at The University of Texas Health Science Centre was a local planning partner. This meeting was dedicated to the memory of L. Joel Martinez, the founder of The CFA, who passed away in November 2003.

http://www.centerforaids.org/rita/0904/summary.htm

Prevention, planning, resistance, toxicity: IAPAC sessions 2004

Report by Mark Mascolini from this medical workshop for doctors held in Chicago earlier this year.

Discussions and presentations covered include transmission risk and ARV treatment, reinfection, perinatal HIV testing, rapid HIV tests, antiretroviral and treatment strategies and a very useful overview of lipodystrophy and metabolic research.

IAPAC Monthly - Vol. 10, No. 6, June 2004.

http://www.iapac.org

HIV and TB meeting

The presentations from the 4th TBHIV Working Group meeting in Addis Ababa on 20-21 September and the CDC TBHIV Surveillance Workshop on 22-24 September are now on-line at:

http://www.who.int/gtb/TBHIV/4thglobalwgmtg/agenda_files/index.htm

Hepatitis coinfection:

Liver transplantation in patients with HIV infection

Several articles and papers have been published online over the last month that address liver transplantation in HIV-positive patients.

A comprehensive & seminal review by the leading HIV-positive liver transplant surgeons at the University of Pittsburgh, a must read; includes results from published transplants data. pdf of article is available to download.

http://www.natap.org/2004/Transplantation/092104_02.htm

The British HIV Association (BHIVA) held a consensus meeting on transplantation in the summer and has produced a document that can be downloaded from the BHIVA website:

http://www.bhiva.org

Overview of current and pipeline hepatitis treatment

An Interview with Melissa Palmer MD, author of a Guide to Hepatitis and Liver Disease that discusses current therapies for HIV/HCV coinfection, new agents in development and nutritional supplements.

http://www.medadvocates.org/resources/thoughtleaders/palmer/palmer.htm#gordon_interview

Online medical education:

HIV inSite Knowledge Base

Managing medical conditions associated with cardiac risk in patients with HIV

Daniel Wlodarczyk MD, August 2004.

http://hivinsite.ucsf.edu/InSite?page=kb-03-01-20

HIV Web Study

Interactive, case-based modules for HIV clinicians from the Northwest AIDS Education and Training Centre at the University of Washington.

http://depts.washington.edu/hivaids/

Newsletters and Journals Online:

SFAF Beta – summer 2004

HIV and hormones - Liz Highleyman

http://www.sfaf.org/treatment/beta/b55/index.html

amfAR Treatment Insider – September 2004

Crunching the numbers on pharmaceutical companies - Elizabeth Paukstis

Sky-high drug prices are now a fact of life in the US, but debate is raging over the reasons why. Read about a variety of viewpoints and get the low-down on how drug companies spend their money.

http://www.amfar.org/cgi-bin/iowa/td/feature/record.html?record=132

Pipelines Flourish, But Not for HIV by Kristen Kresge

Despite robust pipelines of potential drugs, fewer new medicines are reaching consumers. As pharmaceutical companies consolidate their disease targets, anti-HIV drug development could pay the price. Find out the latest status of antiretroviral research

http://www.amfar.org/cgi-bin/iowa/td/feature/record.html?record=134

PUBLICATIONS AND SERVICES FROM i-BASE

UK-Community Advisory Board: reports and presentations

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

Reports and presentations for the ninth meeting, held on 31 May 2004, are posted to the i-Base website and are available in printed format. The training session at this meeting included an introduction to the immune system, a summary of community involvement in UK-based research into vaccines, microbicides and other new prevention technologies, an introduction the International AIDS Vaccine Initiative, an update on post-exposure prophylaxis and updates on microbicides.

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

Transcriptions and slides of training sessions from previous meetings also on the site include:

- An introduction to statistics, by Dr Caroline Sabin
- Genetics, resistance and HIV - Professor Clive Loveday
- Approaches to Salvage Therapy - Dr Mike Youle
- Pregnancy, HIV and Women's Health - Dr Karen Beckerman
- Fertility treatment and sperm-washing - Dr Leila Frodsham
- Access to treatment for UK visitors, refugees and asylum seekers - Linda McDonald
- Resistance, Lipodystrophy and IAS Report - Simon Collins
- TB and HIV coinfection - Dr Anton Pozniak

World CAB Report: focus on international drug pricing

Report from a meeting in February 2004 of community advocates and three major pharmaceutical companies that focussed on pricing issues and global access to treatment.

Available to download as a pdf file. See website below

The i-Base website

Our web address is

http://www.i-Base.info

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

The site gives details about i-Base, the UK Community Advisory Boards (UK-CABs), our phone service and meetings, as well as access to our archives and an extensive range of links. It can be used to order publications and regular subscriptions to be delivered by post or email (as pdf files).

Introduction to Combination Therapy

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

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

Guide to HIV, pregnancy & women's health

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

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

Guide to changing treatment: second-line and salvage therapy

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

Guide to avoiding & managing side effects

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

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

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

Italian treatment guides

We have Italian versions of our three treatment guides: Introduction to Combination Therapy, Guide to Changing Treatment and Guide to Avoiding and Managing Side Effects. For details of what is in each guide, see under the separate headings on these pages. The Italian guides are available in a single printed publication (to order ring the office on 020 7407 8488).

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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: To order copies or subscribe, see below.

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h-tb

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

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