TREATMENT ACCESS

- WHO releases guidelines for use of antiretroviral drugs to treat HIV infection in developing countries
- Mbeki backs down: he shuns dissidents and expands drug treatment programme
- Early access programme offers adefovir for treatment of HBV

CONFERENCE REPORT:
9th CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS (CROI), SEATTLE, FEBRUARY 24-28 2002
- New research points the way for future treatment of women with HIV

WORKSHOP REPORT:
THIRD INTERNATIONAL WORKSHOP ON CLINICAL PHARMACOLOGY OF HIV THERAPY, WASHINGTON, 11-13 APRIL 2002
- Three studies compare gender differences in use of antiretrovirals

ANTIRETROVIRALS

- Amprenavir mutations may significantly affect LPV resistance
- Neuropsychiatric complications of nevirapine treatment
- Resistance mutations continue to accumulate with low-level viral increases
- 24-Week results from Phase III study of HIV fusion inhibitor T-20
- Resistance to template-analogue inhibitors linked to impaired replication
- Abacavir treatment limited by prior NRTI exposure

METABOLIC TOXICITIES AND SIDE EFFECTS

- Paracardial fat in HIV-infected patient resembles pericardial effusion

OPPORTUNISTIC EVENTS

- Filgastim seems to increase survival in AIDS patients but the mechanism remains unclear
- Oral valganciclovir is as effective as intravenous ganciclovir for induction treatment of CMV retinitis

PAEDIATRICS

- CCR5 density on CD4 cells governs course of HIV infection in children
- Saquinavir is a suboptimal treatment for children unless used in combination

PATHOGENESIS

- Measles found to suppress HIV

TREATMENT GUIDELINES

- First audit of BHIVA treatment guidelines reveals suboptimal access to viral load and resistance tests

OTHER NEWS

- New cancer drugs might help HIV — but research not done
- First report of acquired HCV immunity lifts vaccine hopes
- Manganese blocks HIV replication; lab finding points to a potential new class of HIV treatments
- Turmeric may slow multiple sclerosis progression
- 1,500 community representatives expected at Barcelona community forum

ON THE WEB

- Medscape coverage of the 9th Conference on Retroviruses and Opportunistic Infections
- Fibrates and statins and glitazones (Oh My!)
- Nutrition and immunity: you are what you eat
- The role of dietary supplements in HIV
- Using evidence to make nutrition decisions: a look at zinc
- Peripheral neuropathy
- A weapon in the battle against HIV: your immune system

PUBLICATIONS AND SERVICES FROM i-BASE

- A new issue of Positive Treatment News (PTN)
- Changing treatment: an updated guide to second-line and salvage therapy
- French and Chinese translations of our booklet on avoiding and managing side effects
- Tailor-made information for you
- Order i-Base publications via the internet, post or fax
WHO releases guidelines for use of antiretroviral drugs to treat HIV infection in developing countries

The World Health Organisation has issued guidelines for the treatment of HIV in developing nations and included 12 antiretroviral drugs for that indication on its Essential Medicines List, a move that suggests “the debate over whether the world’s poorest AIDS patients are ready for triple therapy has moved from rhetoric to practical planning,” the Washington Post reports.

The guidelines are basically a “short instruction manual” for health care providers in the developing world that recommends when to offer antiretroviral treatment to a patient, which drug combinations to try first, how to determine when a drug regimen is not working and how to amend drug regimens so that they work better.

Although the recommendations outline a standard of treatment “very close to that in the United States,” they also include “a few concessions to the harsh realities of medical care” in the developing world, the Post reports. For example, the guidelines suggest initiating antiretroviral treatment when CD4+ T cell counts fall below 200 per cubic millimetre, a level lower than that commonly used in the United States and other developed nations.

In addition, the guidelines suggest that antiretroviral therapy can be started or altered based on a patient’s clinical condition in situations where laboratory tests are not available (Brown, Washington Post, 23 April).

‘Antiretroviral Treatment Endorsed - The WHO Essential Medicines List’ is updated every two years and identifies drugs that the organisation views as essential for disease treatment. The list is meant to “encourage” governments to make such treatments more widely available.

Nevirapine and zidovudine were previously included on the list for reducing the risk of vertical HIV transmission, but the updated list also recommends that the drugs be used for treatment of HIV in adults and children.

The list also includes 10 other antiretroviral medicines: abacavir, didanosine, efavirenz, indinavir, lamivudine, lopinavir, nelfinavir, ritonavir (low-dose), saquinavir and stavudine.

The WHO stated that the decision to include the drugs on the list of essential medicines was based on “a careful analysis of current evidence of antiretroviral efficacy in developing countries, which shows that these medicines can be used effectively and safely in poor settings” (WHO release, 22 April).

In its guidelines, the WHO recommended the use of triple-drug antiretroviral therapy and listed several drug combinations that can be used in such regimens. One such combination consists of a pill that includes both zidovudine and lamivudine, along with a third drug, such as efavirenz, nevirapine or abacavir.

Outlining which drugs should be used in combination therapy “is a way to avoid all the waste and confusion and tendency to create resistance that exists in all the weird combinations that people came up with before,” Dr Jonathan Quick, WHO’s director of Essential Drugs and Medicines Policy, said.

Quick added that recommending certain drug combinations also encourages generic drug makers to put three drugs in one pill, which simplifies treatment regimens.

But Dr Harvey Bale, director of the International Federation of Pharmaceutical Manufacturers Associations, said that although large pharmaceutical manufacturers do not oppose the inclusion of patented drugs on the essential medicines list, combining three drugs into one pill is difficult and any such combinations must be “thoroughly tested.”

The New York Times reports that large drug makers do not produce such combination pills because the patents to the drugs are often held by several different companies (McNeil, New York Times, 23 April). The WHO hopes that ultimately, three million people in the developing world will be on triple-drug antiretroviral therapy by 2005 (Washington Post, 23 April).

The New York Times reports that the WHO guidelines aim to “silence several sets of critics: drug industry executives who have argued that triple [drug] therapy is too complex and dangerous for poor, illiterate patients; AIDS sceptics like President Thabo Mbeki of South Africa who argue that the drugs don’t work or are toxic; and experts who confuse public health doctors in poor countries by overwhelming them with competing drug combinations.”

Carmen Perez, pharmaceutical director for Médecins Sans Frontières, called the recommendations a “very good victory.” When coupled with the WHO’s recommendations of quality manufacturers released last month, the guidelines provide countries with “the three bits of information they need — the names of the drugs, the quality assurance and the treatment guidelines,” she said (New York Times, 23 April).

UNAIDS executive director Peter Piot added: “The antiretroviral treatment guidelines developed by WHO will greatly assist
The guidelines are timed to coincide with the first round of grants to be issued by the Global Fund to Fight AIDS, Tuberculosis and Malaria. Officials hope that the recommendations will be used by countries that receive money from the fund (Zimmerman, Wall Street Journal, 23 April).

A copy of the guidelines can be viewed online. The Essential Medicines List can also be viewed online.

Global Fund to Fight AIDS, Tuberculosis and Malaria:
http://www.globalfundatm.org/

WHO Guidelines for Use of Antiretroviral Drugs to Treat HIV Infection in Developing Countries (PDF file):

WHO Essential Medicines List:
http://www.who.int/medicines/organization/par/edl/expertcomm.shtml

Source: Kaiser Network Daily Reports

**Mbeki backs down: he shuns dissidents and expands drug treatment programme**

Graham McKerrow, HIV i-Base

President Thabo Mbeki of South Africa has distanced his government from the controversial advice of AIDS dissidents that included denying a link between HIV and AIDS, and dismissing antiretroviral drugs as toxic.

The cabinet has decided to make nevirapine universally available to HIV-positive pregnant women and their children in order to reduce mother to child transmission of the virus. Zidovudine will also be provided at state hospitals as post-exposure prophylaxis for rape survivors and people infected through needlestick injuries.

The South African government is also planning a series of other measures including a massive awareness campaign, negotiations with pharmaceutical companies to obtain cheaper drugs, a campaign against discrimination against positive people, the appointment of a deputy minister of health to focus solely on AIDS, and the expansion of the South African National AIDS Council with more funding and more expertise.

Officials say the government has decided that it must project an image of sensitivity towards people living with AIDS.

And they add that the president now accepts that the pandemic and his government’s response to it have had a negative impact on South African society and the country’s image overseas, and that he will now refrain from voicing his personal views in public and will instead promote the official policy on AIDS.

Mr Mbeki has distanced himself from AIDS dissidents by instructing the health ministry to write to them telling them to stop using the president’s name when signing correspondence. Dissidents, including the Americans Peter Duesberg and David Rasnick, have been in the habit of signing themselves as advisers on “President Thabo Mbeki’s Advisory Panel on AIDS”.

Government spokesman Joel Netshitenzhe said: “We are telling them that there are other members of the panel who hold the orthodox view so they cannot sign themselves as if they represent the view of the entire panel.”

Officials said Mr Mbeki would cut all informal contact with the dissidents and only communicate with them at meetings of the advisory panel.

Furthermore, Peter Mokaba MP, who has become the dissidents’ champion within the ANC, has been instructed to stop speaking out on the subject.

These dramatic shifts in policy follow pressure on the president from many sources including his predecessor, Nelson Mandela, and other leading figures within his own party, the trade union movement and the Department of Health where senior staff have reportedly threatened to resign over the issue.

Officials said there were growing fears in cabinet and ANC circles of “mass mobilisation and hysteria” against the government, which was increasingly regarded in the country as uncaring. There was a growing gulf between the government and sectors of society, they said, and many community organisations were beginning to see the government as an “enemy” on the issue.

The country’s diplomats also reported difficulties explaining South Africa’s policy abroad and said this hampered efforts to raise foreign money for projects in Africa. Pressure has also come at cabinet level from the ANC’s coalition partners, the Inkatha Freedom Party, led by Mangosotho Buthelezi, and from the widely respected former presidential contender, Cyril Ramaphosa, who is now a leading businessman.
The first concrete sign of a change in official policy came in February when the finance minister, Trevor Manuel, trebled the AIDS budget to pay for measures that would include “a progressive roll-out of a programme to prevent mother to child transmission.” (See HIV Treatment Bulletin Vol 3 No 3, page 2).

In an interview with The Star newspaper at the end of April, President Mbeki said the government had had problems “communicating” its policies: “It is critically important that I communicate correct messages.”

He said he was concerned that a message of hopelessness had been conveyed to people infected and affected by the virus, and said a lot could be done by treating curable diseases such as tuberculosis regardless of the person’s HIV status.

Mr Mbeki said: “I think that if people are told the truth, they can get through this. And it is necessary to tell the truth repeatedly.” And he added: “You need to inculcate into the minds of people that they, too, have a responsibility for their health. You can’t be going around having hugely promiscuous sex all over the place and hope that you won’t be affected by something or the other.”

Nelson Mandela said he was “delighted” by the change in policy and believed South Africans would now realise what a brilliant president Mr Mbeki was.

Nono Simela, the head of the Department of Health’s AIDS Directorate, said the end of the argument over antiretrovirals would enable officials to deal with practical issues in fighting the virus.

Blade Nzimande, secretary of the South African Communist Party, said he was glad the cabinet was now “ignoring the political idiosyncrasies of the likes of Mokaba”.

Bantu Holomisa, leader of the United Democratic Movement, welcomed the changes but said the president must demonstrate leadership by “immediately and unreservedly apologising to the people of South Africa, especially the women who have until now been denied treatment for HIV/AIDS in cases of rape”. He said the president should also apologise to the mothers who did not receive treatment that could have protected their newborn children.

Critics of the government pointed out that South Africa has not asked for donor funds to expand its pilot study of antiretrovirals. In May it asked the Global Fund to Fight AIDS, TB and Malaria for 500 million rand (£32.7 million) to fund TB drug research and psychological services for people living with HIV/AIDS, but nothing for the antiretrovirals study.

The latest government statistics show that 4.7 million of South Africa’s 43 million people are living with HIV.

COMMENTS

Those concerned with fighting HIV and AIDS can only welcome the South African government’s change of heart and their new policy announcements. Following the budget statement in February they amount to a commitment to accept the link between HIV and AIDS and the usefulness of antiretroviral drugs. They show a new determination on the part of the South African authorities in the battle against the virus.

Above all, they mean that the South African government is now the enemy of HIV and AIDS, rather than being seen as the enemy of organisations and people in the frontline of the battle against the virus.

The relationship between the government and the AIDS community is transformed and criticism of government policy can be offered in this new atmosphere, as part of a constructive engagement between people working towards the same ends.

However, underlying this U-turn is the strange statement of officials that Mr Mbeki will keep his personal views to himself in future, which suggests that he does not yet believe the accepted, orthodox views on HIV, AIDS and antiretroviral drugs. The government, the health service and AIDS organisations may be able to operate efficiently without the full faith of the state president, and his acquiescence is better than his opposition. But the clear impression remains that they do not have their president’s full, unambiguous support, which is what they deserve.

If they are left to get on with their jobs regardless of the president’s personal – and now to be private - views then all well and good. But unless Mr Mbeki assures his country of a genuine change of heart then there will always be the suspicion that his known but unspoken views still influence policy. What other reason can he provide as to why South Africa has not asked for funding to expand the pilot study into antiretroviral treatment?

We learn from Mr Mbeki’s officials that the government has decided it must “project an image of sensitivity towards people living with AIDS”. How on earth does one explain to a man who now has secret views on the subject that people living with AIDS need rather more than an “image of sensitivity”?
People with AIDS and many others with HIV require access to antiretroviral drugs. The South African government is right to prioritise negotiations with pharmaceutical companies for cut-price drugs. It should also explore the possibilities of domestic production of generic versions of the drugs.

Then can a government that has just cut taxes by R15 billion (£1 billion) foot the bill for these cut-price drugs?

A recent study showed that providing home-based care would cost the country about R1.8 billion (£118 million) a year. Such a policy requires the political will to make it happen. If Mr Mbeki will not provide that will, then his government has a duty to take his words at face value, accept his silence on his true opinions, and give people the care they need.

On prevention, someone who has the president’s ear should talk to him about sex. In his interview with the Star Mr Mbeki says people “can’t be going around having hugely promiscuous sex all over the place and hope that you won’t be affected by something or the other”.

If those last four words are the president’s way of referring to HIV, then he needs to learn about safer sex. Someone send him a leaflet!

Finally, Mr Mbeki should remember Dr Thys von Mollendorff, the hospital superintendent at Rob Ferreira Hospital in Nelspruit, who was sacked for allowing zidovudine to be given to women who had been raped. He should be reinstated immediately.

---

**Early access programme offers adefovir for treatment of HBV**

**Graham McKerrow, HIV i-Base**

Gilead Sciences is introducing an early access programme to make adefovir available on a named patient basis to people in the UK with hepatitis B who are experiencing lamivudine resistance.

The programme provides early access to adefovir (ADV, PMEA, Preveon) 10mg daily to patients with chronic hepatitis B that is resistant to treatment with lamivudine (3TC, Epivir).

Gilead sciences says the programme is aimed at benefiting people who have limited treatment options and are in need of additional therapeutic intervention in order to suppress HBV DNA replication and to prevent progressive liver disease.

A statement from the company says data from three completed phase I-II studies, and interim data from ongoing studies, including two phase III placebo-controlled studies, demonstrate significant anti-HBV activity following treatment with adefovir dipivoxil in patients with HBeAg positive chronic hepatitis B, presumed precore mutant hepatitis B (HBeAg-/anti-HBe+/HBV DNA+), and lamivudine resistant hepatitis B.

An Adefovir Dipivoxil Call Centre has been set up to assist physicians wishing to include a patient in the programme. It is available on 01223 897300, or fax 01223 897282.

---

**CONFERENCE REPORT: 9th CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS (CROI)**

**SEATTLE, FEBRUARY 24-28 2002**

*(See HTB 3,3&4 for other reports from this conference)*

**New research points the way for future treatment of women with HIV**

**Polly Clayden, HIV i-base**

The 9th Conference on Retroviruses and Opportunistic Infections appeared to devote more space to women-specific issues than any previous gathering of this meeting. A whole poster session was focused on the ‘Effect of gender/sex on viral load, pharmacokinetics and response to antiretroviral therapy’, which unfortunately delivered little new, and overall there was little reported with immediate practical, clinical utility. There was however some interesting research that may have important implications for future practical application. (We covered pregnancy and mother to child transmission in HTB 3,4).
Genital tract and HIV viral load

Several studies looked at the presence of HIV RNA in the female genital tract.

A better understanding of these levels, their evaluation and associated factors will, it is hoped, lead to a better understanding of both mother to child and sexual transmission of HIV.

A poster from Dr Cu Uvin and colleagues from Brown and Emory Universities entitled ‘Factors associated with HIV RNA shedding in the female genital tract’ looked at the association between cervicovaginal lavage (CVL) HIV-1 RNA and antiretroviral therapy. [1] This study evaluated plasma viral load, lower genital tract infections and the presence of semen among 97 HIV positive women over a 24-month period.

The women studied were stratified into three groups: A) antiretroviral naïve starting HAART (n=36), B) nucleoside experienced starting HAART (n=26) and C) no past or present antiretroviral therapy. The investigators found a highly significant association between plasma viral load and CVL HIV-1 RNA detection (p=<0.0001). They reported that for each log10 increase in plasma viral load there was a 4-fold increase in detecting CVL viral load. Neither antiretroviral use nor CD4 cell count made any significant difference in HIV-1 RNA in the female genital tract in this study.

In an oral presentation, Dr C Critchlow from the University of Washington reported findings from a study in which it was sought to evaluate whether lower rates of transmission of HIV-2 compared to HIV-1 could be explained by differences in levels of HIV in the genital tract at a similar disease stage [2].

Two hundred and twenty-one women were recruited from the University of Dakar Infectious Disease Clinic in Senegal, and blood and CVL samples were taken to determine HIV RNA levels in each. Out of this group, the women with HIV-1 (n=170) tended to be younger compared to women with HIV-2 (n=51) — 31 and 36 years respectively, and they also tended to present with lower CD4 counts (301 vs. 352 cells/mL) and more advanced disease.

Of the women in which HIV was detected in the genital tract they reported that >1000 HIV RNA copies/mL were more frequently found in women with HIV-1 (46%) than with HIV-2 (0%). They also found that HIV-1, lower CD4 count, higher plasma RNA levels and vaginal pH were associated with higher vaginal HIV RNA levels. The investigators concluded that “Increased rates of vaginal shedding and most likely of transmission seen among women with HIV-1 appears to be attributable to higher viral burden at a given CD4 count among women with HIV-1.”

A poster reporting a small longitudinal substudy of women with HIV-1 (n=11) and HIV-2 (n=8), from the same group found lower CD4 count was associated with the increased likelihood of detecting the presence of HIV RNA in the genital tract as was recent menes and amenorrhoea [3]. The investigators also observed that over this short term (6-weeks) almost half (47%) of the HIV-1 and HIV-2 positive women studied had intermittent detectable levels of HIV in the genital tract. They suggest therefore that studies evaluating factors contributing to HIV transmission relying on a single sample may not reflect vaginal shedding over an extended period of time.

A late breaker presentation by Dr S Benki from the Fred Hutchinson Cancer Research Centre reported findings from a study in which 17 women were followed intensively over a period of one month to investigate the “Relationship between the menstrual cycle and the daily pattern of HIV-1 RNA shedding in the genital tract of HIV-1 infected women” [4].

Throughout one menstrual cycle endocervical swabs and luteinising hormone (LH) measurements were taken daily. HIV-1 RNA was then determined in the cervical swab. HIV-1 RNA was detected in 89% of the samples 402/451. The investigators reported an increase of 0.05 log10 copies per swab as the number of days from the LH surge increased (p=0.004).

This relationship between the menstrual cycle and HIV-1 RNA levels has been analysed previously in several studies but these have generated contradictory data. From this detailed analysis the authors summarise that their findings suggest that, ‘...in cervical mucosa, viral load reaches a nadir during the peri-ovulatory period, and then subsequently increases during the post-ovulatory phase.’

However, methods of collection of female genital secretions vary — the most frequently utilised are: ‘sno-strips’, aspiration, cytobrush and swabs. These differ in the subcompartment that they sample and different methodology may in turn result in significant variation in HIV RNA reported in the female genital tract.

Another poster from Dr Cu-Uvin’s group compared HIV-1 RNA levels using CVL and ‘sno-strip’ collection [5]. The investigators found that the sno-strip collection method detected more HIV-1 RNA in genital secretions in women with detectable plasma viral load than CVL. They suggest that this could be caused by the dilution effect of CVL or the different subcompartments being sampled.

Genital tract and other infections

A small number of studies examined the presence of other viral infections in the female genital tract of HIV infected women.

HIV-positive women are at an increased risk of HPV (human papillomavirus) associated cervical cancer. In an oral presentation, Dr L Conley from CDC Atlanta reported findings from a study conducted to assess the effect of HAART on HPV viral load in vaginal secretions [6].
Plasma HIV-1 RNA and CVL HPV DNA samples were obtained from 44 HIV-positive women over 345 visits – the changes in HPV loads were evaluated from initiation of HAART or from one visit to the next for women on no HAART (n=18), over a six month period.

In this study no significant effect of HAART was observed on HPV load in the female genital tract even among women using HAART who were below the level of detection. The investigators concluded that HPV and in turn the high incidence of cervical disease may persist in HIV-positive women even for those using HAART. They also noted that their findings may be limited by the small number of women in this study.

HIV/HCV coinfection is common among HIV-positive women especially those who are or have been injecting drug users. As with HIV, assessing for HCV presence in the female genital tract could lead to better understanding of sexual and mother to child transmission of this infection.

A poster from Dr M Nowicki and colleagues from the Women Interagency HIV Study (WIHS) reported a comparison of plasma and CVL HCV RNA in 9 HIV/HCV coinfected women [7]. HCV RNA was detected in plasma and CVL in 5/9 of the women evaluated. From four of these paired samples viral sequences from peripheral blood mononuclear cells (PBMC) were analysed. The single strand conformation polymorphism (SSCP) patterns for plasma and PBMC HCV sequences were identical in three women. In the other woman the PBMC-derived sequence pattern was identical to that from CVL, which the investigators believed suggested common origin.

It was concluded that these data suggest the presence of a separate HCV compartment in HIV-1/HCV co-infected women. These findings are interesting, but again it is hard to draw any conclusions from such a tiny study. The role this compartment plays in sexual and mother to child transmission warrants further investigation.

In addition the cytomegalovirus (CMV) was examined in female genital secretions. The role of CMV in sexual transmission of HIV-1 amongst HIV/CMV coinfected men, the subsequent disease progression of HIV, and the association with an increased risk of AIDS for those infected with multiple strains has been the focus of several studies. But less is known about HIV/CMV coinfection in women.

A poster from Dr N Lurain and colleagues reported results from a pilot study to detect and characterise CMV strains in a group of 45 women [8]. Plasma, CVL and oral samples for which the HIV-1 viral loads had already been established were analysed for the presence of CMV DNA. CMV was only detected in CVL samples from women with >2000 copies/mL HIV RNA. Infection with more than one strain was detected in samples from two women. The investigators suggested that after these preliminary results, future studies should focus on the genital tract as a site for interaction and transmission of both viruses.

**Treatment for cervical disease**

Women with HIV are at increased risk for squamous intraepithelial lesions (SIL) ie pre-invasive cervical cancer, as well as invasive cervical cancer. About 50% of HIV-positive women will develop SIL, but reports seem to demonstrate that its treatment is not as successful compared to that of HIV negative women.

A late breaker presented by Dr T Wright from Columbia University compared standard management approaches for SIL in a group of 122 HIV-positive and 257 HIV-negative women in a multi-arm trial conducted during 1994-2000 [9].

Women with satisfactory colposcopic examinations and low grade SIL were randomised to either observation or cryotherapy and women in later stage with high grade SIL were randomised to either cryotherapy or a loop electrosurgical excision procedure (LEEP). Any woman with an unsatisfactory examination (defined as an examination that failed to identify the extent of the lesion – usually because it extended to the cervical canal) had either a cold knife or LEEP diagnostic conization.

The women were interviewed and underwent an examination that included PAP smear, cervicovaginal lavage, colposcopy and a biopsy if indicated. These took place at entry and at four, eight and 12 months.

The investigators reported that all standard treatments for SIL were less effective in women with HIV compared to HIV-negative women. Among women with low-grade SIL randomised to observation alone, HIV-positive women were found to have a significantly lower rate of regression to normal compared to HIV-negative - 24% and 61% respectively (p<0.001) during the follow up period but the rate of progression (to biopsy confirmed hi-grade SIL) among both groups was low – 4% vs 9%. No treatment appeared to be more effective than others for HIV-positive women.

Although findings from this trial have limitations in terms of current HIV care — because when the study was conducted there were relatively few women using HAART — the investigators recommend that because of the high failure rate of treatment and the low rate of progression to high-grade SIL, “observation should be considered in managing biopsy confirmed low-grade SIL in HIV-infected women.”

**Oral contraceptive use and viral diversity**

The majority of HIV-positive women are infected with multiple HIV-1 viral variants early in their infection. It is unknown what factors predict whether multiple variants will be transmitted and what impact this will have on disease progression.
In an oral presentation entitled ‘Correlates of viral diversity in primary HIV-1 infection in women’ several factors were outlined that could affect viral diversity near the time of seroconversion [10]. Presenting author Dr M Sagar’s group had previously shown that the initial HIV-1 proviral population from 60% of women tested is heterogeneous at or around the time of seroconversion.

They found that neither demographic nor behavioural factors had any effect on the complexity of the initial virus population. In addition they found no association with other sexually transmitted infections. They did however find a strong association with initial viral diversity with the use of oral contraceptive pills (p<0.006), Depo medroxyprogesterone (p<0.004) or any form of hormonal contraception (p<0.001) compared to women with an initial homogenous virus population.

They also reported that the median of the first viral load test – taken between four and 12 months post infection – was higher among women with initial viral heterogeneity 100,000 vs 45,709 copies/mL and this difference persisted in results five years post infection. The CD4 counts were also lower – median 394 vs 460. The investigators concluded that: “Hormonal contraception use near the time of infection was associated with acquisition of a genetically complex virus population. An initial heterogeneous virus population is associated with faster disease progression as measured by HIV-1 plasma viral load and CD4 count.”

Bone mineral density and older women

Finally a very welcome focus of research was presented as a poster from Dr Brown and colleagues from Montefiore medical centre [11]. Osteopenia has been recently identified as a side effect for HIV-positive people that may be associated with antiretroviral use. Decreased bone mineral density is also known to occur in menopause as part of the normal aging process of women.

This study analysed the bone mineral density (BMD) in 40 women (19 HIV-positive, 21 HIV-negative) of a median age of 48 years, 50% were defined as post-menopausal and 50% as perimenopausal. Among the HIV-positive women all had used antiretrovirals and 55% had used protease inhibitors. The investigators reported prevalence of decreased BMD to be 50% among HIV-infected postmenopausal women, 44% among HIV uninfected postmenopausal women, 25% among HIV-infected perimenopausal women and 40% among HIV-uninfected perimenopausal women. Of the group of HIV-infected women 60% of PI using women had osteopenia compared to women who had not used PIs.

Although the investigators concluded that “protease inhibitor use is associated with significantly decreased bone mineral density in older women” this association did not reach statistical significance (p=0.04), and there was no mention of other possible cofactors.

Very little in the way of conclusion can be drawn from such a tiny study, and the mechanisms of decreased bone mineral density are not well understood in the HIV-positive, HAART-using population overall. However this study highlights a population that could be at extra risk for this adverse event, and as the average age of the HAART-using population increases it would seem that particularly close observation and monitoring of older women for osteopenia is warranted.

References:

All from the Programme and abstracts on retroviruses and opportunistic infections, February 24-28, 2002, Seattle Washington.
2. Critchlow C, Hawes S, Redman M et al. Detection of human immunodeficiency virus (HIV) type 1 and type 2 RNA and DNA in vaginal secretions among women in Senegal, West Africa. Abs.19
4. Benki S, Mostad SB, Richardson BA et al. Relationship between the menstrual cycle and the daily pattern of HIV-1 RNA shedding in the genital tract of HIV-1 infected women. Abs. LB2
10. Sagar M, Lavreys L, Baeten J et al. Correlates of viral diversity in primary HIV-1 infection in women. Abs 100
**WORKSHOP REPORT: THE THIRD INTERNATIONAL WORKSHOP ON CLINICAL PHARMACOLOGY OF HIV THERAPY**

WASHINGTON, 11-13 APRIL 2002

---

**Three studies compare gender differences in use of antiretrovirals**

Polly Clayden, HIV i-Base

The 3rd International Workshop on Clinical Pharmacology of HIV Therapy included three interesting studies comparing gender differences in aspects of antiretroviral use.

Dr Angela Kashuba from the University of North Carolina presented results from an investigation to evaluate whether PIs and NNRTIs concentrate differently in the male and the female genital tracts[1].

Preceding the main PK meeting in a small round table organised by the Forum for Collaborative HIV Research focusing on ‘Sanctuary sites and viral reservoirs’, Dr Kashuba gave an excellent overview of research to date into antiretroviral penetration into the genital tract. A report will be produced from this meeting, which we will review in a future issue of HTB.

Dr Kashuba summarised genital tract penetration as having potential clinical significance concerning mother to child transmission, post exposure prophylaxis (PEP), sexual transmission and antiretroviral durability.

Multiple CVL and plasma samples were obtained from 5 HIV-positive women on separate days. Prior to [C12h] and 3-4 hours post [C3-4h] morning doses, plasma and CVL samples were taken. The drugs measured were indinavir (IDV), amprenavir (APV), ritonavir (RTV), lopinavir (LPV), nevirapine (NVP), and delavirdine (DLV). The investigators had previously published a report on antiretroviral genital tract penetration and the results were compared to these data.

Median female genital tract to blood plasma ratios were 1.45 for IDV, 0.03 for RTV, 0.05 for LPV, 0.8 for NVP, and 0.5 for DLV. The ranking for penetration in the female genital tract was therefore – IDV>NVP>APV>DLV>LPV=RTV. This compared to male data in which seminal plasma to blood plasma ratios were 0.4-2.0 for IDV, 0.2 for APV, <0.05 for RTV, 0.07 for LPV, and 0.6-1.0 for NVP, the ranking being IDV>NVP>APV>LPV>RTV. [Note: the ranking of drugs was the same for both sexes and the ratio differences may reflect the differences in protein (and therefore protein binding of drug) in the different fluids - semen is more proteinaceous so carries more of these protein bound drugs.]

Despite physiological genital tract differences and differences between the ratios of antiretroviral penetration between genders, it is interesting to observe no great differences between the ranking of the antiretroviral ratios of penetration. Dr Kashuba cited various challenges to measuring drug concentrations in the genital tract including, small volume of samples, limited sensitivity of the assays, limitations of single random time points. What to measure – extracellular vs intracellular? And protein binding considerations, but this issue deserves further exploration.

A poster from Dr David Burger’s group at UMC Nijmegen reported results from a study looking at gender differences in plasma levels of lopinavir. This group had recently published data demonstrating that female HIV-1 infected patients have a higher risk for toxic indinavir levels than males. Through their therapeutic drug monitoring service they observed a similar pattern for lopinavir and so this study was to evaluate a possible correlation.

The study was performed using their clinical database of lopinavir samples from 130 patients (20 female, 110 male), receiving a lopinavir dose of 400mg q12h and a timeframe between intake and sampling of 4-12 hours. Gender and body weight were recorded.

Higher lopinavir levels were observed in female than male patients – 11.7 and 7.0 mg/L respectively (p=0.02). Female patients tended to have lower body weight than males, 63.6 and 72.4 kg respectively, and weight showed an inverse relationship with lopinavir exposure (p=0.007). In a multivariate logistic regression analysis female gender only was significantly related to increased drug exposure.

The investigators concluded that “As a result, female HIV-1 infected patients may be at higher risk for developing lopinavir related toxicity.”

In addition, a poster from Dr M Regazzi and colleagues analysed the PK profile of nevirapine in a cohort of 11 male and 11 female HIV-1 infected patients [3]. They reported higher levels in women than men, which may be attributable to body weight. The authors suggested that this might account for higher incidence of nevirapine-induced rash observed in men than in women.

The Forum for Collaborative HIV Research website is at:

http://www.HIVForum.org

---
A meeting report of the Third International Workshop on Clinical Pharmacology of HIV Therapy, and details of next year’s workshop are at:

http://www.virology-education.com

References:

All from the programme and abstracts for the 3rd International Workshop on Clinical Pharmacology of HIV Therapy 11-13 April, Washington DC

1. Kashuba ADM, Min S, Corbett AH et al. Comparison of protease inhibitor and non-nucleoside reverse transcriptase concentrations in the male and female genital tract. Abs 5.3
2. Burger D, Muller RJ, van de Leur MR et al. Lopinavir plasma levels are significantly higher in female than in male HIV-1 infected patients. Abs 6.5

COMMENT

The major determinant of sex differences in response to antiretrovirals is likely to remain body size. “One size fits all” dosing may make women more likely to respond and also to suffer more toxicities with therapy. Other differences require more women participating in trials and planned analyses of these by subject sex.

ANTIRETROVIRALS

Amprenavir mutations may significantly affect LPV resistance

By Brian Boyle MD, for hivandhepatitis.com

Resistance, cross-resistance and viral fitness are issues that most HIV clinicians and researchers discuss every day. These issues are not only important in planning regimens and understanding genotypic resistance testing, but are also important in planning salvage regimens that may successfully suppress HIV - although perhaps not to undetectable levels - and allow some immune reconstitution.

In a study published in AIDS investigators evaluated the effect of amprenavir (APV, Agenerase) -selected resistance mutations on protease inhibitor (PI) cross-resistance and HIV replication capacity or fitness. The HIV-1 variants were obtained from passage in increasing concentrations of APV, as well as 3’Gag/protease recombinants derived from them. The investigators found that these HIV-1 strains progressively accumulated mutations at protease codons 10, 46, 47, 50 and 84 as well as a p1/p6 cleavage site mutation at codon 449 in Gag.

The sensitivity of the HIV-1 strains to APV decreased with increasing numbers of protease mutations. Changes in the HIV-1 strains sensitivity to lopinavir/ritonavir (LPV, Kaletra) were found to parallel the changes in APV susceptibility. In fact, certain APV -selected mutants conferred greater than 10-fold cross-resistance to LPV, including a mutant with mutations 10F/46I/50V plus GagL449F (19-fold) and 10F/46I/47V/50V plus GagL449F (31-fold). Further, one resistant HIV-1 isolate, that had only two mutations (10F/84V) plus GagL449F, displayed a 7.7-fold increase in LPV IC50. Some cross-resistance to ritonavir (RTV, Norvir) and nelfinavir (NFV, Viracept) was also observed.

Replication capacity or fitness of these HIV-1 variants was also assessed. The replication capacity of viruses containing either 84V or 50V was found to be at least 90% lower the wild-type HIV-1 used as a reference. The order of relative replication capacity was wild-type > L10F > L10F/I84V > L10F/M46I/I50V > L10F/M46I/I47V/I50V.

The authors conclude, “These results indicate that until more comprehensive genotype-phenotype correlations between amprenavir and lopinavir susceptibility are established, phenotypic testing may be preferable to genotyping to detect cross-resistance, and should be considered when switching patients from a failing amprenavir-containing regimen. This study also provides data on the concordance of replication capacity measurements generated using rapid single-cycle growth and competition assays.” This study also indicates the potential complexity of the resistance that develops from antiretroviral usage, especially protease inhibitors, and that planning sequential changes in antiretroviral therapy - with the hope that resistance to one drug will not affect another - is difficult, unpredictable and ultimately unlikely to be successful.


COMMENT

Despite all of the currently available resistance data on protease inhibitors it still remains unclear if any advantage is to be gained by a particular order of sequencing. All of the currently available PI’s are cross resistant to each other, this perhaps being a function of them all being structurally related peptidomimetic compounds. Search behind each sequencing argument and you will usually find some spin related to market positioning of a particular pharmaceutical companies product.

Neuropsychiatric complications of nevirapine treatment

Nevirapine is a non-nucleoside reverse transcriptase inhibitor used to reduce the viral load in HIV infection. Its side effects include hepatotoxicity, gastrointestinal symptoms, and dermatological reaction. Efavirenz, another non-nucleoside reverse transcriptase inhibitor, has a similar structure to nevirapine and can cause insomnia and psychotic reactions. [1] We report three cases of neuropsychiatric sequelae to nevirapine in patients with HIV infection but no history of mental illness. Medline, Embase, and PsychLIT list no reported cases.

Within two weeks of starting nevirapine a 35-year-old man developed low mood and had to stop working because of cognitive impairment and clouding of consciousness. He was admitted after taking an overdose of nevirapine and the treatment was stopped. Five days later, fearing that nursing staff would kill him, he leapt through a third floor window. As the temporal connection to his deterioration was unclear, nevirapine treatment was restarted. After a two-week period of lucidity, he experienced a fluctuating course of impaired consciousness, lability of affect of treatment, and visual hallucinations. Nevirapine was withdrawn and within three weeks he was asymptomatic.

In another case, a 36-year-old woman experienced delusions of persecution and infestation within two weeks of starting nevirapine treatment. Command hallucinations led to an impulsive suicide attempt. In a third case, a 42-year-old woman developed persecutory delusions and depressive thoughts 10 days after starting nevirapine. Treatment with antipsychotic drugs was stopped in both of these cases after several weeks (risperidone, four weeks, and olanzapine, three weeks, respectively). Both patients remained asymptomatic, indicating that a degenerative process was not involved.

These three cases depict a delirium, an organic affective state, and an organic psychosis. The time the patients started nevirapine treatment was clearly related to the evidence of symptoms, and all cases resolved on withdrawal of nevirapine. All cases were reported to the Committee on Safety of Medicines and the manufacturers.

References


Resistance mutations continue to accumulate with low-level viral increases

By Brian Boyle MD, for hivandhepatitis.com

Highly active antiretroviral therapy (HAART) is generally effective at suppressing HIV replication, which allows for significant immune recovery and decreased morbidity and mortality among HIV-infected patients.

Drug resistance is a major cause of HAART failure and several studies have documented that resistant HIV can quickly emerge when viral suppression is incomplete, whether due to prior resistance, poor adherence, poor drug pharmacokinetics or other regimen problems.
Therefore, unless the patient has no other treatment options, it is generally considered ill-advised to continue patients with low-grade viremia on the same HAART regimen, since studies indicate that this treatment approach may lead to the development of further resistance mutations and a lower likelihood of treatment success with subsequent HAART regimens. In a study published in *AIDS*, investigators evaluated, in a ‘real-life’ setting, the appearance of drug resistance mutations when a patient is continued on a failing HAART regimen.

Fourteen patients were retrospectively evaluated, all of whom had a least one undetectable viral load followed by persistent low-grade viremia (< 1,000 copies/ml) or a slow increase in viral load to less than 4,000 copies/mL after at least one year of treatment. Five of the patients were on their first HAART regimen with two nucleoside reverse transcriptase inhibitors (NRTI) plus one protease inhibitor (PI), whereas seven patients were on their second and two on their third line of antiretroviral therapy.

Overall, new primary NRTI or PI mutations appeared in 93% of the patients during the low-grade viremia. In four patients, a drug to which the virus showed genotypic resistance was included in the new therapy and the mean time for viral rebound in these patients was shorter than in the remaining drug-experienced patients or in the naive patients (6.5 versus 10.4 versus 10.2 months, respectively).

Further, there was a trend for resistance mutations to be detected at a lower viral load in NRTI-experienced than NRTI-naive patients. Despite the accumulation of additional mutations, however, sustained increased CD4+ T cell counts could be seen in many of the patients, perhaps due to the decreased viral fitness resulting from the resistance mutations.

The authors conclude: “We have shown here that primary mutations associated with resistance to NRTI, NNRTI or PI can emerge in connection with very low viraemia in patients failing their first or second/third-line therapy. Serial accumulation of further mutations was seen without any significant viral rebound and sustained increased CD4 T cell counts for a long time.

“A low but detectable level of viraemia can thus be sufficient to generate viruses with several resistance mutations, with a possible risk of the exhaustion of future drug options.”

This study seems to reinforce the oft-stated guideline that patients failing antiretroviral therapy - even with relatively low levels of viral rebound - should, if possible, be changed to another regimen prior to further development of resistance mutations that may affect chances for therapeutic success.

Ref: Aleman S, Soderbarg K, Visco-Comandini U et al. Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy. AIDS 2002 May 3;16(7):1039-44


Copyright 2002 by HIV and Hepatitis.com. All Rights Reserved.

**COMMENT**

**Biological plausibility would suggest that if virus is detectable on current therapy it is likely to have advantage relative to other viruses and will be built on the back of a previously selected archived virus which had some, but not as great, an advantage.**

*It should also be remembered that despite the description ‘low level’ viraemia still represents a great deal of viral turnover in an individual.*

---

**24-Week results from Phase III study of HIV fusion inhibitor T-20**

Roche and Trimeris announced 24-week results from the first pivotal Phase III study of T-20, the first in clinical development of an investigational class of antiretrovirals called fusion inhibitors. The results from this first study (TORO 1: T20-301) as well as the results from a second ongoing study (TORO 2: T20-302) will form the basis of the approval submission for the drug to the US Food and Drug Administration and other regulatory authorities.

**TORO 1 (T-20 vs. optimised regimen only)**

In the TORO 1 study, T-20 administered in combination with an individualised antiretroviral treatment regimen was shown to provide a significant additional decrease in the amount of virus in the blood as compared to an individualized antiretroviral treatment regimen alone.

TORO 1 was conducted in 491 HIV-1 infected patients who were treatment-experienced and/or had documented resistance to each of the three classes of currently available antiretrovirals. At baseline, patients had a median HIV RNA level of over 5 log10 copies/mL and extensive prior exposure to multiple anti-HIV drugs.
Patients who received T-20 as part of their combination regimen achieved a reduction in HIV levels of 1.697 log10 copies/mL compared to 0.763 log10 copies/mL for those who were randomised to the control arm, calculated in accordance with the study protocol. The primary efficacy endpoint for the study, the difference in the magnitude of decrease in HIV between the two arms, was 0.934 log10 copies/mL and was statistically significant (p<0.0001). Roche and Trimeris expect to present these data in detail at scientific conferences in the next several months.

“These Phase III results demonstrate that T-20 enhanced the activity of combination therapy over 24 weeks,” said William M Burns, Head of Pharmaceuticals, at Roche.

Safety Results
Through 24 weeks, the incidence of grade 3 and 4 laboratory abnormalities and clinical adverse events was similar between the T-20 and control arms. Additionally, drug discontinuation at 24 weeks was approximately 10 percent overall and was very similar in both arms. While most patients on the T-20 arm experienced injection site reactions, only three percent of patients discontinued the study as a consequence.

Other adverse events (>10 percent), where the incidence was greater on the T-20 arm than on control, were insomnia, headache, peripheral neuropathy, and dizziness. It was not possible to establish a causal relationship between these other adverse events and T-20.

Study Design
TORO 1, previously known as T20-301, and TORO 2 (previously known as T20-302) are randomised, open-label trials that enrolled approximately 1,000 patients at 112 centres worldwide. TORO 1 is being conducted in North America and Brazil, while TORO 2 is being conducted in Australia, Belgium, France, Germany, Italy, The Netherlands, Spain, Sweden, Switzerland and the United Kingdom.

Patients in the trials were treatment-experienced and/or had documented resistance to each of the three classes of currently-available antiretrovirals. In addition, each patient was required to have a plasma HIV-RNA level of greater than 5,000 copies/mL. Patients are expected to undergo treatment for 48 weeks, with an optional 48-week treatment extension.

At entry, genotypic and phenotypic resistance testing was used to aid in the selection of an antiretroviral regimen, consisting of three to five drugs, including if appropriate up to two newly approved or investigational drugs. After selection of the regimen, patients were randomised 2:1 to receive either the regimen in combination with T-20 or the regimen alone. Patients randomised to T-20 receive T-20 administered as one 90 mg subcutaneous self-injection twice-daily.

Early Access to T-20
In November 2001, Roche and Trimeris announced the initiation of the T-20 open-label safety study (T20-305) to provide T-20 to 450 patients around the world. The study is ongoing and is being conducted in Australia, Brazil, Europe, and North America. An expansion of this trial over the next several months will continue to make T-20 available prior to approval for patients with advanced HIV disease who are unable to construct a viable antiretroviral regimen with currently approved agents. Additionally, Roche and Trimeris are committed to starting early access programmes in the second half of this year when increased drug supply is expected to be available.

Source: Press Release. Roche Laboratories and Trimeris, Inc.

COMMENT
With the array of new drugs for HIV in early development the duration of necessity of injection with T-20 may not need be considered indefinite but simply ‘until we have suitable oral alternatives to replace it’. Such replacement would be on a case-by-case basis as oral drugs that act similarly to T-drugs may not be feasible. Additionally, patients may wish to replace agents in their regimens that are contributing more to toxicity than T-20 when new alternatives arise.

Encouraging earlier initiation of T-20 may help to diminish the risk of losing current options in what might be called ‘first salvage’ therapy rather than using T-20 against multi-class resistant virus in ‘deep salvage’. Multiple studies in treatment-experienced patients demonstrate the value of commencing 2 new drug classes simultaneously. Appreciation of the extent of cross-resistance with the nucleoside/nucleotide analog class has underlined the need (when feasible) to delay therapy switch until accumulation of several clearly active new agents has been achieved. If we initiate a new regimen now with our last available approved drug class, failing to achieve full suppression would mean T-20 may also then need to be initiated on a sub-optimal backbone. As a result, both remaining classes may be ‘wasted’ rapidly (through resistance development), for only short-term clinical benefits. If the fusion inhibitors are started in persons embarking now on their last approved drug
class this is very likely to substantially increase the number of optimal responders at this line of therapy, increasing the chances of maintaining patients’ health until other options arrive.

If physicians are able to impart to patients the potential value to be added by including T-20 in their next regimen, rather than saving T-20 until they are ‘desperate’, the need for more complex and costly (both financially and in terms of toxicity) ‘mega-HAART’ ‘deep salvage’ regimens may be averted. ‘Take something a bit more complex now to avoid something really tough next time’.

Resistance to template-analogue inhibitors linked to impaired replication

HIV strains that develop resistance to template-analogue reverse transcriptase inhibitors (TRTIs) also develop crippling defects, according to researchers in New York.

Dr Timothy S Fisher and colleagues at the Albert Einstein College of Medicine in Bronx, New York, studied the effects of TRTI resistance mutations on viral fitness.

Mutations that confer high-level TRTI resistance significantly impaired HIV replication, the researchers found.

They exposed wild-type viruses to RT1t49, a DNA aptamer that binds to the template-primer cleft of HIV reverse transcriptase. Strains with one copy of the resulting mutations (N255D or N265D) developed mild TRTI resistance, while the presence of both polymorphisms was associated with high-level resistance, according to the report.

However, these mutations also interfered with the interaction between reverse transcriptase and the template-primer. As a result, TRTI-resistant strains were unable to replicate effectively, study data showed.

Although TRTI resistance mutations do not necessarily impair reverse transcriptase activity, the overlap between binding pockets for therapeutic aptamers and the template-primer helps select for mutations that do.

“Potent inhibition and a built-in mechanism to render aptamer-resistant viruses replication defective make this an attractive class of inhibitors,” Fisher and colleagues concluded.

Source: Michael Greer, for AIDSWEEKLY

Abacavir treatment limited by prior NRTI exposure

By Brian Boyle MD, for hivandhepatitis.com

It has long been recognised that some of the characteristics of highly active antiretroviral therapy, including high pill burdens and meal restrictions, affect adherence rates. One approach to these problems has been to simplify regimens. Trizivir (abacavir, zidovudine and lamivudine) combines three antiretrovirals in one tablet, which can be taken without meal restriction.

However, some reluctance to using this regimen persists due to previous studies that have indicated that this triple nucleoside reverse transcriptase inhibitor (NRTI) combination is not as effective as a protease inhibitor (PI) in patients with high viral loads and that some induction-maintenance strategies involving therapy with two NAs have had high rates of virologic failure associated with zidovudine (ZDV, AZT, Retrovir) resistance at baseline, poor adherence, and low plasma levels of indinavir during maintenance therapy predicted virologic failure.

In a prospective, randomised, controlled, open-label study reported in The Journal of Infectious Diseases, 163 patients treated with PI-containing combination regimens who had maintained virological suppression (<400 copies/mL) for six months and had a viral load at screening <50 copies/mL were randomised either to continue their current therapy or to change to abacavir (ABC, Ziagen) plus Combivir (lamivudine plus zidovudine).

Patients were excluded from the trial if they had a mutation detected at codon 215, suggesting prior zidovudine exposure and resistance. In February 2000, the simplified regimen was modified to Trizivir.

The median study duration was 84 weeks. In the intent-to-treat analysis of the overall population, virologic failure was more frequent in the ABC-Combivir than in the continuation group, with 13 patients (15%) versus five patients (6.0%), respectively, experiencing treatment failure. In addition, time to virologic failure was also shorter in the ABC-Combivir group.

Finally, 12 patients (15.2%) in the continuation and six (7.1%) in the ABC-Combivir group discontinued the study prematurely.
or were lost to follow-up. Reasons for treatment change because of adverse events in the continuation versus the ABC-Combivir group were gastrointestinal intolerance (6 vs. 1), new occurrence or worsening of lipodystrophy (6 vs. 0), hyperlipidemia (1 vs. 0), nephrolithiasis (1 vs. 0), abacavir hypersensitivity (0 vs. 1), anemia or leukopenia (0 vs. 2), and other (2 vs. 2).

Most of the virologic failures in the ABC-Combivir group (eight [62%] of 13) occurred before week 20, whereas failures in the continuation group occurred between weeks 21 and 49. Resistance data collected indicated that after a switch to ABC-Combivir reemergence of archived resistant virus might be a more important reason for virologic failure than development of new resistance mutations that developed during the simplified therapy.

In particular, a history of previous mono- or dual zidovudine therapy was noted in most patients with virologic failure and was a predictor for virologic failure in the ABC-Combivir group. When patients were stratified by history of mono- or dual zidovudine therapy, the risk of virologic failure among the 31 patients in the simplified group who had a history of zidovudine treatment was 23.5% after 48 weeks and 33.3% after 96 weeks.

The authors conclude: “In the overall population, virologic failure was more frequent (15% vs. 6%; P = .081) and occurred faster in the simplified group (P = .066, log rank test) than in the ABC-Combivir group. The virologic failure rate in the simplified group was at least partially driven by a high failure rate (nine [29%] of 31) among patients with a history of zidovudine mono- or dual therapy. This strategy, therefore, is appropriate only for patients with no prior zidovudine mono- or dual therapy and no suggestion or evidence of resistance to NRTIs.”

Given the recent reports of nucleoside associated mutations (NAMS) developing with a number of NRTIs, not just zidovudine, this precaution should probably extended to any patient who has had significant prior NRTI exposure.

Therefore, changing any patient who has had any significant NRTI exposure from a successful PI or non-nucleoside reverse transcriptase inhibitor (NNRTI) regimen to a simplified ABC-Combivir regimen may be more likely to lead to virologic failure and may be an ill-advised therapeutic strategy.


---

**METABOLIC TOXICITIES**

**Paracardial fat in HIV-infected patient resembles pericardial effusion**

The presence of paracardial adipose tissue should be ruled out in HIV-infected patients on antiretroviral therapy who appear to have pericardial effusion, German investigators suggest in the May issue of the journal Heart. This may avoid unnecessary puncture of the pericardium, which could have “serious consequences,” they add.

Dr T Neumann and associates, from the University Hospital Essen, describe a 52-year-old man with a 10-year history of HIV infection who presented with exertional dyspnea. His treatment regimen included nelfinavir, nevirapine, and stavudine. His body habitus showed the effects of lipodystrophy, and serum levels of triglycerides and cholesterol were elevated.

Transthoracic echocardiography showed no evidence of impaired ventricular filling, but there was a 4mm-wide epicardial space. Repeat echocardiography 10 months later showed an increase in the epicardial space to 18mm, but diastolic function had actually improved slightly, and ventricular function still appeared to be healthy. T1 weighted turbo spin echo magnetic resonance tomography revealed the presence of adipose tissue surrounding the ventricles.

Dr Neumann’s group warns that assuming the diagnosis based only on the echocardiogram could have fatal consequences if aspiration is attempted and the ventricle is punctured in an effort to produce pericardial fluid. They suggest that “T1 weighted sequences with and without fat suppression can clearly distinguish adipose tissue from pericardial fluid,” and that computed tomography can also differentiate between the two.


Source: Reuters Health
OPPORTUNISTIC EVENTS

Filgrastim seems to increase survival in AIDS patients but the mechanism remains unclear
Granulocyte colony-stimulating factor therapy in patients with AIDS-related cytomegalovirus (CMV) retinitis is associated with a 56% reduction in mortality, according to a recent report. However, the reason for this survival benefit does not appear to involve a reduction in bacterial infections.

Prior to the advent of highly active antiretroviral therapy (HAART), neutropenia was a relatively common finding in patients with AIDS, study author Dr Douglas A Jabs, from the Johns Hopkins University in Baltimore, and colleagues note in the March 29th issue of AIDS.

Because neutropenia is an established risk factor for bacterial infection, the authors hypothesised that treatment with filgrastim — granulocyte colony-stimulating factor, which reverses neutropenia — might prevent such infections and thereby improve survival.

To investigate, the researchers retrospectively studied 709 patients with AIDS-related CMV retinitis who were treated between 1990 and 1997. Of these patients, 398 had used filgrastim at some point.

Filgrastim use was associated with a significant reduction in the risks of catheter-related bacteremia and repeat bacterial infection ($p = 0.02$ and $< 0.01$, respectively), Dr Jabs and colleagues found.

However, after adjustment for CD4+ T-cell count and antibiotic/antiretroviral therapy, filgrastim therapy was no longer linked to a significant reduction in these risks. The authors believe this may have been due to the confounding effect of trimethoprim-sulfamethoxazole use.

Despite no clear effect on bacterial infections, filgrastim use was tied to a 56% reduction in mortality ($p < 0.001$), the researchers state.

“Our observation of a large survival benefit with the use of filgrastim, while unexplained by a reversal of neutropenia or reduction of infection, deserves further exploration in a randomised controlled trial of this cytokine in non-neutropenic AIDS patients receiving HAART,” Dr Jabs’ team concludes.

Ref: Davidson M, Min YI, Holbrook JT et al. Use of filgrastim as adjuvant therapy in patients with AIDS-related cytomegalovirus retinitis. AIDS 2002 Mar 29;16(5):757-65

Source: Reuters Health

COMMENT
Similar benefits in advanced disease have also been reported for the immunotherapy agents GM-CSF (molgramostim) and gamma interferon.

Upregulation of phagocytic responses to pathogens may be one mechanism of action as well as improved antigen presentation and perhaps increased IL-2 receptor expression.

Oral valganciclovir is as effective as intravenous ganciclovir for induction treatment of CMV retinitis
Graham McKerrow, HIV i-base

Orally administered valganciclovir appears to be as effective as intravenous ganciclovir for induction treatment and is convenient and effective for the long term management of cytomegalovirus (CMV) retinitis in patients with AIDS, according to the results of a randomised trial reported in the 11 April issue of the New England Journal of Medicine.

Dr Daniel F Martin and colleagues at the Valganciclovir Study Group write: “The results of our study indicate that a twice-daily dose of 900mg of oral valganciclovir for induction therapy in patients with cytomegalovirus retinitis has an efficacy and safety
profile that is similar to the profile for intravenous ganciclovir. The proportions of patients with progression of retinitis during the first four weeks were similar for the two regimens.”

CMV retinitis remains the leading cause of loss of sight in people with AIDS. Induction therapy with ganciclovir, foscarnet or cidofovir, followed by maintenance therapy can effectively make CMV retinitis inactive. If recovery of immune function is not possible, indefinite treatment is needed, and an indwelling catheter to facilitate regular intravenous medication may be required. The cost, risk of sepsis, and effect on quality of life of having a permanent indwelling catheter provoked the search for an orally administered treatment.

Valganciclovir is an orally administered prodrug that is rapidly hydrolysed to ganciclovir. Dr Martin’s team compared the effects of oral valganciclovir with those of intravenous ganciclovir as induction therapy for newly diagnosed CMV retinitis in 160 patients with AIDS.

Eighty patients were randomly assigned to each treatment group. Of the patients who could be evaluated, seven of 70 assigned to intravenous ganciclovir (10.0%) and seven of 71 assigned to oral valganciclovir (9.9%) had progression to CMV retinitis during the first four weeks.

Forty-seven of 61 patients (77.0%) assigned to intravenous ganciclovir, and 46 of 64 (71.9%) assigned to valganciclovir had a satisfactory response to induction therapy.

The median times to progression of retinitis were 125 days in the group assigned to intravenous ganciclovir and 160 days in the group assigned to oral valganciclovir.

The researchers also report that: “The frequency and severity of adverse events were similar in the two treatment groups.” They go on to say that the main difference in safety between the two treatments was related to the mode of administration, with more diarrhoea in the oral valganciclovir group and more catheter-related complications in the intravenous group.

The study was not designed to evaluate the differences between the treatments for maintenance therapy, and the team say this would require a randomised comparison of patients followed up to the time of the progression of retinitis. However, they add: “On the basis of its efficacy for induction, and the pharmacokinetic data, we would expect valganciclovir to compare favourably with both intravenous and oral ganciclovir for maintenance therapy.”

They write that the reduced pill burden and once daily dosing with oral valganciclovir for maintenance treatment may increase adherence and therefore improve outcomes.

In their discussion, the researchers also comment: “Although there is no evidence on the basis of HIV loads and CD4+ cell counts, that highly active antiretroviral therapy affected our primary outcome at four weeks, it almost certainly influenced the observed times to progression of retinitis.”

The researchers end their discussion by advising: “Because of the heterogeneity of the immune response to highly active antiretroviral therapy, the time to the progression of retinitis may vary widely from patient to patient. Careful surveillance for progression of retinitis is therefore recommended throughout treatment.”


COMMENT

Well designed prophylaxis studies are now urgently needed to determine if oral valganciclovir is an effective agent for prevention as well as treatment of CMV retinitis.

PAEDIATRICS

CCR5 density on CD4 cells governs course of HIV infection in children

The density of CC chemokine receptor 5 (CCR5) molecules on the surface of inactivated CD4 cells correlates with disease progression and with treatment response in children vertically infected with HIV. Development of therapy to reduce CCR5
density could therefore be expected to slow disease progression and increase response to treatment, a team of French and Swiss investigators suggests.

Dr Pierre Corbeau, of the Hôpital Saint Eloi in Montpellier, France, and associates monitored the density of CCR5 molecules on CD4 cells in 22 HIV-infected children for 12 months. As reported in The Journal of Infectious Diseases for April 15, the density remained stable over time.

Among 35 therapy-naïve children, aged 10 to 201 months, the CCR5 density was correlated with severity of disease according to clinical and biologic stage (p < 0.001) and annual percentage of CD4 cell loss (p = 0.034). CD4 cell loss was dramatically increased when CCR5 density exceeded 10,000 molecules per cell.

The CCR5 density was also associated with the drop in viral load among 21 children who initiated treatment with two nucleoside inhibitors and one protease inhibitor (p = 0.026).

Dr Corbeau’s team theorises that viral replication is more difficult to block when cells express high densities of CCR5 molecules. Specifically, “In high CCR5 expressers, low residual viremia will result in the productive infection of cells with a high density of membrane CCR5, and replication will be sustained.”

The authors conclude that determination of CCR5 density could aid in determining prognosis and in decision-making regarding treatment.


Source: Reuters Health

**Saquinavir is a suboptimal treatment for children unless used in combination**

**Graham McKerrow, HIV i-Base**

The pharmacokinetics of saquinavir (SQV, Fortovase) in children is different from that of adults, and administration of SQV alone to HIV-infected children will not give consistently efficacious plasma levels, report Swiss researchers. The best way of improving SQV levels in children is through combination therapy with other protease inhibitors that inhibit SQV metabolism, according to researchers at F Hoffmann-La Roche Ltd in Basel, Switzerland.

Dr Sibylle Grub and colleagues investigated the clinical pharmacologic characteristics of SQV given as a soft gelatine capsule, either alone or in combination with nelfinavir (NFV, Viracept) to children and adolescents with HIV.

They assessed the pharmacokinetics of 50mg/kg SQV three times a day (tid) alone to 14 children and compared the results with those in 13 children given 33mg/kg SQV tid plus 30mg/kg NFV tid. They assessed the results after single dose administration and after short- and long-term administration.

They also investigated the pharmacokinetics of a fixed single dose of 1200mg SQV compared with unrestricted weight-adjusted dosing at 50mg/kg.

The results reported in the March issue of Clinical Pharmacology and Therapeutics show that SQV as the sole protease inhibitor resulted in lower SQV exposure in children and adolescents than that reported in adults treated with 1200mg tid.

The researchers report that this appeared to be attributable to markedly higher apparent oral clearance, potentially as a result of increased systemic clearance and reduced oral bioavailability.

NFV combined with SQV reduced apparent oral clearance, increasing SQV exposure in children to levels that approach those in adults. The researchers write: “A significant correlation between average trough concentration and sustained viral load suppression was observed in children. The apparent threshold for maintaining viral load suppression was a mean trough SQV concentration above 200ng/mL.”

PATHOGENESIS

Measles found to suppress HIV

John S James, for AIDS Treatment News

A study in Africa found that viral load was apparently reduced by almost two logs during acute measles infection in children. After they recovered from measles, the HIV viral load came back. [1]

Interpretation was complicated by the fact that no baseline viral loads were available for the children before they came down with measles. Instead, researchers measured viral load in children who had been hospitalised with measles, and found it surprisingly low — a median of 5,339 copies. This compared to 387,000 copies in the same children at a one-month follow-up, after they had recovered from measles. A comparison group of children with HIV but without measles or other acute illness had a median viral load of 228,000.

This reduction was all the more remarkable since an illness like measles would be expected to raise the viral load if it did anything — due to increased immune activation.

COMMENT

At least one other disease — scrub typhus — has also been found to suppress HIV, but only in some patients. [2] [Note: Also hepatitis G].

Clearly we need research to identify the exact mechanism of viral suppression by measles or certain other diseases. It might be possible to use this knowledge to design a new class of treatment for HIV.

References


Copyright © 2002 - AIDS Treatment News. Permission granted for non-commercial reproduction, provided that our address and phone number are included if more than short quotations are used. Subscription lists are kept confidential. AIDS Treatment News, Subscription and Editorial Office: 1233 Locust St., 5th floor Philadelphia, PA 19107 800/TREAT-1-2 toll-free email: aidsnews@critpath.org http://www.aidsnews.org

TREATMENT GUIDELINES

First audit of BHIVA treatment guidelines reveals suboptimal access to viral load and resistance tests

Simon Collins, HIV i-Base

Given the complexity of treating HIV and the relatively rapid change in approaches to treatment, ensuring access to the latest advances is an obvious patient concern. It is unfortunate that unlike France, the UK does not run a database that can track how closely recommendations from expert guidelines are followed in clinical care.

It is therefore important that the British HIV Association (BHIVA) decided to run its own pilot audit in 2001 to evaluate the impact of the UK treatment guidelines, to collect national aggregate data on patterns of prescription and to provide confidential reports to individual units on how their results compared to national figures.

The preliminary results presented at the 8th Annual BHIVA Conference in York on April 19-21 showed that suboptimal access to care remains a cost-related issue at some centres. It also provided an indication of the usefulness and importance of maintaining up-to-date treatment guidelines in the UK.
**Sampling and demographics**

This national clinical audit was from an analysis of 2,044 patient summary sheets from 146 centres. Each centre was asked to provide data from the last 10 consecutively seen patients in September 2001 (last 25 patients for larger centres) concerning when treatment was started, which treatments were used, the aims and outcomes of treatment and use of resistance testing. Each patient questionnaire involved a reasonably detailed treatment history and it is encouraging that centres undertook this additional work in a voluntary capacity.

Although the audit included clinics with both large and small numbers of HIV patients from across the UK the sampling method produced a relative under-sampling of patients from very large centres and was not therefore expected to produce a demographically representative sample of the HIV population.

<table>
<thead>
<tr>
<th>BHIVA audit</th>
<th>SOPHID (CDC reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>73%</td>
</tr>
<tr>
<td>Female</td>
<td>27%</td>
</tr>
<tr>
<td>White</td>
<td>68%</td>
</tr>
<tr>
<td>Black African</td>
<td>24%</td>
</tr>
<tr>
<td>Heterosexually acquired</td>
<td>44%</td>
</tr>
<tr>
<td>Gay Bisexually acquired</td>
<td>45%</td>
</tr>
<tr>
<td>IVDU acquired</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Impact of guidelines**

Nine of 147 centres in the survey (6%) had not seen or read the guidelines although 109/147 (74%) said that they had influenced the care provided. In particular, the guidelines were reported to be useful in the active management of patients' care as well as improving access to funding for treatment and development of local guidelines.

**Current health status**

Although three-quarters of HIV-positive patients currently had a good CD4 count above 200 cells/mm³ (27% 201-350, 23% 351-500 and 25% >500 cells/mm³), 18% had an AIDS defining count of 51-200 cells/mm³ and four percent had advanced AIDS with a CD4 count under 50 cells/mm³.

Forty-four per cent of patients had undetectable viral load <50 copies/ml and a further 14% were <500 copies/ml. Fifteen per cent were between 500-10,000, 7% between 10,000-30,000 and 15% were over 30,000.

Knowing that 75% of patients in the survey were on treatment, then approximately 15% of people in the total survey are currently on 'failing' treatment with a persistently detectable viral load >500 copies/mL. Although the results cannot be exactly extrapolated to the UK national cohort, if we assume 15,000 people are currently on treatment in the UK, this survey provides an indication that 1,200-1,800 people may be currently on a failing combination.

**Treatment prescription patterns**

Current treatment prescription is broadly in line with guideline recommendations. Three or more drugs were being used in 1,479 of the 1,516 regimens of people on treatment. Thirty-six people were using only two drugs and one person was using monotherapy. Additional notes were collected with most of these cases, and this was reported as patient choice or a temporary measure due to complication of concomitant treatment.

Of the 513 patients not on treatment, 77 (15%) had a CD4 count under 200 and a further nine patients had a history of severe symptoms. Only 26 (including 11 newly diagnosed) were reported to be about to start or restart treatment, reflecting a patient group who still choose to delay treatment even when they are at a high risk of HIV progression.

The recommendation to start treatment at a lower CD4 count seemed to be reflected in the audit results, with fewer people starting treatment at CD4 count over 350 cells/mm³ in 2001 than in 2000. However around a quarter of people in each year started treatment with a CD4 count less than 50 copies/mm³ and although the majority of these cases are explained by late diagnosis (39% diagnosed <50 and 42% diagnosed 51-200), small numbers of patients diagnosed at much higher levels chose to delay treatment until their CD4 counts had fallen to the higher risk group.

**Treatment choice and efficacy**

Current treatment also broadly follows guideline recommendations with 97.5% of people using three or more drugs. Breakdown by regimen includes 25% of people using two RTIs and single/boosted PI, 55% using two RTIs and an NNRTI, 8% on triple nucleoside and 12% using other 3+ drug combinations. Latest viral load results for people using three or more drugs showed 59% undetectable <50 copies/ml, 18% <500 copies/ml, 10% between 500-10,000 copies/ml and 10% >10,000.
copies/ml, although a separate breakdown between people just starting a combination compared to people continuing on a failing combination.

**Restricted access to drugs and assays**

Few clinics reported individual drug prescription difficulties: three with Trizivir, two with Kaletra/boosted PIs and one with access to tenofovir. Two areas that were not addressed directly were whether costs play a role in deciding whether or not treatment is offered in primary infection and whether the numbers of drugs that can be provided in mega-HAART combinations for treatment experienced patients is limited by cost, and it would be interesting to include this in a future audit.

However, limited access to resistance testing and viral load testing highlighted serious problems. For example, use of an ultrasensitive viral load test (sensitive to 50 copies/mL) has been recognised as standard of care in most hospitals for more than two years and yet 11 clinics (7.5%) have either no or only limited access to this assay. This is an essential test to confirm a maximally suppressive regimen which itself is probably the primary aim of treatment. It is also essential in order to be able to detect an early-failing regimen and therefore minimise the risk of developing further resistance.

Only 94 of the 146 clinics in the audit (63%) have access to viral load tests that are sensitive to specific subtypes, with 23 clinics (16%) having no access; and 27 centres (18%) were uncertain about whether the tests they used were sensitive to non-B strains. This similarly limits the ability to provide optimal treatment management for people with non-B sub-types at these treatment centres.

It is disturbing to learn that resistance testing is similarly not universally available. Eighty-two per cent of clinics report ability to use resistance tests as clinically required, but 14 (9%) are limited in their use and five clinics (3.4%) report not being able to use these tests at all. People at these centres who require access to these tests would be well-advised to register at another centre, although if denial of services is based on costs, then this is an option that would no doubt be encouraged by those health authorities.

**Summary**

In summary, this preliminary analysis audit provides an important overview of current treatment provision and it is hoped that the 2002 audit can include a larger proportion of patients. Results from individual centres will remain confidential and this was decided in advance of the audit in order to encourage clinics to take part. Individual reports are however available to clinics on request so they can see how the evaluation of their unit compared to the national average.

BHIVA guidelines are available to download in pdf format from:

http://www.bhiva.org/guidelines.htm


http://www.regordane.demon.co.uk/bhiva/

http://www.bhiva.org/
COMMENTS

The current organisation of AIDS medical research makes it very difficult to get a new drug into the first human testing, to establish a proof of principle that it might work. Industry is reluctant to do this — not so much because it is expensive (industry does pay for the large clinical trials needed for drug approval, which cost much more), but because the reward is too distant. Once there is positive human data, it is much easier to raise money and interest for further research.

The case of topoisomerase inhibitors is unusual in that these drugs have gone through the entire approval process for cancer. Therefore, the first human trial for HIV would be much less expensive, since formulation, tolerable dosing, toxicity, and some long-term safety issues have already been worked out. Still, this work wasn’t done, and no one is doing it today.

Since these drugs are already in use, it would be quick and easy to see if there were an effect on viral load in persons treated for cancer who also happen to have HIV. If a major reduction in viral load could be documented, it would be much easier to get further research started. Then the next step could be a small trial in which the drugs were prescribed for selected patients.

The first topoisomerase inhibitors are given by injection, but a new one — Orathecin, formerly named Rubitecan — now waiting for FDA approval for pancreatic cancer, is taken orally. All can have serious side effects. It is not known whether smaller doses could be used in HIV treatment. Indeed, since the research has not been done, no one knows whether these drugs, in any doses, could have any value in treating HIV.

We also need more investigation into the problems in licensing policies and elsewhere that block early human research that would be strongly in the public interest. As Goldman points out in his article, there may not be any single villain in this story — each company and government agency may have done what it was supposed to do. Lack of a villain can make it harder to mobilise public interest for reform. Still, the system is not working — and is costing many lives, if any of the drugs that should have been tested would in fact be useful.

As a lawyer who works in intellectual property in the entertainment industry, Goldman had the background to be among the first to investigate the complicated tangle of legal rights that has blocked these drugs and probably others from being tested as they should. Now that he has shown the way, other activists without this specialised background can help develop the investigation.

A major problem in AIDS treatment today is that many patients need new drugs, and the “pipeline” of potential new antiretrovirals is disappointing. The biggest single block in the pipeline — the obstacles to the small human trials that could establish proof of principle — needs much more attention.

http://www.aegis.com/countries/us.html
http://www.fda.gov/

First report of acquired HCV immunity lifts vaccine hopes

A report in the Lancet suggests that some people can acquire immunity against chronic hepatitis C virus (HCV) infection, echoing earlier findings in chimpanzees. Despite the ‘alarming’ rate of infection within the study cohort, the authors say their discovery could help in the search for an effective HCV vaccine.

HCV is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million people are chronically infected with HCV, and 3–4 million people are newly infected each year. HCV is spread primarily by direct contact with human blood, and is therefore common among those who share needles without adequate sterilisation.
From a local community of intravenous drug users, Shruti Mehta and fellow epidemiologists at Johns Hopkins School of Public Health used blood tests to identify 164 people who had never been infected with HCV and 98 who had been infected but had cleared the infection.

Of participants who had not been infected previously, 21% became infected with HCV during the two-year study period. In contrast, 12% of participants who had already cleared an HCV infection in the past became infected again.

"Those who previously recovered from infection and were then infected again often resolved the new infection, suggesting that immunity could be developed that promotes recovery," said David Thomas, co-author. "This is important because prior studies that showed that you could be reinfected cast doubt on the prospects of developing an effective vaccine."

Although re-infection did occur in the study, these infections usually cleared and would not be expected to cause disease, claim the researchers.

Furthermore, co-infection with HIV had a significant impact on the likelihood of becoming infected with HCV, the report indicates. People who were not infected with HIV were 12 times less likely to develop chronic HCV infection than those who were HIV positive.

In a related editorial, David Grant (Memorial University, Canada) comments: 'While the most positive interpretation of this unique study offers hope that protection against HCV can be acquired, the immunogenicity of human vaccines still pales compared with that of genuine infections. The need for continued creative research in vaccine design is emphatically underlined by the, at best, part protection against persistent secondary infection conferred by clearance of primary infection with HCV itself.'


Source:
http://www.mediscover.net

Manganese blocks HIV replication; lab finding points to a potential new class of HIV treatments

Johns Hopkins scientists have found that simply increasing manganese in cells can halt HIV’s unusual ability to process its genetic information backwards, providing a new way to target the process’s key driver, the enzyme reverse transcriptase.

By measuring DNA produced by a related reverse transcriptase in yeast, the Hopkins team discovered that higher than normal levels of manganese, caused by a defective gene, dramatically lowered the enzyme’s activity. The scientists then proved that HIV’s reverse transcriptase responds to manganese in the same way.

Hopkins graduate student Eric Bolton determined that the defective gene is PMR1, whose protein carries both manganese and calcium out of cells. Using special yeast developed by others at Hopkins, he discovered that manganese stops reverse transcriptase, the team reports in the 26 April issue of Molecular Cell.

"These results really point to a never-before-proposed way to try to stop HIV in its tracks — that simply manipulating concentrations of a metal, manganese, can have a profound effect on reverse transcriptase," says Jef Boeke, professor of molecular biology and genetics at the school’s Institute for Basic Biomedical Sciences. “We expect the human equivalent of PMR1 could be a good target for developing new drugs against HIV.”

Retroviruses like HIV use reverse transcriptase to make copies of their DNA from RNA, the opposite of how genetic information is usually processed in cells. Each retrovirus has a distinct version of the enzyme, identical in function but different in form and sequence, says Boeke, also a professor of oncology.

The scientists found that each reverse transcriptase they studied has at least two places where manganese and the similar metal magnesium can “dock.” Having these spots filled with the right metal is crucial for the enzyme’s activity — its ability to read a particular set of RNA, the scientists learned. When the metals’ balance is out of whack, the enzyme doesn’t work properly, they report.

“Most reverse transcriptases we studied prefer to bind magnesium. At the very least they were more active when magnesium was bound to them,” says Boeke. “But a little extra manganese changes the activity of the enzyme.”

Normally, charged magnesium ions outnumber those of manganese by the thousands inside cells. Having just three times more manganese than normal can cut the activity of HIV’s reverse transcriptase in half, the scientists report, even though there’s still much more magnesium.
HIV’s ability to adapt and overcome drugs means that current treatments like AZT, which target reverse transcriptase directly, generally stop working over time. Using a combination of drugs helps block the virus on many fronts, but finding new drugs or a new class of drugs is needed to help keep the virus at bay. The new work suggests that targeting a cell’s manganese transporter could be an effective way to stop HIV from replicating, without targeting HIV’s reverse transcriptase directly.

“We’ve been working under the idea that studying reverse transcriptase in yeast may help improve understanding of retroviruses and lead to new ways to deal with HIV,” says Boeke. “By studying yeast genetics we made an important discovery about how HIV works and have identified a target for a new class of anti-retroviral drug. It was completely unexpected, but very satisfying.”

The yeast that were missing PMR1 appeared fine, suggesting that targeting the manganese transporter in humans may be relatively safe, the scientists suggest. It’s not known whether targeting manganese levels will have a therapeutic benefit, but the mantra of HIV treatment is to reduce the number of copies of the virus.

Source: Johns Hopkins University media release

Turmeric may slow multiple sclerosis progression

Preliminary studies in mice suggest that curcumin, a compound found in the curry spice turmeric, may block the progression of multiple sclerosis (MS).

Dr Chandramohan Natarajan, of Vanderbilt University in Nashville, Tennessee, observed that mice injected with curcumin showed little or no disease symptoms, while untreated animals went on to develop severe paralysis.

“We got a very good inhibition of the disease by treating with curcumin,” Dr Natarajan said. He presented the findings at the annual Experimental Biology 2002 conference.

Interest in the potential neuroprotective properties of curcumin rose after studies found very low levels of neurological diseases, such as Alzheimer’s disease, in elderly Indian populations. Added to this were studies confirming curcumin as a potent anti-inflammatory agent, effective in wound healing. And just last autumn, researchers at the University of California, Los Angeles reported that curcumin appeared to slow the progression of Alzheimer’s disease in mice.

In their 30-day study, Dr Natarajan and co-researcher Dr John Bright administered 50- and 100-microgram doses of curcumin, three times per week, to a group of mice bred to develop experimental autoimmune encephalomyelitis (EAE). They then monitored the mice for signs of MS-like neurological impairment.

In contrast, mice given the 50-microgram dose of the curry compound showed only minor symptoms, such as a temporarily stiff tail. And mice given the 100-microgram dose appeared completely unimpaired throughout the 30 days of the study.

The results did not surprise Dr Natarajan. In Asian countries, such as India and China, where people eat more spicy foods and more yellow compounds like curcumin, reports of MS are “very, very rare,” he pointed out. He said the doses the mice received were roughly equivalent in human terms to those found in a typical Indian diet.

Just how curcumin might work to thwart the progression of demyelination remains unclear. But the Nashville researchers believe it may interrupt the production of IL-12, which plays a key role in signalling immune cells to attack the myelin sheath.

Dr Natarajan stressed that “we have to do a lot of work on this,” including examining other potential mechanisms by which curcumin slows EAE and, potentially, MS.

The work remains preliminary, and MS patients should follow their doctor’s advice when it comes to treating the disease. Still, Dr Natarajan said adding a little curry to the diet couldn’t hurt. “I think using this spice in their food could be of help,” he said.

Source: Reuters Health

1,500 community representatives expected at Barcelona community forum

Fifteen hundred community representatives will gather at the Community Forum in Barcelona just before the start of the International AIDS Conference, allowing them to share their experiences, knowledge and contacts with other participants from around the world.

The Forum (called the Punto de Encuentro) will run throughout the day of 7 July 2002 at the Fira de Barcelona, which is also the venue for the 5-day XIV International AIDS Conference. The morning plenary will consist of keynote presentations from activists and community leaders from around the world, and will focus on issues such as the impact of the previous International
AIDS Conference on South Africa; The Global Fund to Fight HIV/AIDS, TB and Malaria; and a presentation on community achievements and challenges that lie ahead.

The afternoon programme is informal and has been created to allow participants to meet one another, establish useful networks, and to learn from one another’s successes and mistakes.

“The afternoon programme of the Community Forum allows people infected or affected by HIV to come together and communicate with others who work in the same region and in the same field. This is a unique opportunity for conference delegates to learn lessons or gain experience from someone else who has been working on a similar project. We allow community representatives to gain time by learning from a process that has already happened in another region,” explained Hernando Muñoz Sanchez, Community Forum coordinator.

The XIV International AIDS Conference will be held in Barcelona, Spain from 7 to 12 July 2002. It will attract up to 15 000 delegates from all over the world, including leading scientists and clinicians, health care workers, public health agencies, people living with AIDS, politicians, NGOs and the media.

The conference is organised by the International AIDS Society (IAS) and the Fundació Barcelona SIDA 2002. It is co-organized by the Joint United Nations Project for HIV/AIDS (UNAIDS), the International Community of Women Living with HIV/AIDS (ICW), the Global Network of People Living with HIV/AIDS (GNP+), the International Council of AIDS Service Organizations (ICASO) and Red 2002 (a Spanish-based network of NGOs).

Source: media release, XIV International AIDS Conference

http://www.aids2002.com

---

**ON THE WEB**

**Medscape coverage of the 9th Conference on Retroviruses and Opportunistic Infections**

10 post-meeting reviews, certified for CME (continuing education medical professionals)


**Antiretroviral therapy CME**

Treatment of Antiretroviral-Naive Patients, by Daniel Kuritzkes, MD

Advances in Understanding the Mechanisms and Importance of HIV Drug Resistance, by William A O’Brien, MD, MS

Investigational Antiretrovirals, by Joseph J Eron, Jr, MD

Pharmacokinetic and Pharmacogenomic Issues in Antiretroviral Therapy, by Stephen Becker, MD

**Complications of HIV disease CME**

Lipodystrophy and Metabolic Abnormalities: Some Movement But No Solutions, by Donald P Kotler, MD

Opportunistic Infections: Still Important and Still Evolving, by Henry Masur, MD

Hepatitis and Liver Disease in HIV-Infected Patients, William G Powderly, MD

**HIV pathogenesis and transmission CME**

HIV Transmission: Epidemiology, Biology, and Prevention, by Myron S. Cohen, MD, and Mina C Hosseinipour, MD, MPH

The Mother-Child Duet: Vertical Transmission of HIV, by Karin Nielsen, MD, MPH

Clinical Insights From Pathogenesis-Focused Studies, by Steven G. Deeks, MD

**Fibrates and statins and glitazones (Oh My!)**

ACRIA Update, Spring 2002 - Vol. 11, No. 2

It’s hard to say what’s more frustrating - the fact that we still don’t know what causes lipodystrophy, or the fact that we still don’t know how best to treat it.
Even if researchers eventually conclude that specific antiretrovirals are responsible for the more dangerous manifestations of this syndrome - most notably increases in lipid levels and insulin resistance - it’s not clear what this pronouncement will actually mean for people with HIV.

For example, it’s not as if any of us can afford to avoid the protease inhibitors.

http://ww2.aegis.org/factshts/network/simple/protease.html

They remain one of the most powerful virus-clobbering tools we have, and many of us wouldn’t get very far without them.

Full text at:

---

**Nutrition and immunity: you are what you eat**

ACRIA Update, Spring 2002 - Vol. 11, No. 2

People with HIV often take micronutrient supplements, but the research has not yet proven what the most useful dosages are for these individuals. Certain nutrients may directly influence the immune system’s ability to fight infection. For example, cells that are supplemented with vitamin D appear to prevent Mycobacterium avium complex (MAC) from growing in macrophages from HIV-positive patients:


This article will briefly review selected micronutrients and their known functions in the complex immune system.

Full text at:

---

**The role of dietary supplements in HIV**

ACRIA Update, Spring 2002 - Vol. 11, No. 2

There’s a lot more to life than viral load and CD4 counts. And increasing evidence shows that taking a few extra supplements a day may help in a variety of ways.

Full text at:

---

**Using evidence to make nutrition decisions: a look at zinc**

ACRIA Update, Spring 2002 - Vol. 11, No. 2

Evidence-based medicine provides the framework for decisions around clinical practice and treatment guidelines in HIV disease. There is growing pressure in the field of nutrition to make recommendations, especially with regards to supplementation, using this rigorous method of evaluating the evidence. The strength of a recommendation, ranging from “should always be offered” to “should never be offered,” depends on the quality of evidence that is available. The gold standard is the randomised clinical trial, usually a double-blinded, placebo-controlled intervention study, which decreases bias and gives the most objective results. The weakest evidence is considered to be “expert opinion.”

In nutrition, there have been only a few randomised clinical trials, which makes it difficult to find proof of benefit or proof of cause and effect. Instead, we often rely on in vitro (test-tube) studies, epidemiological evidence (population studies), animal studies, and anecdotal evidence such as case reports and hearsay. As a result, expert opinion often serves to guide our decisions. Nutrients are hard to study with the usual scientific methods because there are complex interactions between the gut, immune system, viral replication and the nutrients. The body’s way of handling a systemic infection is called the acute phase response. When this occurs, the metabolism of micronutrients is altered, making it difficult to accurately assess deficiency.

Full text at:
Peripheral neuropathy
A Publication of the San Francisco AIDS Foundation

Of the many symptoms associated with HIV/AIDS and its treatment, peripheral neuropathy (PN) can be among the most painful and debilitating. The most common estimate is that about one-third of people with AIDS experience some degree of nerve damage. However, PN usually occurs in the later stages of HIV disease, and many people experience mild or no symptoms. Nerve damage may be caused by HIV itself, by opportunistic infections (OIs) such as cytomegalovirus (CMV), or as a side effect of certain anti-HIV drugs, notably ddl (didanosine, Videx), ddC (zalcitabine, Hivid), and d4T (stavudine, Zerit). In people with HIV/AIDS, PN most often affects the feet, the lower legs, and later the hands, causing numbness, tingling, and/or pain. Fortunately, there are medical treatments and other measures people with HIV/AIDS can take to ameliorate neuropathy symptoms and improve their quality of life.

Full text at:
http://www.thebody.com/sfaf/winter02/pn.html

A potent weapon in the battle against HIV: your own immune system
Project Inform Perspectives 34 - March, 2002

The goal of HIV vaccines is to teach the immune system new and hopefully better ways to win the battle against the virus. There are different types of immune responses, those we were born with (innate immunity) and those we “learn” (acquired immunity). HIV vaccines exploit the side of the immune system that is learned (acquired) by providing information to cells in new ways in hopes of enhancing their learning and making them more effective fighters.


PUBLICATIONS AND SERVICES FROM i-BASE

A new issue of Positive Treatment News (PTN)
The latest issue of Positive Treatment News, our magazine for positive people, looks at adherence (missed any pills recently - need any advice?), the latest information about side effects and treatments, and the benefits and risks of joining a drug trial or study. There is also a detailed look at weight loss and what can be done about it, the official treatment guidelines, salvage therapy and treatment information provision for the African community. To order copies, see below.

Changing treatment: an updated guide to second-line and salvage therapy
A 16-page guide to resistance testing, intensifying treatment, treatment interruptions, switching drugs to avoid side-effects, experimental drugs and drugs available through expanded access programmes.

HIV i-Base treatment guides are reviewed every six months to keep them up-to-date.

Since the previous edition several new treatments have become available to use in salvage therapy:
• The nucleotide tenofovir (Viread) has been approved for use in second-line therapy. This drug can work against virus that has low level resistance to AZT, 3TC and other nucleosides.
• T-20 has started trials in the UK for people resistant to current drugs - with a limited expanded access programme expected to follow later in the year. T-20 will have activity against any resistant virus.

Other changes to this edition are to the sections on phenotypic resistance testing, treatment interruptions and Mega-HAART (and the Optima Study) and changing treatment because of side effects. The sections on expanded access and experimental treatments have also been updated. To order copies, see below.

French and Chinese translations of our booklet on avoiding and managing side effects
This booklet 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 was 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. To order copies, see below.

**Treatment information request service**

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

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

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

http://www.i-base.org.uk/

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

All publications are available free of charge — including bulk orders for the UK or single copies for other countries.
**Subscription Fax-Back Form**

Please use this form to amend subscription details for HIV Treatment Bulletin (DrFax) and/or Positive Treatment News, and to order single or bulk copies of other publications.

| Name: __________________________________ | Position: __________________________ |
| Organisation: _____________________________________________________________________ |
| Address: _____________________________________________________________________ |
| Tel: __________________________________ | Fax _____________________________ |
| E-mail: _____________________________________________________________________ |

**HIV Treatment Bulletin (HTB)**
- [ ] by Email (PDF format)
- [ ] by Post

**Guide To Avoiding and Managing Side Effects** *(August 2001)*
- IN ENGLISH
  - 1
  - 5
  - 10
  - 25
  - 50
  - 100
  - Other_____

*Also available in FRENCH and CHINESE*

**Introduction to Combination Therapy** *(December 2001)*
- IN ENGLISH
  - 1
  - 5
  - 10
  - 25
  - 50
  - 100
  - Other_____

*Also available in several other languages - please state how many of each of the translations you require*

- FRENCH
- ITALIAN
- SPANISH
- GREEK

**Changing Treatment - Guide to Second-line and Salvage Therapy** *(April 2002)*
- 1
- 5
- 10
- 25
- 50
- 100
- Other_____

**Positive Treatment News (PTN)** *from Spring 2002*
- 1
- 5
- 10
- 25
- 50
- 100
- Other_____

**Paediatric HIV Care** *(March 2001 - Report from i-Base Paediatric Meeting)*
- 1
- 5
- 10
- Other_____

**Adherence planners and side effect diary sheets** *(In pads of 50 sheets - for adherence support)*
- 1
- 5
- 10
- Other_____

**Please fax this form back or email a request to HIV i-Base:**

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