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(hyperlinked)

EDITORIAL

This issue of HTB leads with a treatment alert circulated to doctors in the US. The reasons for its inclusion are made clear in the comments section on page 4. It is still the general rule that European patients have to wait at least six months more than people in the US for drugs to be fully licensed.

However, the simplest safety measure is to monitor drug levels. Patients using new drugs particularly need therapeutic drug monitoring because of multiple drug interactions or pre-existing hepatic or renal damage.

Providing necessary pure compound for independent laboratories to develop and validate drug level monitoring assays prior to widespread use in expanded access programmes is a key patient safety issue. It would save the guesswork involved as unforeseen interactions are discovered even post registration.

UK treatment guidelines are published this month and are available on the BHIVA website (www.bhiva.org), in html and pdf format.

The World Trade Organisation has attracted much publicity for – and many people have welcomed – its agreement on allowing generic drugs in developing countries but many activists and NGOs see the agreement as a disaster for positive people in poor countries. A statement issued by 14 NGOs describes the deal as "a 'gift' bound tightly in red tape". This month we analyse the issues surrounding this controversy.

The day we went to press (24 September, 2003) WHO decided to declare the failure to deliver AIDS medicines to those who need them a global health emergency... really?

The good news on access to treatments is that the South African cabinet has announced a complete change of policy and will distribute antiretrovirals in public hospitals. However, India, which has the second biggest epidemic after South Africa, focuses all its attention on prevention. We report on a Supreme Court challenge to the Indian government that hopes to force the government to provide treatment as well.

This issue of HTB also includes reports from the 1st South African AIDS Conference, which was held in Durban in August and was a useful meeting, but has received little coverage elsewhere.

TREATMENT ALERT

Important new pharmacokinetic data for atazanavir sulfate (Reyataz™) in combination with tenofovir disoproxil fumarate (Viread®)

The following is a Dear Doctor letter from BMS circulated to US doctors on 8 August. For comment see next page.

Dear Health Care Provider,

Bristol-Myers Squibb Company would like to make clinicians caring for HIV-infected patients aware of important new pharmacokinetic (PK) data concerning the coadministration of atazanavir sulfate (Reyataz™) and tenofovir disoproxil fumarate (Viread®, Gilead Sciences Inc.). Two studies have been conducted to evaluate the potential PK interaction between atazanavir sulfate and tenofovir disoproxil fumarate (tenofovir DF), and an additional ongoing clinical study has provided preliminary data on the safety profile of this combination. Data from these trials are currently under review by the [US] Food and Drug Administration. For more details on these studies, please refer to the Study Information section below.

The following observations were made from these three trials:

Study AI454-181: In healthy volunteers atazanavir AUC and Cmin were decreased by approximately 25% and 40%, respectively, when unboosted atazanavir sulfate 400 mg was coadministered with tenofovir DF 300 mg once daily (QD) as compared to atazanavir sulfate alone. In addition, an increase of approximately 24% in tenofovir AUC was observed.

Study PUZZLE 2 (ANRS 107): Atazanavir AUC and Cmin were decreased by approximately 25% and 23%, respectively, when atazanavir sulfate 300 mg and ritonavir 100 mg (boosted atazanavir sulfate) were coadministered with tenofovir DF 300 mg QD, as compared to atazanavir sulfate 300 mg and ritonavir 100 mg administered without tenofovir DF to HIV-infected patients.

For the combination of boosted atazanavir sulfate with tenofovir DF, the atazanavir AUC and Cmin observed in the Puzzle 2 study were approximately 1.2 and 4 fold higher than the respective values observed for unboosted atazanavir sulfate, 400 mg given alone, to healthy volunteers in Study AI424-181.

Study AI424-045: Interim safety data from an ongoing clinical trial suggest that the treatment emergent adverse events of moderate or severe intensity are comparable for boosted atazanavir sulfate in treatment experienced patients and for unboosted atazanavir sulfate treated patients in other clinical trials.

Based on these results:

Clinicians should use caution when administering unboosted atazanavir sulfate with tenofovir DF. Unboosted atazanavir sulfate may be less effective due to decreased atazanavir concentrations in patients taking atazanavir sulfate and tenofovir DF. As a result, the coadministration of unboosted atazanavir sulfate with tenofovir DF may lead to loss or lack of virologic response and possible resistance to atazanavir sulfate.

If atazanavir sulfate is coadministered with tenofovir DF, consideration should be given to administering atazanavir sulfate 300 mg with ritonavir 100 mg and tenofovir DF 300 mg (all as a single daily dose with food), until additional data are obtained. Coadministration of atazanavir sulfate 300 mg and ritonavir 100 mg QD is currently under clinical investigation.

The increase in tenofovir AUC does not appear to be associated with increased toxicity over 24 weeks.

STUDY INFORMATION:

Study AI454-181 conducted by Bristol-Myers Squibb (BMS) Pharmaceutical Research Institute

Design: Phase I, open-label study in healthy subjects to evaluate whether the PK parameters of either unboosted Reyataz 400 mg QD or tenofovir DF 300 mg QD were affected by their coadministration. The PK parameters of atazanavir sulfate 400 mg QD administered with food were compared to those of atazanavir sulfate 400 mg QD when coadministered with tenofovir 300 mg QD and food.

Puzzle 2 (ANRS 107) Trial - PK sub-study conducted by Taburet et al.

Design: An ongoing efficacy study and PK sub-study in highly treatment-experienced HIV-infected subjects. HIV-infected subjects experiencing failure on a protease inhibitor (PI)-containing regimen were treated for the initial two weeks of the study with atazanavir sulfate 300 mg QD plus ritonavir 100 mg QD substituted for the failing PI. Current nucleoside reverse transcriptase inhibitors (NRTIs) were continued for the initial two-week period after which time they were replaced with tenofovir DF 300 mg QD and a second NRTI chosen by genotypic testing. Atazanavir pharmacokinetics were determined at Week 2 before the introduction of tenofovir DF and again at Week 6.

Study AI424-045 conducted by Bristol-Myers Squibb (BMS) Pharmaceutical Research Institute

Design: An ongoing 48-week, Phase III, randomised, multinational, open-label three-arm trial of 358 highly treatment-experienced HIV-infected subjects. One arm of this study is evaluating the efficacy, safety and tolerability of the combination of atazanavir sulfate 300 mg and ritonavir 100 mg QD coadministered with tenofovir DF 300 mg QD and one NRTI.

Sincerely,

Sally Hodder, MD

Vice President, Virology Medical Affairs， Bristol-Myers Squibb Company

C O M M E N T

There are several important reasons why this issue of HTB carries a Dear Doctor letter circulated to US doctors, for a new drug, atazanavir, which is still not yet approved in Europe.

The first is that in practice it is already being used by UK patients – either in trials or on the expanded access programme. So this information is important, and although this data on the interaction was presented in February 2003, [1] we still receive calls to the i-Base phoneline over six months later from patients on routine doses of both drugs whose doctors are not aware of the interaction.

The second is that the interaction is with tenofovir and many of the people using one will be likely to want to use the other. Both drugs are taken once daily with food. Because they are both recent drugs, and tenofovir has activity against some levels of nucleoside resistant virus, they are both likely to be used in treatment-experienced patients.

The third is a safety issue not addressed in the BMS letter – that of the other side of the two-way interaction: tenofovir reduces atazanavir but atazanavir also increase levels of tenofovir. Un-boosted atazanavir, given at 400mg standard dose increases tenofovir AUC by 24%. This level is not clinically important. However, atazanavir AUC and Cmin increase by up to 10-fold when a lower 300mg dose of atazanavir is boosted by 100mg ritonavir. There is no data on what happens to tenofovir levels with boosted atazanavir, or published data on the mechanism. So, this 10-fold increase in atazanavir has at least the potential to have a knock-on effect on the levels of tenofovir, perhaps pushing the interaction to a clinically important level. We cannot understand how the ritonavir boosting can be recommend under these circumstances.

Data from patients using boosted atazanavir and tenofovir in the BMS045 treatment experienced study did not show any increase in

reporting of tenofovir-related toxicity, but this involves small numbers of patients followed for a short time. [2] Until more data is available, clinicians should at least be aware of this potential interaction.

In addition to the issue of ritonavir boosting, this raises the issue of access to both 150mg and 200mg formulations of atazanavir in the UK and the expanded access programme. As we went to press, UK patients had only just received access to the 150mg dose that had previously been delayed by ethics committee approval. Until then, as capsules cannot be split in the same way as a pill can be cut in half, this had left people the option of either boosting 400mg atazanavir with 100mg ritonavir – presumably reaching even higher levels – or increasing the dose of unboosted atazanavir to 600mg.

Given that atazanavir was approved and available in the US since May 2003, it is unacceptable that UK patients have to take this uncertainty over dosing. Again, as we went to press the TDM lab in Liverpool University had still not been given the pure compound needed to develop a therapeutic drug monitoring (TDM) assay for atazanavir, which takes 6-8 weeks to develop and validate. So, patients currently can only guess, and continue to guess until this is available. In their favour, BMS is looking to support a programme for TDM for UK patients who need to confirm drug levels. We hope that this programme becomes available quickly.

Finally, on an issue of patient care, it is useful to point out specific timelines and understand why these interactions are dealt with poorly from an individual patient concern. For interaction data to be presented to the February Retrovirus meeting it had to be available several months earlier. The details of the two-way interactions presented at ICAAC were available in July. There should be a regulatory requirement for basic interaction data not to be withheld until a conference presentation but released early as an issue of public safety.

The initial atazanavir expanded access programme has now enrolled. Unlike every previous expanded access programme, the UK ethics committee responsible capped enrolment. A new named-patient programme is available for the period prior to licensing. Physicians should call Dr Ian Hitchcock at BMS on 0208 754 3684.

A similar interaction, between lopinavir/r (Kaletra) and tenofovir is reported in ICAAC poster A-1617 (see Conference reports for details of access). Lopinavir levels are slightly reduced and steady-state tenofovir levels increased by 31%. On the basis of short-term data, neither change is thought to be clinically significant.

References

1. A. M. Taburet, C. Piketty, L. Gérard et al. Pharmacokinetic parameters of atazanavir/ritonavir when combined to tenofovir in HIV infected patients with multiple treatment failures: a sub-study of Puzzle2-ANRS 107 Trial. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 537.
2. Badaro R, DeJesus E, Lazzarin A, et al. Efficacy and safety of atazanavir (ATV) with ritonavir (RTV) or saquinavir (SQV) versus lopinavir/ritonavir (LPV/RTV) in combination with tenofovir (TFV) and one NRTI in patients who have experienced virologic failure to multiple HAART regimens: 16-week results from BMS AI424-045. 2nd IAS Conference, Paris 2003. Abstract 118.

TREATMENT GUIDELINES

British 2003 HIV treatment guidelines are published online

Simon Collins, HIV i-Base

The British HIV Association (BHIVA) has published the 2003 UK treatment guidelines online in both html and pdf file format.

http://www.bhiva.org/

http://www.bhiva.org/pdf/2003/guides/BHIVA_2003_Guidelines.pdf

This is the first major revision for more than two years and contains many significant changes. These include:

• Treatment should aim to be initiated while CD4 count is above 200 cells/mm^3 or at higher levels if symptomatic. Exact timing depends on various factors, including short-term risk.

• Triple nucleoside combinations previously recommended such as Trizivir (AZT/3TC/abacavir) are not now recommended, even for patients with a lower baselines viral load.

• d4T is not recommended for first line therapy due to increased association with lipodystrophy.

• Unboosted PI regimens are not recommended for first choice due to poorer pharmacokinetics, and less convenient dosing.

• The committee believes there is no definitive evidence on which to base a preference for either choice of nucleosides or choice of PI or NNRTI.

• Considerations for regimens include ease of adherence and minimising toxicity, and should take account of individual factors such as hepatitis B/C, risk of cardiovascular disease, diabetes, psychiatric disease, and lifestyle.

• Treatment in primary HIV infection is recommended if needed to relieve severe symptoms but is not generally recommended

otherwise, unless as part of a clinical trial.

• Use of resistance testing is recommended for all treatment naïve patients prior to starting treatment. In practice, this means that people should receive or have a sample stored for later testing when diagnosed.

• Therapeutic drug monitoring (TDM) is seen as being of value in specific circumstances, such as reducing toxicity, and adjusting doses in significant hepatic or renal impairment.

• Interrupting or stopping treatment may benefit patients who started treatment earlier than currently recommended – ie with a high pre-treatment CD4 count (specified as 'perhaps 300 cells/mm^3'). The importance of careful monitoring is stressed.

• New sections include monitoring tests, management of patients who are using treatment combinations not now recommended in the guidelines (such as Trizivir or d4T), and a table on drug costs.

• Sections on the management of side effects such as lactic acidosis, metabolic changes and lipodystrophy have been updated and include, for example, a stronger recommendation for New-Fill).

The guidelines will also be published as a supplement to the October issue of HIV Medicine.

TREATMENT ACCESS

South Africa delays deregistering nevirapine

Polly Clayden, HIV i-Base

The Medicines Control Council (MCC) of South Africa issued a press release on 12 September announcing that in view of additional data brought to their attention since the decision to deregister nevirapine for use in combating mother to child transmission, the time period for Boehringer Ingelheim to submit new evidence had been extended. It explains that new data must be submitted on the use of nevirapine in combination with other antiretrovirals for use for this indication.

The press release also says: "Appropriate treatment of the mother and the newborn child is also imperative, and the MCC urges healthcare professionals to use available interventions to improve the survival and health status of both mother and child."

Ref: MCC Press Release, 12 September 2003

Disagreement greets a new deal on patent protection and generic drugs for poor countries

Graham McKerrow, HIV i-Base

Two years after being told - in paragraph six of the 2001 Doha Declaration - to find a solution to the conflicting interests of pharmaceutical companies and the needs of poor people requiring medicine in developing countries, the World Trade Organisation reached agreement in Geneva on 30 August to allow developing countries to import cheap, generic drugs. Or, they sold the poor down the river to protect the patents and profits of the rich western pharmaceutical companies. Take you choice.

While some hailed the agreement as providing new opportunities for developing countries to distribute generic drugs, several NGOs said the agreement bound generic drugs in so much red tape that it was effectively unworkable.

Supachai Panitchpakdi, the director general of the WTO told journalists: "This is an historic agreement for the WTO." The Lancet reported that the agreement "will make it easier for poor countries to import cut-price generic drugs made under compulsory licensing."

Kenyan and South African ambassadors at the meeting also welcomed the agreement, but leading NGOs criticised it saying it protected the multinational pharmaceuticals and the high prices of their products and so would continue to keep treatment from people who need it.

Compulsory licences allow a government to permit the production of generic drugs without the consent of the patent holder. The WTO agreed to waive the rule that compulsory licences must be for the domestic market of that country, a rule that prevented generic drugs being exported to other nations. As most poor countries are too poor to manufacture medicines for their population, this rule has deprived millions of people of the treatment they need. Poor nations need to be able to import generic drugs from countries where they are produced, such as India and Brazil.

The US worked hard to protect the rights of the pharmaceutical giants and in response to American demands only the poorest countries can benefit from the new agreement. Middle income countries like Mexico and South Korea had to promise not to use compulsory licences except in times of national emergency.

The US trade representative Robert Zoellick told the Lancet that the agreement succeeded in "striking the right balance between addressing the needs of the poorest countries while ensuring intellectual property protections that foster the future development of lifesaving drugs".

The deal was criticised by NGOs working in the field who said the regulations surrounding the implementation of compulsory licences made them unworkable. Médecins Sans Frontières and Oxfam issued a joint statement saying it would do little to cut the prices of medicines. "Today's deal was designed to offer comfort to the US and the Western pharmaceutical industry," said Ellen 't Hoen of MSF. "Unfortunately, it offers little comfort for poor patients. Global patent rules will continue to drive up the price of medicines."

Céline Charveriat of Oxfam said the new agreement included a "burdensome system" of regulation that would not help the production of generic drugs, and that developing countries would have little alternative to the high prices and long-term monopolies of brand-name medicines.

Below Mauro Guarinieri, Chair of the European AIDS Treatment Group, looks at the latest deal and examines its shortcomings.

TRIPS agreement will not save lives

Mauro Guarinieri, for HIV i-Base

When I read the final version of the paragraph six solution dated 30 August 2003, it was difficult to believe that any country and particularly developing countries in their right senses would have agreed to such a charter for slavery.

The TRIPS (trade-related aspects of intellectual property rights) Agreement, right from its very beginning, had nothing to do with innovation or scientific advancement but was a treaty signed through coercion and blackmail for market control, market dominance, market segmentation and market exclusion.

The TRIPS Agreement, crafted in close consultation with the pharmaceutical industry, succeeded absolutely in this respect. The paragraph six solution has reinforced the market exclusion of the developing countries. They cannot export any product to another developing country without being closely watched and monitored. The outcome will be that countries in need of affordable medicine will be essentially unable to implement the 'solution', because it contains too many unnecessary conditions and restrictions.

"This 'solution' is a failure for people with AIDS, and people everywhere dying of treatable diseases," said Asia Russell of Health GAP. "The current solution is designed to placate US drug companies and guarantee ever-expanding market share, not to increase access to affordable generic medicines for dying people", she added.

The original intention of the talks was to facilitate the supply of affordable generic drugs for developing countries. However, the agreement has thrown up new legal, economic, and political obstacles to ensuring production and export of generic medicines in the future:

Extra anti-diversion measures

One of the worst features of the 30 August paragraph six solution is that pertaining to the diversion of products made for countries not having the manufacturing capacity. The statement puts further demands on packaging and labelling that are likely to increase the cost rather than reduce it. The extra requirements on diversion seem to be exclusively aimed at further discouraging countries and producers from using the system.

New powers to TRIPS Council

The statement introduces an extended role for the TRIPS Council and the WTO in policing the system. The WTO secretariat, the TRIPS Council and the Chair of the TRIPS Council will now begin to routinely review the issuing of individual licences, and the WTO will now as a matter of expected practice, oversee the use of compulsory licensing in the most intimate terms, looking at the terms of individual licences, evaluating the basis for deciding if manufacturing capacity is insufficient, or reviewing or second guessing any of the new terms and obligations that the new implementation language introduces into the regulation of compulsory licensing of patents on medicines.

"The people who negotiated this agreement have given the world a new model for explicitly endorsing protectionism," said James Love, from the Consumer Project on Technology. "The United States, Europe, Canada, Australia, Japan and other developed economies will be allowed to bar imports from developing country generic suppliers under completely irrational protectionist measures that are defended by the WTO Secretariat and its most powerful members as a humanitarian gesture," he added.

EU Trade Commissioner Pascal Lamy already started to misuse the deal: "This is a crucial demonstration that the Doha Development Agenda is more than just fine words." Lamy attacked a position endorsed by his own parliament that was a far more elegant and rational solution to the export issue. The European Parliament Amendment 196 was 52 words long. The

new WTO deal has more than 3,200 words. The extra 3,150 words were not needed and will create a morass of uncertainty and gamesmanship.

“Today, countries can use compulsory licences for import, because a supply of generic versions of many drugs is available somewhere on the world market,” said Celine Charveriat of Oxfam. “What Members do not seem to take into account is that the burdensome system being put in place does nothing to ensure that generic production will happen in the future. Rather, developing countries will have little alternative to the high prices and long-term monopolies of brand-name pharmaceutical companies.”

Once again, the World Trade Organisation has shown its real face. The WTO still represents the most ambitious and perverted effort to resubjugate the economies of the countries of the South to serve the interests of transnational corporations. Its legacy is greater poverty, inequity, gender inequality, and indebtedness throughout the world. Among many others, AIDS is a silent war that claims six people every minute. These deaths are due to the criminal attitude of wealthy nations and multinational corporations that have constantly ignored the urgency of expanding free and universal access to treatment for HIV/AIDS and continuously attempted to erode the reach and strength of the declaration approved by WTO members in Doha. Eight years of the WTO had already produced an unacceptable death toll. Now it is time to say: “Enough is enough”.

On the positive side, the new agreement completely rejects the efforts of the US, Japan, the European Union and the WTO Secretariat to limit the scope of diseases for compulsory licensing, and it also does not require high standards such as epidemics or emergencies.

Mauro Guarinieri, is Chair of the European AIDS Treatment Group

http://www.eatg.org

Sources:

CPTech Statement on WTO deal on exports of medicines

MSF and Oxfam press statement on WTO drugs deal

Health GAP statement on WTO ‘consensus’ on access to medicines

The approved text, as reported by the WTO:

http://www.wto.org/english/tratop_e/trips_e/implem_para6_e.htm

Joint press release from MSF and Oxfam

http://www.accessmed-msf.org/prod/viewcategorydocs.asp?catid=3&subcatid=525

Further information:

http://www.guardian.co.uk/wto

Joint statement by 14 NGOs dismisses TRIPS deal as a ‘gift bound in red tape’

This is the full text of the statement issued by the organisations named below*

The 30 August WTO deal on exports of generic medicines is being presented as a gift to the poor. However, it is a “gift” bound tightly in red tape. As a measure of trade policy, it contradicts the basic principles of the WTO and free trade.

The good news is that the developing countries resisted pressure from the United States, the European Union, Japan and other developed economies to limit the agreement to only a few diseases or for only extraordinary circumstances.

For a WTO “deal” to be more than a public relations exercise for a new round of trade rules, it should actually work in practice. The WTO took a 52-word mechanism that was endorsed by the European Parliament in 2002 and created a 3,200-word maze of red tape that was plainly designed to frustrate and undermine the objective of protecting public health and promoting access to medicine for all.

These are the main problems with the rules:

1. The WTO is requiring the issuance of two compulsory licences when the new mechanism is used.

2. The WTO has added many constraints on the business practices of the generic companies.

3. The WTO deal introduced an extra layer of uncertainty by stating that the system should not be an instrument to pursue industrial or commercial policy objectives, creating uncertainty over the role that will be played by the businesses that manufacture and sell generic drugs.

4. The decision leaves unclear whether or not economic efficiency is a grounds for determining a lack of manufacturing capacity in the importing country. The lack of clarity on this issue has been defended as a matter of “creative ambiguity”, but already the US is telling the Philippines and other countries that they will oppose “economic efficiency” as grounds for allowing a country to import generics.

5. The deal gives the WTO itself new authority to second guess and interfere in the granting of individual compulsory licences to generic companies.

6. The United States and other developed economies now have greater opportunities to pressure and stop developing countries from issuing compulsory licences.

The current decision is only a temporary waiver, and a permanent amendment to the TRIPS is scheduled for 2004. We call upon the WTO member countries to draft an amendment to the TRIPS that simplifies and clarifies the procedures and removes unnecessary obstacles to the export of medicines to address public health problems.

We also call upon every country that does not have access to medicines for all to begin to use the TRIPS flexibilities, and the 30 August 2003 decision, to provide affordable medicines to the poor. We urge countries to resist implementation of TRIPS plus obligations in regional or bilateral trade agreements. If the framework imposed on countries by the WTO cannot be used effectively to promote public health and access to medicines for all, then poor countries should not be obligated to issue patents on medicines.

* This statement was issued by: ACT Up Paris, Consumer Project on Technology, Consumers International, Essential Action, European AIDS Treatment Group, Health Action International, Health GAP, International People's Health Council, Médecins Sans Frontières, OXFAM International, People's Health Movement, SEATINI, Third World Network and Women in Development.

An activist's view from the WTO meeting in Cancun

Mauro Guarinieri, HIV i-Base

Some protesters wanted to be as colourful and disruptive as they were when the World Trade Organisation met in Seattle in 1999, which gave birth to a global protest movement, but attention focused on the WTO's meeting at Cancun in September for different reasons. The real drama involved the delegates from 147 nations engaged in negotiations aimed at making life fairer for poor countries struggling against a rigged global trading system.

However, there was protest in Cancun. A welcoming speech by Mexican President Vicente Fox was delayed by demonstrators and, just as delegates at the fifth ministerial meeting of the WTO were being welcomed with close attention to protocol, several miles away about 4,000 protesters marched through the town and tried to knock down fences preventing them from entering the meeting area. During the rally 56-year-old Lee Kyang Hae of the Korean Farmer's Organisation stabbed himself in front of police to draw attention to the grave situation that farmers across the world face because of the liberalisation of commerce. While Lee was killing himself, holding a placard saying "WTO Kills Farmers", Rubens Ricupero told delegates that although "the rhetoric of global trade is filled with promises … the reality of the international trading system today does not match them". He explicitly mentioned in his message "the sick and the dying, whose suffering has been needlessly prolonged by lack of access to affordable medicines".

Ricupero, speaking to delegates on behalf of UN Secretary General, Kofi Annan, said that the paragraph six 30 August deal on medicines should be flexibly implemented, so that developing countries can gain access to medicines.

Although medicines were not on the agenda of the ministerial meeting in Cancun, AIDS activists criticised the deal reached by WTO Members on 30 August. Activists pointed to complicated new obligations placed on generic manufacturers and importing and exporting countries, which meant that the "solution" would be difficult if not impossible to implement. These impediments include the requirement for compulsory licences in both importing and exporting countries, the creation of new avenues for bullying countries that try to use the deal, and public and private efforts by the US to exclude countries that may have some manufacturing capacity but don't have domestic production because they lack economic efficiency.

The WTO's next step is to create a permanent amendment to TRIPS that would permit countries to obtain exported generic medicines. Activists demanded that the permanent amendment return to the letter and the spirit of the Doha Declaration — which prioritised access to medicines for all — by removing the new conditions imposed by this temporary waiver.

Dr Yusuf Hamied, Chairman and Managing Director of Cipla, the largest supplier of generic AIDS medicines to poor nations, said that the "political compromise" reached by WTO delegates in Geneva was "an invitation to disaster". He added: "The decision is a certain death sentence for millions of people… It creates new bureaucratic hurdles that did not exist before this decision. It will discourage companies from seeking to supply these life saving medicines."

The good news is that the developing countries resisted pressure from the United States, the European Union, Japan and other developed economies to limit the agreement to a few diseases and extraordinary circumstances. The bad news is that the WTO has already started to undermine its own agreement, forcing Cambodia into major concessions on generic AIDS drugs as part of its WTO joining package.

According to two Cambodian Charities, Cambodia had been forced to stop using generic drugs immediately and implement TRIPS by 2007 rather than delay it to 2016 as least developed countries (LDCs) are allowed to do under the terms of the WTO's 2001 "Doha Declaration". "This is another example of double standards and hypocrisy," said country representative Mike Bird.

"It is apparent that Cambodia's accession treaty will go beyond what was negotiated by LDCs in Doha, particularly in the area of intellectual property." At the same time the US already started telling the Philippines and other countries that they will oppose "economic efficiency" as grounds for allowing a country to import generics, a position that clearly contradicts the same principles of the WTO and free-trade.

Mauro Guarinieri is Chair of the European AIDS Treatment Group

http://www.eatg.org

South African cabinet rules that public hospitals should provide ARVs

Graham McKerrow, HIV i-Base

The South African government has instructed its health minister, Manto Tshabalala-Msimang, to draw up, within one month, a plan to make antiretroviral therapy available in public hospitals. There have been false dawns and apparent u-turns by the South African government in the past, but this move does seem to bring to an end four years of inactivity by President Thabo Mbeki's government.

Domestic and international anger has been aroused over the years by Mr Mbeki's questioning of the causal link between HIV and AIDS and the refusal of his government to provide ARVs. There have been several announcements that official policy had changed – promises that were never fulfilled.

This change of heart appears to be different because it was taken by the full cabinet, arises from a joint report by the health ministry and the treasury, and because it has resulted in an instruction that an operational plan be drawn up within a month.

The Treatment Action Campaign (TAC) issued a statement welcoming the cabinet's endorsement of the report, which found that between 500,000 and 1,7 million South African lives could be prolonged with ART and that the country could afford to provide the treatment in public hospitals. TAC said: "There is cause for celebration and optimism."

Shortly before the cabinet's decision, the TAC learnt that the announcement was imminent and members persuaded Zackie Achmat, one of the organisation's leading figures, to start treatment. He had refused treatment while the government refused to treat other people.

The announcement was accompanied by other related and significant moves. It was announced that some of the money and expertise for providing the treatment would be supplied by the Bill Clinton Foundation. The Global Fund to Fight AIDS, TB and Malaria announced that a $27 million grant it has been waiting to give to organisations in South Africa for work including ARV treatment – but which was held up by the government – had finally been accepted.

A statement issued by the special cabinet meeting said: "Cabinet decided that the Department of Health should, as matter of urgency, develop a detailed operational plan on an antiretroviral treatment programme. The Department will be assisted in this work by South African experts as well as specialists from the Clinton Foundation AIDS Initiative who have not only offered to contribute to this effort, but have also been of great assistance in commenting on the work done thus far. It is expected that this detailed work would be completed by the end of September 2003."

The TAC statement said: "This is a critical step to develop a more comprehensive treatment and prevention plan for managing the HIV/AIDS epidemic. Properly implemented, this will restore hope, dignity and life for millions of people in our country, and, hope throughout the continent.

"The TAC National Executive will formally suspend the civil disobedience campaign and reconsider pending litigation early next week. We welcome Cabinet's bold step today but we also remember the anguish, pain and unnecessary loss of lives over the last four years."

AIDS leads to 600 deaths in South Africa a day.

The government statement on the special cabinet meeting can be read at, and a pdf of the full Report of the Joint Health and Treasury Task Team can be downloaded from (click on full report):

http://www.gov.za/speeches/8aug03.htm

TAC's response is at:

http://www.tac.org.za/newsletter/2003/ns08_08_2003.htm

Indian government taken to court over lack of treatment

Graham McKerrow, HIV i-Base

The Indian government is being taken to the country's Supreme Court in a public interest petition that says poor people with HIV who require hospital care and drugs are given no treatment "in any public hospital" and are "simply left to die".

The petition filed by the Voluntary Health Association of Punjab (VHAP) also names the National AIDS Control Organisation, all States and all Union Territories.

India has between 3.8 million (government estimate) and 5.5 million (an NGO estimate) people with HIV, even though government policy has concentrated on prevention rather than treatment. The Supreme Court petition seeks a direction from the court to the governments to recognise and implement the right of people to treatment, and to provide free access to antiretroviral therapy (ART).

The petitioners point out that India has an advantage over other developing countries in that 10 of the 12 anti-HIV drugs recommended by the World Health Organisation are produced by Indian pharmaceutical companies. They argue that the cost of providing ART is less than the cost of treating opportunistic infections and they want to see a complete change of government policy so that India uses compulsory licences to make generic versions of patented drugs available to its own people.

Further information:

http://www.rediff.com/news/2003/aug/04aids.htm

http://bmj.com/cgi/content/full/327/7411/360-c

C O M M E N T

Much international attention has been focused on South Africa in the last four years and people inside and outside that country have tried to persuade the government that it must act to treat as well as prevent HIV. Emotions were particularly fuelled in that case because South Africa had the worst HIV epidemic in the world and it seemed the lack of action was prompted by President Thabo Mbeki's refusal to accept a causal link between HIV and AIDS.

Now, as we report above, South Africa has had a change of heart and is preparing a treatment programme. Clearly, it is time for the spotlight to move to other nations that have yet to act, and that list must include India, where the epidemic is second only to South Africa and the immorality of the inaction of the government is magnified by the existence of Indian pharmaceutical companies, like Cipla, manufacturing low cost generic antiretrovirals.

Phase 2 of India's National AIDS Control Programme (NACP), supported by the World Bank, focuses on prevention, but leaves citizens with no right to treatment. Pressure must be exerted for treatment and care to be a major part of the NACP Phase 3. The Voluntary Health Association of Punjab (VHAP) hopes the Supreme Court petition will be the first step towards such a policy change. The VHAP executive director, Shri Manmohan Sharma, has appealed for help, urging supporters to write to local and national media about the case. "The more this case gets publicity, the more chances there are of a favourable verdict," he says.

Activists in India have issued a prayer for the successful conclusion of the Supreme Court case. It prays for the court to direct the respondents to provide free and equitable access to ARVs, to review public policy, to create the necessary health infrastructure and to declare a national emergency and invoke the compulsory licensing provisions of the TRIPS Agreement so that treatment can be provided using generic drugs.

It is predicted that in the coming years India will overtake South Africa as having the worst AIDS pandemic in the world, with 35 million positive people by 2015. There is clear evidence that treatment is not only humanitarian of itself, but also a necessary part of prevention; there is now every reason to make India a major focus of international attention.

CONFERENCE REPORT

43rd Annual ICAAC

14-17 September 2003 in Chicago

The 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) took place as this issue of HTB went to press.

HTB reports of data from this meeting will be included in the next issue.

The conference abstracts are available for a limited time on the conference website. Click on the 'itineray builder' link for browse or search access to abstracts.

http://www.icaac.org/ICAAC.asp

Early reports from this meeting are produced on several websites.

HIVandHepatitis.com

http://www.hivandhepatitis.com

The Body.com

http://www.thebody.com/confs/icaac2003/icaac2003.html

NATAP

http://www.natap.org

Medscape (requires one-time free registration)

http://www.mescape.com

CONFERENCE REPORT

South African AIDS Conference

Durban, 3-6 August 2003

This meeting was South Africa's first national AIDS conference. President Thabo Mbeki was notable for his absence and the opening ceremony saw Minister of Health Manto Tshabalala-Msimang defend the government's inaction in addressing the spread of HIV/AIDS.

Talk in the corridors focused on the Medicine Control Council's decision to review nevirapine for mother to child transmission and the ever more urgent need for a national treatment plan.

Meanwhile, despite unbelievable odds, many small projects reported delivering antiretrovirals very successfully in resource-poor settings.

All references are to the programme and abstracts of the South African AIDS Conference, Durban, 3-6 August 2003.

Township project is a model for care in resource poor settings

Polly Clayden HIV i-Base

A poster from Medecins sans Frontiers (MSF) describes their rigorous selection procedure, adherence support and excellent outcome of Africa's best known - and model - pilot antiretroviral programme, in Khayelitsha, South Africa. [1]

Khayelitsha is a township outside Cape Town with approximately 500,000 inhabitants of which 10% are estimated to be HIV-positive. The choice of the township by MSF "…was in itself an opportunity to prove that an ART programme can be undertaken in even the poorest conditions in a primary health care setting." [2] MSF began its project there in 1999 and the antiretroviral programme was initiated in May 2001.

Eligibility for the programme is based both on medical criteria – WHO stage III/IV and symptomatic HIV/AIDS - and additional criteria including a community assistant to help with adherence, disclosure of HIV status, residency in Khayelitsha and prompt attendance to three appointments over at least four months.

Each candidate's folder is presented anonymously to a selection committee comprising different community representatives including people living with HIV. All services, including antiretrovirals, standard monitoring and OI management, are provided free and generic drugs are used as far as possible. The programme takes a multidisciplinary approach to healthcare delivery, and adherence support is rooted firmly in the community working with the Treatment Action Campaign.

The investigators presented results for 288 patients of which 70% were women, with a median age of 31 years, a median CD4 count of 42 cells/mm3, a median viral load of 5.2 logs and 52% with AIDS on initiation of therapy.

They report 84.3% survival at 18 months on treatment despite low median CD4 cell count on initiation and a mean increase in CD4 of 221 cells/mm3 per year. Adherence is excellent with patients reporting taking 95% of their doses. An impressive 90% of patients had undetectable viral loads at three months and 83% at one year.

A research letter from MSF published in the September issue of AIDS reporting polled results from seven projects in resource poor settings (including the Khayelitsha project) describes similar findings – with a probability of survival at six months estimated at 89.5% [95% CI 86.8-92.1] and among those surviving an estimated probability of remaining on treatment of 94% [95% CI 91.8-96.1]. [3]

A recent article in the New York Times, announcing: "Africans outdo Americans following AIDS therapy", describes the Khayelitsha project as having "…extraordinary levels of compliance". [4]

References

1. Coetzee D, Goemaere E, Boulle A et al. Appropriate selection criteria promote good outcomes for patients on antiretroviral therapy in resource poor settings. Abstract T3-P26
2. HIV/AIDS treatment in South Africa proves success in the poorest countries 12.08.2002 http://www.msf.org
3. Tassie JM, Szumilin E, Calmy A et al. Highly active antiretroviral therapy in resource-poor settings: the experience of Medicines sans Frontieres. AIDS 17 2003:1995-1997
4. McNeil DG. Africans outdo Americans in following AIDS therapy. New York Times, September 3, 2003

Projects band together to buy lowest-cost generic drugs

Polly Clayden HIV i-Base

Established in February of this year by a group of 19 South African treatment projects, the Generic Antiretroviral Procurement Project (GARRP) aims to improve access to ART through the promotion of good quality generic antiretrovirals at the lowest possible cost.

In a session focusing on generic antiretrovirals Colwyn Poole and Wilbert Bannenberg described the operation, scope and "The world of GARPP".

There are currently 10 GARPP-associate projects providing 600 people with treatment in the public sector. Models of care vary but members have contractual obligations to GARPP: all must meet the minimum standard of care by the Southern Africa HIV/AIDS Clinicians Society guidelines on use of antiretrovirals, use WHO-recommended regimens and share experience and knowledge of implementation in a variety of settings.

GARPP will only procure generics approved by the South African Medicines Control Council (MCC). Currently registered are zidovudine, lamivudine, stavudine, nevirapine and lamivudine/zidovudine combined. However, it recognises that there are significant gaps – there are no registered generic paediatric formulations and no three in one fixed dose combinations, which are only being manufactured by generic companies and which Dr Eric Goemaere of MSF described as "extraordinarily useful for adherence". So GARPP is applying for exemption from MCC registration for those products where clinically indicated.

"GARPP can get a first-line combination of ARVs for 308 Rand [£26.13] per month, more than four times lower than the current retail price for the same combination and about 1.5 times lower than the price the government would get if benefiting from the best offers of originator companies," Poole explained. GARPP believes these prices can be reduced even further.

They anticipate that this network will extend to 30 projects with 4,000 patients over the next year.

"GARPP will take all necessary steps to ensure that we are able to procure these life saving drugs."

References

1. Poole C, Darder M, Karim QA et al. Antiretroviral therapy provision in the public sector and the Generic AntiRetroviral Procurement Project (GARPP) Abstract T4-S2-A8
2. Bannenberg W and Darder M. The Generic Antiretroviral Procurement Project (GARPP). Abstract T4-S2-A9

For further information, contact Wilbert Bannenberg, Managing Director – wilbert@wanadoo.nl or about membership Colwyn Poole colwynp@mweb.co.za

MTCT-Plus operates in Cote D'Ivoire, Kenya, Mozambique, Rwanda, South Africa, Thailand, Uganda and Zambia

Polly Clayden HIV i-Base

The MTCT-Plus initiative provides HIV care including antiretrovirals to HIV-positive women identified during pregnancy, and their families. This project was launched in 2001 as a response to Kofi Annan's "Call to Action". It utilises antenatal care as an entry point to HIV treatment and acknowledges that MTCT programmes in resource poor settings have generated cohorts of HIV-positive women without access to treatment for their own health.

Representatives from MTCT-Plus, including principal investigator Wafaa El-Sadr, provided an overview of the project since enrollment started in February of this year. Sites have now been established in Cote D'Ivoire, Kenya, Mozambique, Rwanda, South Africa, Thailand, Uganda and Zambia and a multidisciplinary "essential package" has been developed that is family focused and includes both clinical and psychosocial services, including adherence support, for adults and children.

Training of healthcare teams has been conducted and a central procurement system established for medications, including antiretrovirals, and supplies through UNICEF. Medications, including generics, on the WHO pre-qualified list are used. They have developed a system of data collection and programme evaluation that includes sharing information between sites to assist in programme development.

As of 30 May, 574 patients have been enrolled at seven MTCT-Plus programme sites including 405 adults and 169 children.

In a completely uplifting presentation, Dr Sylvester Kimaio from Eldoret, Kenya described his experiences. So far, 240 adults and 90 children have been enrolled into Eldoret's programme.

Recently they have begun initiating HAART in the second trimester for their pregnant patients and unsurprisingly the transmission rate in his cohort has gone into freefall. "In the west they don't use nevirapine for MTCT they use full HAART," he explained. "We thought: 'Why not us?' We have already started that programme so we will be very successful with our PMTCT." In fact, he continued: "We are hoping that our PMTCT is so successful that we can take some of the spaces for the children and give them to the mothers."

He concluded his talk with a picture of one of his patients: "She has five children… we don't have to look after orphans… she looks after them herself."

Ref: El-Sadr W, Kimaio S, Hardy T et al. The MTCT-Plus initiative: A model for comprehensive family-focused HIV care and treatment in resource limited settings

Links

http://www.mtctplus.org

email: mtctplus@columbia.edu

CONFERENCE REPORT

Further reports from 2nd IAS Conference on HIV Pathogenesis and Treatment

Paris, 13-16 July 2003

See also HTB Vol 4, No 7

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

All references are from the programme and abstracts of the 2nd IAS Conference on HIV Pathogenesis and Treatment, 2003 unless otherwise stated.

A searchable pdf file for the conference abstract book is available to download at:

http://www.ias.se/search/search.asp?search=118&searchtype=4&pageID=1110

New atazanavir information

Jules Levin for NATAP.org

Kate Squires, of the University of Southern California, reported new information regarding atazanavir (ATV) at the Bristol-Myers Squibb Symposium at the IAS Conference.

Squires addressed the results of BMS ATV Study 034, which compared ATV to efavirenz (EFV), each combined with AZT/3TC. In this study through week 48 BMS reported 32% of patients receiving ATV had <50 copies/ml (ITT) and 37% taking EFV had < 50 copies.

Although the percentage of patients who had <50 c/ml were about the same for both treatment groups, observers were confused as to why the viral response to EFV was so low and why it was lower than seen in other EFV studies. Regarding <400 c/ml, the previously reported data from Study 034 was that 70% of patients taking ATV had <400 c/ml and 64% of patients taking EFV had <400 c/ml at week 48 (ITT).

At the BMS Symposium, Squires reported data related to this (see Table 1 and 2).

She said that viral load samples in the BMS 034 Study were collected in PPT tubes and were spun and frozen in situ prior to shipping to a centralised lab. Additional samples were collected at study visits week 12, 24, and 48 in EDTA tubes (spun, separated, frozen, and were shipped from the study site).

Squires presented new information on the effect of using PPT vs EDTA tubes on viral load measurements. Duplicated samples were assayed after collection in PPT or EDTA tubes.

Five hundred and eight-four patients were evaluable (300 on ATV, 284 on EFV): there were 805 patients in the main study at enrollment; 584 represents 88% of the 661 subjects treated for 48 weeks; 584 represents 73% of all 805 patients treated in the main study. Squires said the sample handling methodology affected the viral load responses.

Table 1: Effect of using PPT vs EDTA tubes on viral load measurements at Week 48 *(LOQ = limit of quantification)*

	LOQ <400 c/ml		LOQ <50 c/ml	
	EDTA	PPT	EDTA	PPT
ATV	93%	83%	86%	53%
EFV	96%	85%	93%	57%

Table 2: Percent undetectable by continent

LOQ <400 c/ml for ATV:

	EDTA	PPT	Absolute Difference
Overall	95%	84%	+11%
No America	94%	89%	+ 7%
Europe	98%	75%	+23%
So America	93%	80%	+13%
Asia	95%	96%	- 1%
Africa	90%	87%	+ 3%

LOQ <50 c/ml:

	EDTA	PPT	Absolute Difference
Overall	89%	55%	+34%
No America	88%	58%	+30%
Europe	89%	36%	+53%
So America	88%	45%	+43%
Asia	94%	89%	+ 5%
Africa	87%	58%	+29%

Source: NATAP.org

http://www.natap.org/2003/IAS/day20.htm

C O M M E N T

Although these data were presented at a pharmaceutical satellite meeting and not within the 'peer reviewed' context of the main meeting, it is important to be aware of these new results. It goes some way to allay the concerns over potency of atazanavir (and efavirenz) seen in this atazanavir registrational study.

Boosted PI therapy antiretrovirals in treatment-experienced patients: SQV/r, ATV, ATV/r

Graeme Moyle for NATAP.org

New data on the use of antiretroviral regimens in individuals who have experienced failure on at least one prior antiretroviral combination mainly focused on comparative data between different protease inhibitor based regimens. The main contenders for this market currently dominated by lopinavir/r (Kaletra) are atazanavir and saquinavir. New data on fosamprenavir, a third option to lopinavir/r now in advanced development, were not presented. In general, the great challenge with organising studies in treatment experienced patients is creating a large enough population to have adequate statistical power and to avoid modest differences in entry characteristics influencing trials outcome.

MaxCmin2: Saquinavir/r vs. Lopinavir/r [1]

The MaxCmin studies are a series of comparative randomised trials evaluating the efficacy and tolerability of boosted protease inhibitor drugs in mixed patient populations, including approximately equal proportions of individuals commencing protease inhibitors for the first time, individuals responding to protease inhibitor therapy but experiencing tolerability or adherence issues and individuals who have failed a prior PI regimen.

In MaxCmin1, saquinavir 1000mg BID/ritonavir 100mg BID was compared with Indinavir 800mg BID/ritonavir 100mg BID. The intention to treat outcome of the study favoured the saquinavir group, whereas in the as treated analysis virological success was similar. Saquinavir/r demonstrated a clear lipid advantage relative to Indinavir/r.

In MaxCmin2, saquinavir 1000mg BID/ritonavir100mg BID was compared with lopinavir 400mg BID/ritonavir 100mg BID (as Kaletra) in 339 individuals. Baseline characteristics indicated that 48% of patients in each group were PI naive and 32% of individuals were virological failures on a prior PI based regimen. The median baseline CD4 cell count was 240 cells/mm3 and baseline viral load 4.5log (31,000 copies/ml) with 21% of individuals less than 400 copies/ml at baseline. No significant differences between groups were observed at baseline. By intention to treat (exposed) analysis at 48 weeks of follow-up for HIV RNA less than 50 copies/ml, the proportion of patients undetectable was 57% for the saquinavir/r and 65% for the lopinavir/r groups (p= not significant). The on treatment analysis however, favoured saquinavir/r with 75% less than 50 copies/ml compared with 70% on the lopinavir/r arm (p= not significant).

For the endpoint of time to virological failure (ITT/exposed, failure including all discontinuations as well as 'true' viral failure) the lopinavir group significantly outperformed the saquinavir group (p=0.009). Differences in the time to virological failure in the on-treatment analysis were not observed. The main driver of differences between the groups was the number of individuals who discontinued from the saquinavir/r group for non-fatal adverse events (20/172 versus 13/167 for the saquinavir and lopinavir groups, respectively) and patient choice/non-compliance (13/172 versus 5/167 for the saquinavir and lopinavir groups, respectively). Overall, 29% of saquinavir and 13% of lopinavir patients discontinued the study (p= 0.001) with 48% of discontinuations being due to non-fatal adverse events. No difference in the risk or time to a grade 3 or 4 adverse event was seen between the arms. No differences between the immunological response was observed between arms.

The interpretation of these results is quite difficult as it would appear the only differences in performance of the drugs is observed when individuals who discontinued for non-fatal adverse events or personal reasons are taken into account. The reasons for these patients discontinuing is likely to lie in two aspects of saquinavir administration. Firstly, the saquinavir arm required individuals to take six capsules twice daily compared with the three capsules twice daily in the lopinavir arm. Additionally, the Fortovase formulation of saquinavir was used in this (and the Maxcmin1) study, this formulation is generally considered to be less well-tolerated than the hard gel Invirase formulation. Reformulation of saquinavir as a hardened tablet taken as two tablets (500mg tablets) twice daily plus one capsule of ritonavir twice daily is currently in advanced development and may well remedy many of the obstacles to saquinavir use.

BMS 043: unboosted atazanavir vs. lopinavir/r [2]

This was a randomised open-label comparative study of atazanavir 400 mg QD versus lopinavir/r 400/100 mg BD in individuals failing a protease inhibitor based regimen. Two new nucleoside analogues were chosen on the basis of resistance testing. One hundred and fifty patients were randomised into each arm, with 144 people in the atazanavir group and 148 in the lopinavir/r group commencing therapy. Baseline CD4 count was 288/mm3 in the atazanavir group and 261/mm3 in the lopinavir/r group, with the median viral load being 4.18 and 4.14 log, respectively. Baseline resistance testing suggest fewer patients had viruses susceptible to atazanavir (72%) compared with lopinavir/r (86%), although the proportion of patients with >4 protease inhibitor mutations at baseline was similar between groups (26 versus 23%, respectively). Both drugs were well tolerated over 24 weeks of follow-up with just one person in the atazanavir group and four in the lopinavir/r group discontinuing due to adverse events.

At 24 weeks of follow-up the atazanavir group had experienced a mean reduction in viral load of -1.67 log compared with 2.11 log in the lopinavir/r group. Analysis by time average difference estimates indicated a significant advantage for the lopinavir/r group (p=0.0032). As a result of these analyses the study was discontinued. By intention to treat analysis, the proportion of patients achieving less than 400 copies/ml was 59% and 77% for the atazanavir and lopinavir/r groups respectively. Using the 50 copies/ml cut-off, the values were 38 and 54%, respectively.

Factors associated with a virological response to atazanavir (achieving a viral load less than 400 copies/ml at week 24) included a baseline IC 50 <2.5-fold above control, exposure to < 2 protease inhibitors and the absence of any nucleoside analogue mutations in the baseline sample. Indeed, when subjects with no nucleoside analogue mutations at baseline were considered the mean reduction in viral load at 24 weeks in the atazanavir group (n=32) was 1.96 log as compared with 2.06 log in the lopinavir/r group (n=26).

Changes in lipids favoured the atazanavir group with a 2% decline in total cholesterol, a 6% decline in LDL, a 12% increase in HDL and 2% decline in triglycerides as compared with the lopinavir/r group where total cholesterol rose 17%, LDL rose 5%, HDL increased 18% and triglycerides increased 55%.

Of note, these analyses were performed excluding individuals who received or commenced lipid-lowering therapy during the study and thus may be considered conservative analyses. The main adverse effect associated with atazanavir use is elevation of indirect bilirubin. Only 3% of individuals receiving atazanavir reported clinical jaundice although 22% of individuals were noted to have a grade 3/4 bilirubin elevation.

BMS-45 study: boosted atazanavir vs. lopinavir/r [3]

Metabolism of atazanavir is inhibited by administration with ritonavir. Both the maximum concentration and the elimination half-life of atazanavir are affected, leading to substantial increases in atazanavir exposure and trough concentration over the 24-hour dosing interval. Using 300mg of atazanavir with 100mg of ritonavir (ATV/r) leads to an atazanavir exposure that is approximately threefold higher at trough than the exposure observed with 400mg of atazanavir dosed alone.

The BMS 045 study randomised 358 individuals who had failed at least two prior regimens including exposure to all three approved drug classes to receive either ATV/r (n=120), ATV 400mg QD plus saquinavir 1200mg QD or lopinavir/r 400/100mg BD. During the first two weeks of the study, participants maintained their background nucleoside analogue therapy and switched their failing PI or NNRTI to their randomised new therapy. After two weeks, the background NRTI therapy was switched to include tenofovir plus one new nucleoside analogue based on resistance testing. Baseline demographics for the ATV/r, ATV/SQV 1200mg QD and lopinavir/r 400/100mg BD indicated patients were well matched for viral load (4.44, 4.42 and 4.47 log, respectively) and CD4 cell count (317,286, and 286/mm3, respectively). Duration of prior antiretroviral therapy, number of agents within each class to which individuals have been exposed and baseline susceptibility to atazanavir and lopinavir were similar across groups.

The regimens were generally well-tolerated with 6%, 12% and 5% of ATV/r, ATV/SQV and LPV/r groups respectively discontinuing. Adverse events were the cause of discontinuation in 3, 4, and 2% of individuals in each group, respectively.

The mean change in viral load through week 24 was 1.88, 1.62 and 1.89 for the ATV/r, ATV/SQV and LPV/r groups, respectively. For the ITT: time to loss of virological response (ITT:TLOVR) analysis, using the 400 copies/ml cut-off the proportion of patients undetectable at week 24 was 64, 44 and 62%, respectively. Using the less than 50 copies/ml cut-off the proportion of patients undetectable was 39, 23 and 42%, respectively. Detailed statistical analysis was not provided, however limited data suggested that in no analysis was a difference observed between ATV/r and LPV/r but that both groups consistently outperformed the ATV/SQV arm.

Lipid data favoured the atazanavir regimens. Comparing ATV/r with LPV/r, total cholesterol fell by 8% compared with a rise of 3%, LDL cholesterol fell by 10% compared with a decline of 4% and triglycerides fell by 2% compared with a rise of 31% in the two groups, respectively. In general, the group containing ATV/SQV had a similar impact on lipids as ATV/r.

During the study 7% of individuals randomised to ATV/r, 12% of individuals randomised to ATV/SQV and 15% of individuals randomised to LPV/r commenced lipid lowering therapy. These differences in the requirements for lipid lowering therapy between agents that perform similarly virologically may have important resource implications.

Regarding adverse events, diarrhoea was reported by 3% of ATV/r and 11% of LPV/r recipients whereas jaundice occurred in 6% and scleral icterus in 3% of ATV/r recipients but in no patients in the LPV/r group. Grade three or four bilirubin elevation was reported in 45% ATV/r recipients but <1% of LPV/r recipients.

Discussion

These three studies presented at the IAS conference provide health care professionals with an opportunity to consider which protease inhibitor regimens are the best choice when a protease inhibitor drug is needed.

In individuals experienced with a protease inhibitor these studies would suggest that un-boosted atazanavir and atazanavir combined with saquinavir may be less good choices than either lopinavir/r, atazanavir/r or saquinavir/r. Atazanavir/r appears to have lipid advantages relative to lopinavir/r.

Additionally, atazanavir/r provides therapy in the form of three pills QD compared with three pills BD with lopinavir/r and six pills BD with saquinavir/r. The downside to atazanavir/r is clearly the frequency of elevation of indirect bilirubin. Data from these studies however, would suggest that this infrequently leads to a diagnosis of jaundice or to atazanavir discontinuation. Ongoing efforts to reformulate saquinavir into a more compact tablet form are likely to address some of the key obstacles to the more widespread use of this agent. The boosted protease inhibitor market is becoming very competitive.

References

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2. Nieto-Cisneros L, Zala C, Fessel WJ et al. Antiviral efficacy, metabolic changes and safety of atazanavir (ARV) versus lopinavir/ritonavir (LPV/RTV) in combination with 2 NRTIs in patients who have experienced virologic failure with prior PI-containing regimen(s): 24-week results from BMS AI424-043.Abstract 117.
3. Badaro R, DeJesus E, Lazzarin A et al. Efficacy and safety of atazanavir (ATV) with ritonavir (RTV) or saquinavir (SQV) versus lopinavir/ritonavir (LPV/RTV) in combination with tenofovir (TFV) and one NRTI in patients who have experienced virologic failure to multiple HAART regimens: 16-week results from BMS AI424-045. Abstract 118.

Source:
http://www.natap.org/

HIV Viral Dynamics: viral fitness, genetic diversity, progression, co-receptor use

Mike Youle, MD for NATAP.org

The only criticism I had of the Paris meeting, apart from the perennial rudeness of French waiters, was that some of the parallel sessions became so full that there was only standing room (sometimes five deep) and since my advanced age no longer allows

me to stand for more than 15 minutes without calf pain I retreated into rooms that normally I would not visit. Thus I found myself in a fascinating series of presentations on viral dynamics, chaired by Mark Wainberg and Jean-Luc Darlix.

Firstly, a group from the Institut Pasteur and The University of Saarland in Germany showed data on quantifying HIV DNA from the reverse transcription to integration so essentially trying to work out how many virions are needed to infect a new cell [1]. They showed in an elegant series of experiments that the intracellular enzyme proteasome degrades up to 75% of incoming virions. Combining this data with other studies the conclusion was that the fraction of HIV RNA that gets converted into provirus could be as low as 1%. Thus, since the spleen cells they examined had on average 3-4 proviruses each, it suggests that 300-400 virus particles are required for the infection of an individual cell. They also showed that there is rampant recombination of viruses with up to 29% difference between viruses within an individual cell. Doug Richmann questioned if this data could be validated in cells within infected individuals whilst Vincent Calvez from Paris suggested that cell to cell spread of virus may be more important explaining why the switch from non-syncytial inducing (R5) virus to syncytial inducing (X4) virus may herald a rapid decline in health.

This led nicely onto the second presentation from the team of Eric Arts at Case Western Reserve University, which, working with the Institute of Tropical Medicine in Antwerp, is following a cohort of patients over a protracted period of time to evaluate the relationship between HIV fitness and viral genetic diversity [2].

It is known that several factors have an impact on progression of disease; viral load, possession of nef, use of either CCR5 or CXCR4 co-receptor. In this study they used growth competition assays to compare the fitness of viruses from 12 individuals followed for 2-5 years as well as assessing the genetic diversity of the HIV quasispecies by sequencing a section of the envelope of at least 10 clones from the same patient sample used to estimate the fitness. What they showed was that as time passed the viruses within an individual become gradually fitter and their genetic diversity (variability) and divergence from the original strain increase. So for example: Patient K was followed over six years during which his T4 count dropped from 800 to 400 with a concomitant rise in viral load of 1 log. Four isolates were examined over this time period, which showed a doubling of viral fitness with a rise in diversity and divergence. Across the 12 patients there was a marked correlation between ex vivo fitness and genetic diversity ($p<0.003$). When HAART was commenced, there was a reduction in viral fitness that paralleled the drop in viral load and rise in T4 count.

HIV viral fitness was also correlated with time from seroconversion ($r=0.08$; $p<0.001$). The presenter questioned whether treatment might reduce the fitness of the virus. Doug Richmann suggested that resistance might be a simpler explanation. However, none was found in the samples examined. This study raises the question of why the epidemic is not accelerating if fitness is rising constantly from time of infection. Much as in the previous abstract, this may be a reflection of a genetic bottleneck in the cellular level during transmission, which reduces fitness back to lower levels. A further question was asked about what co-receptor these viruses were using. The answer was all R5 except for the last sample of Patient K where the virus had become dual tropic, fitting well with the idea that time is an important factor in determining co-receptor usage and disease progression. What this study suggests is that perhaps it may be better to treat early to reduce viral fitness, diversity and the speed of progression, a nice idea if we had completely non-toxic therapy.

A study from Albany Medical College and the New York State Department of Health examined the dynamics of R5 and X4 viruses after the commencement of HAART in eight individuals (six female) [3]. In patients with X4 virus there was a marked suppression of these viruses within two weeks, from the blood, whilst the trajectory of clearance of R5 virus was much slower. A shift in co-receptor usage in the female genital tract also occurred but the dynamics differed from the blood due to R5 viruses persisting for a much longer period. These changes did not seem to be linked to the density of particular co-receptors, cellular activation or cytokine production. Work on characterising any resistance in these isolates is ongoing.

Jacques Reynes from Montpellier then showed data that argued, however, that the density of CCR5 receptors may be an important determining factor in HIV replication [4]. Using flow cytometric techniques, he determined the density of the CCR5 co-receptor on peripheral blood T4 cells in 23 subjects (eight women and 15 men) who underwent a 30 day interruption in HAART. T4 varied between 300 and 1739 (median 724) and their viral load was <200. CCR5 density appears to vary for around 4-24,000 molecules/cell and remains reasonably stable over time. In this study there was a strong correlation between the CCR5 expression and viral load rebound. For R5 densities <8,000 molecules/cell viral load rose to <100,000 copies/ml whereas those who rebounded to >100,000 copies/ml had densities over 8,000 molecules/cell ($r=0.71$; $p<0.001$). These results emphasise the role of CCR5 density in in vivo HIV replication. Thus, therapies such as the new CCR5 receptor blockers SCH D (Schering) and UK-427,857 (Pfizer) may offer a therapy, which not only is effective but also has a greater efficacy in those patients with the greatest potential for progression. Only clinical studies will inform as to whether this is true, however it is tantalising to hope that the arrival of these blockers may have an added advantage to those with high viral loads.

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Pulmonary hypertension: finally a treatment trial!

Judith Aberg MD, for NATAP.org

There is little data regarding the true incidence of primary pulmonary hypertension (PPH) among HIV-infected patients. Autopsy series prior to the introduction of HAART suggested that PPH was significantly more common among people infected with HIV (incidence of 0.5%) compared to the "general population" (incidence 0.01-01%). Prognosis is extremely poor among persons with PPH and it is estimated that the survival rate among HIV-infected patients with PPH at two years is between 32-46%.

The pathogenesis of PPH is not completely understood. There is limited evidence to suggest that endothelin-1 over expression may be the primary cause of PPH. Endothelin-1 is a potent vasoconstrictor (narrows the pulmonary blood vessels). Bosentan (trade name Tracleer) is an orally administered dual endothelin-receptor antagonist that has been shown to improve exercise capacity and cardiopulmonary haemodynamics in non-HIV infected patients with pulmonary arterial hypertension. This is the first study I am aware of studying its effects in HIV-associated PPH.

This is an open-label, non-comparative, multi-centre trial evaluating the efficacy and safety of bosentan in HIV infected patients with PPH. Patients with HIV-associated PPH and NYHA functional class III received bosentan for 16 weeks (62.5 mg bid for four weeks; thereafter 125 mg bid) with either >3 months antiretroviral therapy (ART) or not on ART and CD4 count >100 cells/mm3. Patients with portal hypertension, cirrhosis or liver enzymes >3 x upper limit of normal were excluded.

Safety was assessed by CD4 cell count, viral load, liver function and adverse events. Efficacy was assessed by exercise capacity, NYHA class and haemodynamics (right heart catheterisation). The study was to enrol 30 patients; however an interim analysis of the first 10 subjects revealed significant results and enrolment was closed at 17 subjects. Results were reported on 16 subjects who completed 16 weeks of study.

Baseline characteristics of the 16 subjects are as follows: nine male, age 39 + 8 years, one HBV co-infected, three HCV co-infected, median CD4 count 333 cells/mm3, and seven subjects with HIV VL <400 copies/ml.

After eight weeks, there were no significant changes in CD4 count or the number of patients with suppression of HIV-1 RNA, suggesting no significant effect of bosentan on control of HIV infection. Adverse events included cramps (n=2), headaches (n=4), ALT/AST >3 x ULN (n=2), leg edema and/or weight gain (n=6), which improved with diuretics.

At 16 weeks, subjects improved their six-minute walk distance from 333–20 to 424–14 m (P<0.001), NYHA class (14 improved to Class I or II; two remained in Class III) and cardiac index (2. – 0.2 to 3.4 – 0.2l/min/m2; P<0.001). Significant decreases in pulmonary vascular resistance (781–64 to 476–64 dyn.sec/cm5; P<0.001), and mean pulmonary arterial pressure (51.7–3.4 to 43.3–3.8 mm Hg;P=0.051) were also observed. No patient died, required epoprostenol therapy or hospitalisation for pulmonary arterial hypertension during the study. One patient subsequently died although the cause of death was unknown but did involve illicit drug use. These preliminary results suggest that bosentan significantly improves PPH symptoms, functional status, exercise capacity and haemodynamics similar to those reported in the HIV seronegative population.

Bosentan appears safe when given concomitantly with antiretroviral therapy and is well-tolerated. One has to be cautious about this as the actual ART regimens were not discussed and there may be significant drug interactions as discussed below.

Nevertheless, this is extremely welcome news. I have had several patients die in the past from PPH. I have one woman who is now on bosentan for over one year and is clinically doing well. Her exercise capacity and functional status have improved remarkably. So, it is nice to see a study that supports its use. I have had concerns of potential drug interactions with bosentan. The package insert states it is a substrate of CYP2C8/9, 3A4 and induces CYP2C8/9, 3A4.

There is a large list of potential interactions as follows:

Cyclosporine: Bosentan may enhance the metabolism of cyclosporine, decreasing its serum concentrations by 50%; effect on sirolimus and/or tacrolimus has not been specifically evaluated, but may be similar. Cyclosporine increases serum concentrations of bosentan (approximately 3-4 times baseline). Concurrent use of cyclosporine is contraindicated.

Glyburide: An increased risk of serum transaminase elevations was observed during concurrent therapy with bosentan. Concurrent use is contraindicated.

HMG-CoA reductase inhibitors: Agents metabolised via CYP3A4 may be decreased by bosentan; includes atorvastatin, lovastatin, and simvastatin.

Ketoconazole: May increase the serum concentrations of bosentan; concentrations are increased approximately two-fold; monitor for increased effects. Many interactions have not been specifically evaluated, but may be extrapolated from similar interactions with inducers/inhibitors of CYP3A4 and CYP2C8/9 isoenzymes.

Key potential interactions are summarised as follows:

Anticonvulsants: Bosentan may increase the metabolism of selected anticonvulsants; includes ethosuximide, phenytoin, tiagabine, and zonisamide. The effect of concurrent therapy with enzyme-inducing anticonvulsants on bosentan concentrations has not been established.

Antipsychotics: Bosentan may enhance the metabolism (decrease the efficacy) of antipsychotics; monitor for altered response; dosage adjustment may be needed.

Calcium channel blockers: Bosentan may enhance the metabolism of calcium channel blockers, decreasing their clinical effect.

Corticosteroids: Bosentan may enhance the metabolism of corticosteroids, decreasing their clinical effect.

CYP2C9 inhibitors: May increase the serum concentrations of bosentan; includes amiodarone, fluoxetine, sulfonamides, ritonavir, zafirlukast.

CYP3A4 inhibitors: May increase the serum concentrations of bosentan; includes amiodarone, cimetidine, clarithromycin, erythromycin, delavirdine, diltiazem, dirithromycin, disulfiram, fluoxetine, fluvoxamine, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nevirapine, propoxyphene, quinupristin-dalfopristin, ritonavir, saquinavir, verapamil, zafirlukast, zileuton.

Doxycycline: Bosentan may enhance the metabolism of doxycycline, decreasing its clinical effect; higher dosages may be required.

Oestrogens: Bosentan may increase the metabolism of oestrogens and reduce their efficacy.

Hormonal contraceptives: Bosentan may enhance the metabolism of hormonal contraceptives, decreasing their clinical effect; an alternative method of contraception should be considered.

Methadone: Bosentan may enhance the metabolism of methadone resulting in methadone withdrawal.

Protease inhibitors: Serum concentrations may be decreased by bosentan. Avoid concurrent use of agents metabolised by CYP3A4 or CYP2C8/9.

Warfarin: Bosentan may increase the metabolism of oral anticoagulants; monitor for changes in INR. Significant changes in INR not observed in clinical trials. In addition, the manufacturer recommends avoiding bosentan in moderate to severe hepatic impairment.

Bosentan is associated with a high incidence (11%) of significant transaminase elevations, indicating a potential for serious hepatic injury. Based on animal studies, bosentan is likely to produce major birth defects if used by pregnant women. Ideally, one would like to have pharmacokinetic studies with protease inhibitors and the NNRTIs but it is doubtful these will be done. Usually these patients are on multiple other medications, so it may be difficult to predict the various interactions and one will need to monitor these patients closely for side effects and efficacy. The real test will be whether one can show a survival benefit over time which preliminary data fortunately suggests.

Ref: Opravil M, Sitbon O, Gressin V et al. Safety and efficacy of bosentan in pulmonary arterial hypertension associated with HIV infection. Abstract 1007.

METABOLIC COMPLICATIONS

New guidelines for the evaluation and management of dyslipidaemia in HIV patients on HAART

Recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group

HIVandHepatitis.com

Dyslipidaemia is a common problem affecting HIV-infected patients receiving antiretroviral therapy. Since publication of preliminary guidelines in 2000, numerous studies have addressed the risk of cardiovascular disease, the mechanisms of dyslipidaemia, drug interactions, and the treatment of lipid disorders in HIV-infected patients.

In addition, updated recommendations from the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) have been published that materially affect the clinical approach to lipid disorders in the general population.

A working group of clinical scientists, consisting of members of the Cardiovascular Subcommittee of the AIDS Clinical Trials Group, updated the preliminary recommendations to assist clinicians in the evaluation and treatment of lipid disorders among HIV-infected adults.

Data regarding the prevalence and incidence of dyslipidaemia and cardiovascular disease in HIV-infected patients, pharmacokinetic profiles for hypolipidaemic agents, and treatment trials of dyslipidaemia in HIV-infected patients were considered. Although the implications of dyslipidaemia in this population are not fully known, preliminary data indicate increased cardiovascular morbidity among HIV-infected individuals, suggesting that measures to reduce cardiovascular risk should be provided.

The expert panel recommends that HIV-infected adults undergo evaluation and treatment on the basis of NCEP ATP III guidelines for dyslipidaemia, with particular attention to potential drug interactions with antiretroviral agents and maintenance of virologic control of HIV infection.

When drugs become necessary, the expert panel recommends as initial therapy pravastatin or atorvastatin for elevated low-density lipoprotein cholesterol levels and gemfibrozil or fenofibrate when triglyceride concentrations exceed 500 mg/dL.

Download pdf file of guidelines at: http://www.hivandhepatitis.com/recent/guidelines/IDSAguidelines_ for_dyslipidemia..pdf

Treatments for lipoatrophy. Are there improvements? Are they noticeable?

Donald P Kotler MD for NATAP.org

Introduction

Of all of the changes that are included in the umbrella-term, 'lipodystrophy', fat loss or lipoatrophy has been the most difficult to manage. Treatment options are limited; no therapy has received FDA approval. Several studies have suggested that factors which influence the development of lipoatrophy, and those that promote fat accumulation, are different. The treatments proposed for lipoatrophy and fat accumulation differ as well. Treatments for fat accumulation that have been reported in the literature include diet and exercise, growth hormone (Serostim), and metformin (Glucophage). Treatments for lipoatrophy that have been reported include antiretroviral switches and treatment with thiazolidinediones (glitazones). The published results on these two therapies will be reviewed.

What is normal?

In order to put the effects of therapy in context, it helps to know what is normal fat content and distribution, quantitatively. Table 1 lists average DXA results from two groups of healthy adults. The data from control group C1 were published from our laboratory (1) and include both men and women. The data from control group C2 were taken from the initial publication about lipodystrophy by Carr and colleagues (2). Total fat content is similar in men and women but is higher as a percentage of weight in women (30%) than in men (21%). In contrast, fat-free mass is substantially higher in men, as demonstrated previously by others. There is a difference in the percentage of fat that is central (trunk) and peripheral (limb), with women having more fat peripherally than do men, a difference also shown by others. The results in the men studied by DXA in New York City and Sydney, Australia are very similar. The average man studied in New York has 36.7 pounds of fat, of which 19.4 pounds are in the trunk and 15.6 pounds are in the limbs (6.2 pounds per leg and 1.6 pounds per arm).

Table 1: Fat-free mass, total body fat content and its distribution in healthy adults

	Fat-free mass	Total fat	Trunk fat	Limb fat
C1 female	39.4	17.7	8.3	9.1
C1 male	59.4	16.7	8.8	7.1
C2 male	59.6	17.9	9.4	7.2

Data as kg;
C1=healthy male adults, St Luke's-Roosevelt Hospital Centre (1),
C1=healthy female adults, St Luke's-Roosevelt Hospital Centre (1),
C2=healthy male adults studied in Sydney, Australia (2)

How different is body composition in subjects with lipodystrophy?

Table 2 lists average DXA results, at baseline, taken from subjects in three published studies in which abacavir was switched for d4T (3-5). Most or all of the subjects studied were male. Average fat-free mass, when reported, was not substantially different from the controls. Total and limb fat averaged 2.5-5 kg lower in the lipodystrophy groups than in the controls, while trunk fat was slightly higher in subjects with lipodystrophy than in the controls. The ratio of trunk-to-limb fat was about 2.5 times higher in subjects with lipodystrophy than in controls. The absolute amount of fat in the arms and legs were about one half that of the controls.

Table 2: Baseline body composition in HIV subjects with lipoatrophy

	Fat-free mass	Total fat	Trunk fat	Limb fat
Carr(3)	58.6	12.6	9.1	3.5
John(4)	——	——	——	5.5
Moyle (5)	67.3	14.3	10.8	3.5

What is the effect of switching antiretrovirals?

Table 3 lists the absolute and percentage changes in fat-free mass, total fat, trunk fat, and limb fat, again estimated from the published papers, using the patients who switched from d4T to abacavir. The switch did not affect fat free mass in any study. In the study by Carr et al (MITOX), total fat mass rose by around 9%, while limb fat rose by 11% and trunk fat rose by 15% after six months (3). The change in limb fat was statistically significant. However, the subjects were unable to detect the change in fat content. The data were updated to a two year follow up, during the Fifth Workshop on Lipodystrophy (6). There was continued increase in limb fat totaling a 36% increase from baseline values. However, the changes continue to be clinically

inapparent in many patients. In addition, the 36% rise represents about one third of the difference between the subjects at baseline, and controls. In this study, measures of visceral fat did not change, nor did the presence and size of buffalo humps.

John and colleagues from Perth, Australia also studied subjects who switched from d4T to abacavir to prevent or reverse lipoatrophy, and noted an increase in absolute limb fat of about 500 gm over 48 weeks (4). The change, while statistically significant compared to those who continued therapy, is the equivalent of about 4 ounces of fat per limb. No clinical correlations were reported.

Moyle and colleagues from London performed a complicated switch study, and the results in 10 subjects who switched from d4T to abacavir are listed in the table (5). Total fat rose by 3.5 kg, or almost 25% after one year. The increase was split relatively equally between trunk and limbs. Because of the loss of limb fat, the increase in limb fat after one year, 1.7 kg, represented almost one half of the difference between baseline and control values. Visceral fat content was unaffected by the switch. Surprisingly, self-assessment and quality of life scores did not change over 48 weeks. One might question the robustness of the measurement tool, though the group size, at 10, is very low for a subjective scale to show significant changes.

Table 3: Changes in fat-free mass, total body fat, trunk and limb fat after switching antiretrovirals

	D fat-free mass	D total fat	D trunk fat	D limb fat
Carr (3)	-0.4 (0.07%)	1.1 (8.7%)	1.4 (15.4%)	0.4 (11.4%)
John (4)	—	—	—	0.5 (9.1%)
Moyle (5)	-0.7 (1.0%)	3.5 (24.5%)	1.8 (16.6%)	1.7 (48.5%)

(3) switch from zerit to abacavir, 24 weeks, 109/111 male,
(4) switch to combivir/abacavir, 48 weeks, all male,
(5) switch zerit to abacavir, 48 weeks (genders not specific)

To summarise, switching from d4T to abacavir leads to a statistically significant increase in limb fat with progressive rises over periods up to two years. However, the degree of increase does not return limb fat to normal. In addition, there is a relative wide variation in individual results.

What is the effect of therapy with thiazolidinediones?

Four studies have reported the effects of therapy with thiazolidinediones, three using rosiglitazone (Avandia) and one using pioglitazone (Actos). Jarvinen and colleagues from Helsinki performed a placebo-controlled trial using 8 mg of rosiglitazone for six months, and was unable to show a statistically significant difference in either visceral (VAT) or subcutaneous (SAT) adipose tissue by whole body MRI (7). Gelato and colleagues from Stony Brook performed an open-label study in eight subjects, and demonstrated a 23% increase in mean SAT and a 21% fall in mean VAT by single slice CT scanning (8). No clinical correlations were reported. Calmy and colleagues from Geneva reported on an open-label trial of pioglitazone for six months and documented significant increases in total fat, trunk fat, and leg fat (9). They reported that some subjects noted improvement ranging from modest to substantial, while others noted no change, and some even reported progression of the changes. Hadigan presented the results of a randomised, placebo-controlled trial of rosiglitazone at the recent 5th Workshop on Lipodystrophy. Therapy was placebo-controlled for three months, then followed by three months of open-label; therapy (10). A 5% increase in leg fat by DXA, which was not statistically significant, was noted at three months. However, an increase in abdominal subcutaneous fat of 8%at three months and 12% at six months were found, and were statistically significant. Trunk fat and VAT did not change. No clinical correlates were reported.

Table 4: Effect of thiazolidinediones on body fat content and distribution

	TAT	%D TAT	SAT	%D SAT	VAT	%D VAT
Jarvinen (7)	3050	2.9	1140	5.3	1920	1.6
Gelato (8)	264	-1.5	26	23	-30	-21
Calmy (9)	—	20.1	—	28	—	17.3
Hadigan (10)	—	—	—	12	—	-0-

(7) RCT, 24 weeks, whole body MRI, (8) Open-label, 6-12 weeks, single slice CT, (9) Open-label, 6 months, DXA (SAT for limb, VAT for trunk fat), (10) RCT, 24 weeks, single slice CT

Discussion

Three points are worthy of discussion. The first is that both antiretroviral switching and thiazolidinedione therapy may lead to some reversal of lipoatrophy. The fact that these two completely different approaches may have benefit supports the contention that the development of lipoatrophy is multifactorial, or at least that treatment approaches may be multi-pronged. Furthermore, the results indicate that the process of lipoatrophy is not irreversible.

A wide intra-individual variation in treatment effects was seen in several of the studies, which suggests that medications and other factors variably affect body fat content and distribution in different subjects. In other words, one or another antiretroviral may be the major cause of lipoatrophy in some subjects while other factors, eg a rigorous exercise training programme plus anabolic steroids may be more important in others. It is important to note that no study reported complete reversal of lipoatrophy, though it might have occurred in some subjects. This author's experience is similar, in that many patients show little change after switching or even discontinuing antivirals, or with thiazolidinedione therapy, while a few patients have an excellent response.

An unanswered question is how much of a change is noticeable. Several of the studies did not report clinical correlations and others remarked that the increases in limb fat or SAT were unappreciated or labeled as mild by the subject. Subject perception was not a primary endpoint in any study and most of the studies were grossly underpowered for this question. Prospective studies using validated instruments in larger study groups will be needed to determine if the changes in limb fat/SAT after switching antiretrovirals or treating with thiazolidinediones are clinically relevant in addition to being statistically significant.

Source: NATAP.org
http://www.natap.org/2003/aug/082503_2.htm

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Rosiglitazone significantly increases triglyceride and cholesterol levels and does not improve HAART-associated lipoatrophy

HIVandHepatitis.com

HAART is associated with metabolic adverse events such as insulin resistance and lipodystrophy, that is, atrophy of subcutaneous fat and/or accumulation of intra-abdominal fat. Currently, there is no pharmacological treatment for lipoatrophy (fat loss).

Glitazones, a novel class of insulin-sensitising anti-diabetic agents, increase subcutaneous fat in patients with type 2 diabetes. There are no controlled studies of glitazones in patients with HAART-associated lipodystrophy (HAL).

In this randomised, double-blind, placebo-controlled study, conducted by researchers at the Helsinki University Central Hospital, Helsinki, Finland, 30 patients with HAL received either rosiglitazone (8 mg daily) or placebo for 24 weeks.

Baseline characteristics were compared to a group of 30 age-, sex- and weight-matched HIV-negative controls. At baseline, patients with HAL had 1.8-fold ($P<0.001$) more intra-abdominal and 2.4-fold ($P<0.05$) more liver fat than HIV-negative controls, who had 1.8-fold ($P<0.001$) more subcutaneous fat than the patients.

Study results

After 24 weeks of treatment, rosiglitazone had no effect on body weight, subcutaneous or intra-abdominal fat (magnetic resonance imaging), total body fat (bioimpedance analysis), anthropometric measurements or serum leptin concentrations (a circulating marker of adipose tissue mass).

However, rosiglitazone decreased % liver fat (spectroscopy) and serum insulin concentrations, and normalised liver function tests.

During the first 12 weeks of rosiglitazone treatment, serum triglycerides increased from 3.5 +/- 0.5 to 6.5 +/- 2.0 mmol/l (from 310 +/- 44 to 575 +/- 177 mg/dl) (P<0.05) and serum cholesterol from 6.0 +/- 0.4 to 7.8 +/- 0.7 mmol/l (from 232 +/- 15 to 301 +/- 27 mg/dl) (P<0.01).

The authors conclude: "Contrary to data in other patient groups, rosiglitazone did not increase subcutaneous fat in patients with HAL after 24 weeks of treatment. Rosiglitazone seemed to ameliorate insulin resistance judged by the decreased serum insulin concentrations and % liver fat."

"Rosiglitazone unexpectedly caused significant increases in serum triglyceride and cholesterol concentrations, which must be carefully monitored if glitazones are used in these patients."

Source: HIVandHepatits.com

http://www.hivandhepatitis.com/recent/metabolic/dyslipidemias/082903b.html

Ref: Sutinen J et al. Rosiglitazone in the treatment of HAART-associated lipodystrophy - a randomised double-blind placebo-controlled study. Antiviral Therapy 8(3): 199-207. June 2003.

HIV WASTING

US approves and Europe rejects Serostim (recombinant growth hormone) for treatment of HIV-related wasting

Simon Collins, HIV i-Base

On 29 August 2003 the US Food and Drug Administration (FDA) granted full approval for Serostim (somatropin; recombinant growth hormone for injection), which is indicated for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance.

FDA granted Serostim accelerated approval in 1996, a special regulatory status granted by the FDA for approval of a drug that is used to treat patients with serious or life-threatening illnesses, and provides meaningful therapeutic benefit over any existing treatments.

Under the terms of the accelerated approval, Serono conducted a multi-centre, confirmatory placebo-controlled study with Serostim. Data from this trial substantiate previous study findings of increased lean body mass and improvement in physical strength. In addition, patients in this study perceived an improvement in their wasting symptoms and in quality of life.

Since 1996, rHGH has been widely prescribed in the US, although this has been through insurance-based healthcare and against the background of concerns for the high cost.

Within a week of the US decision the EMEA in Europe confirmed that it will not grant approval for the same drug for the same indication.

In April 2003, the European Medicines Evaluation Agency rejected Serono's application to market Serostim for AIDS-related wasting syndrome. Serono formally appealed this decision in July, and following an expert meeting on 2 September the EMEA announced that the original April decision would be upheld and marketing authorisation would not be recommended.

Source: Serono press release

http://www.aidswasting.com/aids/serostim/news_pop.html

http://www.serostim.com/

FDA full label

http://www.fda.gov/cder/foi/label/2003/20604se7-027_serostim_lbl.pdf

EMEA summary of opinion to appeal – 3 September 2003

http://www.emea.eu.int/pdfs/human/opinion/447503en.pdf

COMMENT

The FDA approval was a consequence of the presentation of additional data from a recent trial by Serono as requested in 1996 when they

granted conditional approval.

In contrast, in Europe Serono had no approval for the use for Serostim in wasting. The data from the recent multicenter trial showed a clear anabolic effect of Serostim in the study population as assessed by bicycle exercise.

However two major concerns were expressed by the EMEA with regard to this trial: first most patients included did not seem to fulfill the criteria of HIV-wasting, and second, the translation of bicycle workout into clinical benefit was difficult to accomplish. Other concerns raised were a negative impact of Serostim on lipoatrophy.

In addition the issue of a relapse of wasting after discontinuation of Serostim remained unresolved by the present data. The current transatlantic split will keep Serostim on the market, but will make it available for European patients with wasting only under exceptional circumstances, if at all.

SIDE EFFECTS

Testosterone therapy prevents loss of lean body mass, improves mood and libido in HIV positive women and increases bone mineral density in HIV positive men

Ronald Baker PhD for HIVandHepatitis.com

Low testosterone levels are common in both men and women with human immunodeficiency virus (HIV) infection and may contribute to loss of lean body mass and AIDS wasting.

Causes of low testosterone levels are complex and may include chronic illness, HIV infection and its complications, medications used to treat HIV and opportunistic diseases, and normal aging-related declines.

In the majority of studies addressing the use of testosterone treatment in HIV-infected patients, testosterone has been found to help prevent loss of lean body and muscle mass. Whether the combination of exercise and testosterone is more effective in preventing loss of lean body mass than either therapy alone is not yet clear and warrants further study.

In addition to its effects on body composition, testosterone treatment results in improved mood and libido in HIV-infected women and increased bone mineral density in HIV-infected men. Testosterone may thus make a valuable contribution to the treatment of HIV-infected individuals.

Source: HIVandHepatitis.com

http://www.hivandhepatitis.com/recent/ois/082903e.html

Ref: Dobs A et al. Role of testosterone in maintaining lean body mass and bone density in HIV-infected patients. International Journal of Impotence Research (2003) 15, Suppl 4, S21-S25. August 2003.

Only time with HIV infection and not specific antiretroviral therapy is associated with decreased bone mineral density

HIVandHepatitis.com

The aim of this cross-sectional analytical study was to describe the alterations in the bone metabolism of HIV-seropositive patients and evaluate the effects of antiretroviral therapies. Published in the September 5, 2003 issue of AIDS, this cross-sectional analytical study was undertaken by researchers at the Medical Science School of the National University of Cordoba and Rawson Hospital, Cordoba, Argentina.

A total of 142 subjects (113 male, 29 female), aged 20-45 years were divided into four groups: group A, 33 HIV-seropositive antiretroviral-naive patients; group B1, 36 HIV-seropositive patients on antiviral therapy for over one year, without protease inhibitors (PI); group B2, 42 HIV-seropositive patients on combined therapy containing PI for over one year; and group C, 15 healthy, HIV-seronegative subjects.

Bone mineral density (BMD) was determined by dual energy X-ray absorptiometry in total body, lumbar spine and proximal femur; and evaluation of serum osteocalcin, d-pyridinoline, parathyroid hormone (THP), calcium and phosphate, and urine calcium.

BMD was significantly lower in HIV-seropositive patients in comparison with healthy controls, in all sites studied. However, no statistical differences were observed among all groups of HIV-infected patients, independently of the antiretroviral therapy.

There was a significantly higher occurrence of osteopaenia and osteoporosis in HIV-infected patients in comparison with controls ($P < 0.0001$), with no differences among treatment-naive patients and either of the treatment groups. Bone formation and resorption markers were similar among all studied groups. There was a significant correlation in all bone sites between time of infection and BMD ($P < 0.02$).

BMD was significantly lower in HIV-seropositive patients in comparison with controls in lumbar spine, proximal femur and total body, without significant differences among treatment-naive patients and either of the treatment groups.

Only time with HIV infection and not specific therapy was associated with BMD decreases.

Source: HIVandHepatitis.com

http://www.hivandhepatitis.com/recent/toxicities/bone/082503c.html

Ref: Bruera D et al. Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. AIDS 17(13): 1917-1923. September 5, 2003.

IMMUNE TREATMENTS

IL-2 induced increases in CD4 counts are blunted by use of prednisone

Simon Collins, HIV i-Base

Early results from the large international ESPRIT study presented to the IAS conference this summer confirmed the ability of several courses of IL-2 to dramatically increase CD4 counts. However, IL-2 is associated with difficult side effects during the five-day administration periods including moderate to severe fatigue, myalgia and fever in up to 90% of subjects.

These symptoms are thought to be proinflammatory responses related to elevations in tumour-necrosis facto-alpha (TNF-alpha) and IL-6 that occur with IL-2 treatment. As corticosteroids inhibit production of TNF-alpha, a small pilot study looked at whether prednisone could reduce the side effects without reducing CD4 increases.

Dr Jorge Tavel and colleagues from NIAID randomised 19 patients to one of four treatment groups (A-D): IL-2 + placebo (A), IL-2 + prednisone (B), prednisone alone (C) and placebo alone (D). Five patients were in each arm except the placebo arm, which had four patients. IL-2 was dosed at 7.5 MIU sc BID for each five day cycle, with cycles repeated every two months. Prednisone was dosed at 0.5mg/kg/day orally for seven days every two months, coinciding with the administration of IL-2.

Increases in CD4 count were 452, 110, 27 and 135 in groups A, B, C and D respectively. All subjects in group A showed significant CD4 increases, but concomitant use of prednisone blunted or in some cases prevented this in subjects in group B.

Although higher toxicity was reported in group A compared to B the researchers question whether these differences were significant. No difference in fatigue or dose reductions of IL-2 were reported between the groups A and B, although temperature was 0.4 C lower in those patients receiving prednisone.

Although prednisone decreased levels of proinflammatory cytokines during IL-2 cycles, these responses appear to be critical to IL-2 induced CD4 increases.

The authors conclude that IL-2 dose reduction in combination with use of nonsteroidal agents, is the best approach to manage toxicity and maximise response.

Ref: Tavel JA, Sereti I, Walker RE et al. A randomised, double-blinded, placebo-controlled trial of intermittent administration of interleukin-2 and prednisone in subjects infected with human immunodeficiency virus. J Infect Dis. 2003 Aug 15;188(4):531-6.

http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db= PubMed&list_uids=12898439&dopt=Abstract

TREATMENT INTERRUPTION

Treatment interruption shows no benefit in drug-resistant HIV infection

NIAID news release

Prescribed interruptions in antiretroviral therapy - so-called "drug holidays" - may hasten disease progression in a subset of HIV-infected individuals, namely those whose treatment has been rendered significantly less effective by the development of resistance to multiple anti-HIV drugs (MDR-HIV). This was the finding in a study by researchers supported by the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health (NIH).

As reported in the 28 August 2003 issue of The New England Journal of Medicine, researchers found that study participants who underwent a four-month structured treatment interruption had more HIV-related complications and poorer immune response than did individuals who took antiretroviral drugs continuously throughout the study.

"Interruption of treatment has become increasingly common among HIV-infected individuals," says NIAID Director Anthony S Fauci MD. "This study helps to clarify the effects of treatment interruption in one group of patients and emphasises how important it is for people to join clinical trials to help answer questions that will improve patient care."

As used in this study, structured treatment interruption involves discontinuing all anti-HIV drugs for a defined period of time to allow the repopulating virus to regain susceptibility to anti-HIV drugs. Previous studies of individuals infected with MDR-HIV have shown that drug-sensitive variants of the virus re-emerge and become predominant after therapy is stopped. Treatment interruptions have also been used to give people time off from multiple medications that may be difficult to take and have toxic side effects.

"We had hoped that a structured treatment interruption would be beneficial for people experiencing treatment failure due to multidrug-resistant HIV," says study chair Jody Lawrence MD, of the Department of Medicine at the University of California, San Francisco. "However, our results indicate that this strategy does not work and should be avoided by this group of HIV-infected individuals. Continuing therapy guided by HIV drug resistance testing proved to be a better approach."

Conducted by NIAID's Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA), the MDR-HIV study by Dr Lawrence and colleagues is the first randomised clinical endpoint study to examine the effectiveness of structured treatment interruption in people with few remaining treatment options. The study enrolled 270 participants with MDR-HIV who had HIV levels of more than 5,000 copies per milliliter of plasma. About one half of the participants were randomised to a four month interruption of treatment before starting a new optimised anti-HIV treatment regimen. The other half (the control group) immediately started a new optimised regimen. Physicians were given the results of two types of HIV drug-resistance tests to help them choose the optimised regimen.

After an average follow-up of nearly 12 months, 22 of the 138 individuals in the treatment-interruption group had either died or experienced disease progression, defined by the occurrence of one or more AIDS-defining condition. In contrast, 12 of the 132 people in the control group (those who received continuous therapy throughout the study) had died or had their disease worsen. Participants in the treatment-interruption group also had persistently fewer CD4 T-cells and showed no benefit in HIV viral load response or quality of life relative to the control group.

"This trial was conducted because community and healthcare providers were interested in finding better treatment strategies for people with treatment failure and multidrug-resistant HIV," says Sandra Lehrman MD, director of the Therapeutics Research Program in NIAID's Division of AIDS. "The strengths of the study," she notes, "are the number of volunteers who participated in the study, the length of follow-up and the fact that there was a randomised comparison with a control group. These features allowed the researchers to study the overall impact of structured treatment interruption, including the effects on AIDS-related illnesses, HIV viral load, CD4 T-cell count and quality of life."

"It is important to remember," adds Dr Fauci, "that the failure of treatment interruption seen in this study pertains only to individuals who had drug-resistant HIV and detectable virus in their blood when they entered the study. For individuals who are being successfully treated with anti-HIV medications, other studies have shown that cycles of treatment interruptions for shorter periods may be of potential benefit to conserve medications and reduce drug-related toxicities."

COMMENT

The duration of the treatment break at four months was longer than other researchers have recommended for such experienced patients. However around 25% of the interruption group restarted therapy earlier, after just over two months.

Eight deaths occurred in each arm, so including deaths and disease progression together when presenting the summary confused these results. However a significantly greater number of progressions occurred in the interruption arm (17 vs 4, HR 6.04 95%CI 1.8-20.8). Most of the cases of disease progression in the interruption group also occurred after treatment had been restarted and not during the

interruption period. Patients taking an interruption had more new AIDS-defining illnesses.

Median CD4 count at baseline was around 150 cells/mm3 and 125 cells/mm^3 in the interruption and continued treatment arms and median CD4 nadir in each group was around 30 cell/mm^3. However during the months 0-4 the interruption group dropped to a median of 80 cells/mm^3 lower than the continued treatment arm.

An interruption of two months in the French GigaHAART study showed a greater benefit in the interruption arm compared to patients who continued on therapy. The GigaHAART study used regimens with eight or more drugs compared to the median 3.6 drugs in the US study.

Perhaps the key to an interruption relies on individualising the length of the break depending on closely monitoring a patient's response (every 2-4 weeks). Short-term out growth of resistant virus by wild-type virus show this occurs after two months and several studies have suggested that viral fitness similarly increases at this time.

Ref: J. Lawrence et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. The New England Journal of Medicine 349(9):837-46 (2003).

http://www.thebody.com/niaid/2003/sti_benefit.html

Full text:

http://www.natap.org/2003/aug/082903_1.htm

MATERNAL HEALTH AND MOTHER TO CHILD TRANSMISSION

Postnatal transmission of HIV to breastfed infants following short course ZDV regimen

Polly Clayden, HIV i-Base

Postnatal transmission of HIV-1 is of great concern among populations where breastfeeding is common practice. It is also speculated that risk of postnatal transmission could be greater following a maternal intervention due to rebound in maternal viral load after antiretroviral discontinuation.

A report published in the July issue of AIDS pooled data from two trials:

ANRS 049a DITRAME (Abidjan, Côte d'Ivoire and Bobo-Dioulasso, Burkina-Faso) and RETROCI (Abidjan) in order to assess the postnatal transmission risk in a breastfeeding population after a maternal short course zidovudine (ZDV, AZT) regimen.

HIV-positive pregnant women were randomised at 36-38 weeks' gestation between September 1995 and February 1998, to receive 250 mg or 300 mg oral zidovudine or placebo: one tablet twice daily until the start of labour. DITRAME participants then received a single oral zidovudine dose of 500 or 600mg, and RETROCI participants 300mg every three hours until delivery. DITRAME participants only then received a seven-day post partum maternal treatment of 500 or 600mg per day. There was no infant drug component in this study.

Postnatal transmission was defined as a child with a negative HIV-1 PCR at age 30 days who later became infected as defined by a positive HIV-1 PCR, or if aged 15 months, a positive HIV serology.

Of the 479 infants eligible for analysis, at 24 weeks 23/254 in the zidovudine arm (9.8%) and 19/225 (9.1%) in the placebo arm had become infected by postnatal transmission. The investigators reported the culmulative risks of postnatal transmission to be similar in both arms, at ages six, 12 and 24 months the risks were 3.4%, 9.2% and 9.8% vs 3.4%, 6.8% and 9.1% in the zidovudine and placebo groups respectively.

They reported the culmulative risk to be much higher among mothers with lower CD4 counts, ie less than 500 cells/mm3 than among those with higher than 500 cells/mm3 CD4. Among the women with lower CD4 cell count, they found 24 month postnatal transmission risks of 21.8% and 16.1% in the zidovudine and placebo arms respectively. This represented 86% and 68% of the cases in the respective arms.

Multivariate analysis evaluating intervention, maternal CD4 cell count and maternal viral load, revealed that at 24 months the zidovudine effect was not significant (hazard ratio zidovudine to placebo, 1.15; CI, 0.57-2.31). Maternal CD4 cell count of less than 500 cells/mm3 at study entry however, tripled the hazard for postnatal transmission compared to women with greater than 500 CD4 cells/mm3 (HR, 3.14; CI, 1.31-7.49). Women with higher plasma viral load at study entry also increased the hazard (HR, 2.65 for 1 log increase; CI, 1.75-4.00).

This study is the first to report that postnatal transmission risk is associated with maternal CD4 and viral load. The investigators raise the important issue that because postnatal transmission risk is substantially higher in women with a low CD4 count and

that these women also have a higher risk of opportunistic infection and death "…maternal HAART would be specially beneficial for these women, both for themselves and also to reduce postnatal transmission".

They conclude "…comprehensive and tailored approaches are especially needed for women with advanced HIV disease in order to fulfill the recently agreed United Nations target of reducing MTCT by 20% by the year 2005".

Ref: Leroy V; John M. Karon JM; Alioum, A et al for the West Africa PMTCT Study Group. Postnatal transmission of HIV-1 after a maternal short-course zidovudine peripartum regimen in West Africa. AIDS 2003,17: 1493 – 1501.

Subtype differences in mother to child transmission

Polly Clayden, HIV i-Base

Results from a large African mother to child transmission (MTCT) cohort study reported in July AIDS, evaluated the impact of HIV-1 group M subtype variation on transmission rates in this setting where multiple subtypes are circulating.

Women attending an antenatal clinic in western Kenya were enrolled in a prospective study (1996-2000) of MTCT. This trial conducted a subtype analysis of p24*gag* and gp41*env* identified potential recombinants, and their role in MTCT was determined.

Among the women for whom HIV-1 subtype and HIV transmission status were available (n=414), transmission occurred in 80/414 (19.3%). The investigators reported higher transmission rates among women with subtype D compared with subtype A in either the gp41 region [31.6 versus 16.1%, relative risk (RR) 2.0, p= 0.002] or p24 region (29.9 versus 18.0%, RR 1.7, p= 0.02). They found subtype A to be most prevalent (73%) compared to subtype D (18.6%) in the gp41 region and also the p24 region - 70.1% and 19.1% subtypes A and D respectively.

The investigators reported that women with discordant subtypes 103/398 (25.9%) in these two regions were more likely to transmit HIV (28.2 versus 17.00%, RR1.7, p=0.01) compared to women with concordant subtypes.

They also found that among women with viral subtype combinations there were significantly higher MTCT rates (p<0.009) among women with D/D, D/A or A/D combinations compared to women with other subtype combinations. Rates were A/A 14.9% in comparison to: D/D 32.4% (RR 2.2 p=0.009), D/A 29.0% (RR 1.9, p=p=0.005) and A/D 42.3% (RR 2.8, p=0.002).

After adjusting for viral load, episiotomy or perineal tear, placental malaria and low birth weight, multivariate analysis revealed women with subtype combinations D/D, D/A and A/D to have an increased risk of MTCT (AOR 3.5, 2.5 and 6.2; p=0.005, 0.05 and 0.0003 respectively) compared to women with A/A viral combination. Transmission rates among women with other subtype combinations were not significantly different to those with A/A combination.

Overall, the authors found MTCT to be significantly more frequent among mothers infected with subtype D compared with subtype A. They hypothesised: "…that viruses with subtype D are either more virulent or have better fitness capacity or altered cellular tropism for placental cells that results in higher MTCT rates." Or they suggest an alternative explanation may be that "…subtype A viruses are less fit and may be transmitted less efficiently from mother to child."

The also note that the difference in viral subtypes has a bearing on future MTCT intervention trials using current antiretroviral therapy regimens which were designed on the basis of subtype B viruses. They highlight a recent study in Uganda in which a higher rate of nevirapine resistant mutations were observed in women with subtype D compared to subtype A following single dose nevirapine prophylaxis. They conclude: "Any future intervention trials should thus consider the effect of these subtype-based differences both on transmission efficiency and for the emergence of drug-resistant mutations. These findings may also have relevance to clinical management and effective vaccine design."

Ref: Yang, C; Li, M; Newman R D et al. Genetic diversity of HIV-1 in western Kenya: subtype-specific differences in mother to child transmission. AIDS 2003, 17:1667 – 1674.

Influence of mothers' health and survival on children's survival

Polly Clayden, HIV i-Base

Mother to child HIV transmission interventions that ignore maternal health are unlikely to confer longer term benefit to child health and survival, irrespective of a child's serostatus.

A study published in the August issue AIDS evaluated the impact of maternal HIV on child health including both the direct effects to a child of HIV infection and the indirect effects due to parental mortality, and reports a 3.2-fold increase in mortality risk to children born to HIV-positive mothers.

Mother and child survival data from a Ugandan cohort from 15 villages in the Masaka district followed by the Medical Research Council (MRC) between 1989 and 2000 was analysed. This included records from approximately 10,000 people using annual

censuses and serological surveys to collect data on births, deaths, and adult HIV serostatus. Mother and child records were linked and child mortality risks (per 1,000 births) and hazard ratios (HRs) for child mortality according to maternal HIV serostatus were assessed.

Of the 3,727 children born during the study period 415 (11%) died during and 716 (19%) left the study district and 2,596 were still alive. The mother's HIV status at birth was ascertained for 3,004 (81%) children, of whom 218 (6%) were born to HIV-positive mothers.

Maternal and infant mortality were highly correlated and the investigators reported that "in the year leading up to and following a mother's death children experienced mortality rates that were five times higher than those with living mothers".

Infant mortality risk was higher for HIV-positive than HIV-negative mothers – 225 per thousand live births [95% CI, 174-385] versus 53, as was child mortality risk – 313 [95% CI, 174-289] versus 114.

After controlling for child's age and sex, the investigators found independent predictors of mortality in children were: mother's terminal illness or death (HR = 3.8); mother being HIV positive (HR = 3.2); child being a twin (HR = 2.0); teenage motherhood (HR = 1.7) and maternal absence (HR = 1.7).

"The very high mortality of mothers who die within a few years of giving birth suggests that simply reducing vertical transmission might not proportionately reduce the mortality risks in children of infected mothers," the authors write. They add: "Programmes aimed at the welfare of children should take into account the independent effect of mothers' HIV and vital status."

Ref: Nakiyingi JS; Bracher M; Whitworth JAG et al. Child survival in relation to mother's HIV infection and survival: evidence from a Ugandan cohort study. AIDS 2003, 17: 1827-1834.

PAEDIATRICS

Higher than currently recommended NVP dose shows greater efficacy in HIV-infected children

Polly Clayden, HIV i-Base

Nevirapine (NVP, Viramune)) has been available for paediatric use in the UK since August 1997 through a compassionate access scheme (running until March 1999).

Investigators from St Mary's Family Clinic, Paddington and North Manchester General Hospital conducted a case note review of 74 children using NVP-containing combination therapy under this scheme at 96 weeks from initiation.

Nevirapine was dosed at the discretion of the paediatrician, according to the manufacturer's guidelines – a starting dose of 120mg/m2 per day increasing to 300mg/m2 daily for children less than eight years and 240mg/m2 daily for children eight years and over if no rash occurred.

Children were categorised as "high" if dose greater than 300mg/m2, "recommended" 240-300mg/m2 and "low" less than 240mg/m2 per day (or the equivalent liquid formulation dose).

Seventy-four children, 36 boys and 38 girls, were enrolled in the study, with a median age of 5.2 years, viral load of 5.1 log copies/ml and CD4 percentage of 13.5%. Twenty-eight children were antiretroviral naïve, of the 46 pretreated children, 13 had previously received a PI containing regimen and all children were NNRTI naïve. All but four children received NVP as part of a new combination.

Overall, in intent to treat analysis 20 children (33%) had an undetectable viral load below 400 copies/ml at week 96.

In children using nevirapine and NRTI who received a high dose of NVP significantly more had an undetectable viral load at week 24 (p=0.012) and 96 (p=0.007) compared to those on recommended or low doses. Sixty per cent had undetectable viral loads at week 96, compared with 17% on recommended doses. Among a group of six children that were both drug naïve and receiving a high dose of NVP the proportion of patients with an undetectable viral load was 67% at week 12, 100% at week 24, 83% at weeks 48 and 96. This was statistically significantly higher than in other children receiving NVP and NRTI at weeks 24 (p=0.006), 48 (p=0.031) and 96 (p=0.007). The difference between children receiving once or twice day NVP was not statistically significant.

The investigators also reported that CD4 cell percentages increased significantly, with median values sustained above 25% by week 48 onwards. CD4 cell percentages were not significantly different between high, recommended and lower doses of NVP. But data were missing for five to 10 children from weeks 12 to 96 receiving higher doses of NVP.

Median z-scores for both weight and height increased significantly during 96 weeks of treatment. Adverse events included rash which occurred in 15/74 children (20%), of which four (5%) were severe (grade 3-4) and required cessation of treatment.

There were no cases of Stevens-Johnson syndrome. There was no significant difference in adverse events between children who received the different doses.

The investigators note that this is one of the largest reported cohorts of children receiving NVP to date and with 96 weeks follow up also one of the longest paediatric studies.

They report: "Our data suggest that a higher dosage of nevirapine than currently recommended by the manufacturer is needed to achieve satisfactory virological response." Adding: "A maximum tolerated dosage has never been established in children. Given the tolerability of the drug, the lack of dose-related toxicity, and the better virological response associated with the higher dose, we recommend that doses should be maintained well above 300mg/m2 per day." And they conclude: "The search for well-tolerated regimens that fully suppress viral replication long-term in children continues, and nevirapine appears to be a valuable component of such combinations."

HEPATITIS COINFECTION

HIV-HCV co-infected patients have poorer response to HCV therapy

Brian Boyle MD, for HIVandHepatitis.com

Hepatitis coinfection, and in particular hepatitis C virus (HCV), have become significant causes of morbidity and mortality among HIV-infected patients. Unfortunately, response rates to interferon and ribavirin, the primary treatment for HCV, appear to be lower in HIV/HCV coinfected than in HCV monoinfected patients.

In an open label, uncontrolled, multicentre study presented at the 2nd IAS Conference (July 14-16, 2003, Paris, France), investigators analysed factors related to sustained virologic response (SVR) or nonresponse (NR) in a cohort of 128 coinfected patients receiving Peg-Intron (pegylated interferon alfa-2b, 1.5 microgram/kg/week) plus Rebetol (ribavirin, 800 mg/day). In this study, patients with HCV genotypes 1 and 4 were treated for 48 weeks and genotypes 2 and 3 were treated for 24 weeks.

Seventy-two patients had completed 24 weeks post-treatment follow-up at the time of the report. The mean viral load and CD4 count in these patients was 2.5 log10 copies/mL and 425 cells/mm3, respectively.

The overall SVR rate (ie, an undetectable HCV RNA at week 24 of follow up) was 26.4%. The SVR rate was higher for patients with HCV genotypes 2 and 3 (47.6%) than for those with HCV genotypes 1 and 4 (19.5%).

With regard to treatment outcome, there were no significant differences in response rates regarding gender, median age or median CD4 cell count at baseline.

Finally, patients who showed an early treatment response with undetectable HCV RNA at week 12, were significantly more likely to achieve SVR.

The authors conclude: "Overall sustained response rates in HIV/HCV coinfected patients treated with [pegylated interferon and ribavirin] are lower compared with historical data from HCV monoinfected patients. However, several factors affect treatment outcome. Genotypes 2 and 3 favour sustained treatment response. Moreover, early response appears to be a predictive factor in coinfected as well as in HCV monoinfected patients."

Source: HIVandHepatitis.com

Ref: Voigt E et al. Factors related to outcome of treatment with pegylated interferon alpha 2b (PEG INF) plus ribavirin (RBV) in HCV-HIV coinfected patients. Abstract 976. The 2nd IAS Conference on HIV Pathogenesis and Treatment. July 13-16, 2003. Paris, France.

C O M M E N T

The predictive value of early response is no surprise, as it has been shown multiple times in HCV-monoinfected patients. The poorer response to treatment is one of the obstacles in treatment of coinfected patients unfortunately extending to pegylated formulations of interferon, shown for example in the French RIBAVIC trial.

Time on anti-HIV therapy is a protective factor for liver fibrosis in HIV-HCV coinfected patients

To assess the factors associated with liver fibrosis in HIV and hepatitis C virus (HIV/HCV) coinfected patients eligible for anti-HCV therapy, researchers performed an observational, single centre, cross-sectional study of 180 HIV/HCV coinfected

patients who underwent liver biopsy between May 1998 and November 2001.

A total of 126 patients with a known date of HCV infection were evaluated. Liver fibrosis was defined as a Knodell stage of fibrosis 1-4.

The mean age was 36.7 (3.8) years, 81% were male and had a mean age of 20.5 (3.8) years at HCV infection. Mean CD4 cell count and plasma HIV-1 RNA load at the time of biopsy were 552 cell/mm3 (239) and 2.5 log10 (0.9), respectively.

One hundred and eighteen patients had been on antiretroviral therapy (ART) for a median of 45 months (Q1-Q3: 21-75) and 84 on protease inhibitor for a median of 12.0 months (Q1-Q3: 0-29.5); 55 had an AIDS event or a CD4 cell count nadir < 200 cells/mm3 prior to biopsy.

Median histological activity index was 6 and 27% had a Knodell stage of fibrosis 0. On the multivariate analysis time on ART, CD4 cell count at the time of liver biopsy, age at HCV infection acquisition and alcohol intake (> 50 g/day) were associated with liver fibrosis.

The authors conclude: “ART should be a priority in HIV-HCV coinfected patients eligible for anti-HCV treatment as it is a protective factor for liver fibrosis.”

Source: HIVandHepatitis.com

http://www.hivandhepatitis.com/hiv_hcv_co_inf/081503a.html

Ref: Tural C and others. Time on antiretroviral therapy is a protective factor for liver fibrosis in HIV and hepatitis C virus (HCV) co-infected patients. Journal of Viral Hepatitis 10(2): 118-125. March 2003.

C O M M E N T

One hypothesis would be that antiretroviral therapy improves immune function and enables the body to control HCV better, achieving a situation similar to monoinfected patients.

This may slow down the fibrosis rate, as coinfected patients otherwise show a more rapid progression of fibrosis. This study confirms earlier data from Benhamou published in Hepatology in 2000.

TB COINFECTION

CDC study shows rifampin/pyrazinamide therapy can cause severe liver damage

Graham McKerrow, HIV i-Base

Treatment of latent TB with a two-month therapy regimen of rifampin and pyrazinamide (RZ) can cause severe liver damage and even death, according to a study by the US Centers for Disease Control and Prevention (CDC).

The CDC has previously reported surveillance data of severe liver damage in patients treated with a daily and twice-weekly two-month regimen of RZ. To estimate the incidence of severe liver damage they collected data on patients in the United States who received treatment between January 2000 and June 2002. [1] CDC found reports of 48 latent TB patients with confirmed cases of severe liver injury after receiving the treatment. Eleven patients died. As a result the American Thoracic Society and CDC now recommend that this regimen should not normally be offered to people with latent TB.

The agency recommends a nine-month regimen of isoniazid as the preferred treatment for latent TB. [2] It also says that rifampin and pyrazinamide should continue to be used in multidrug regimens for the treatment of active TB disease.

Ref: Centers for Disease Control and Prevention (CDC); American Thoracic Society. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection - United States, 2003. MMWR Morb Mortal Wkly Rep. 2003 Aug 8;52(31):735-9.

CDC summary:

http://www.cdc.gov/nchstp/tb/pubs/tbfactsheets/250110.htm

1. CDC. Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations – United States, 2001. *MMWR* 2001;50 (No.34).

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5034a1.htm

2. CDC. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. MMWR 2003; 52 (No. 31).

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

OTHER NEWS

Impact of the HIV epidemic in sub-Saharan Africa on the pattern of HIV in the UK

Polly Clayden, HIV i-Base

A report published in July AIDS describes the epidemiology of HIV infection acquired in Africa and among African communities in the UK using national HIV and AIDS surveillance data to the end of December 2001.

The investigators report 9,993/48,226 (21%) of all reported HIV infections diagnosed during the study period were probably acquired in Africa and that of these 90% of these infections were acquired heterosexually.

Numbers of diagnoses of HIV infection acquired in Africa have increased rapidly, with rises in infections from southeastern and southern Africa predominating recently. Among those living with diagnosed HIV infection in 2000, 4,883/21,291 (23%) were described as black African, 81% of whom lived in London. The proportion living in London has declined over successive prevalence surveys.

The authors conclude: "The future of HIV infection among Africans living in the United Kingdom is unpredictable, and continued surveillance of the situation is essential."

Ref: Sinka, K; Mortimer J; Evans, B et al. Impact of the HIV epidemic in sub-Saharan Africa on the pattern of HIV in the UK AIDS 2003, 17: 1683 -1690

Dutch pharmacies sell medical marijuana

Graham McKerrow, HIV i-Base

Pharmacies in the Netherlands started selling medical marijuana in September – to people with a doctor's prescription. More than 2,000 pharmacies are legally obliged to stock the drug and to provide advice on how to use it. They encourage people to make cannabis tea rather than smoke it. The drug is sold in 5g bags and in two strengths and costs 40 euros for the milder version and 50 euros for the stronger version – which is about twice the price charged in Dutch coffee shops.

About 7,000 to 10,000 patients with a variety of conditions including, AIDS, cancer, multiple sclerosis, Tourette's syndrome and rheumatoid arthritis will be entitled to prescriptions, and for the first time the drug will be covered by health insurance.

Marijuana remains officially prohibited under Dutch law, although the authorities tolerate the sale of small quantities. The Dutch parliament approved the change of policy on medical use by a large majority in 2001. Medical marijuana has been legal in Holland since March this year but pharmacies were given an extra seven months to stock their shelves and educate staff. Medical marijuana growers and pharmacies need licences exempting them from prosecution.

Canada, Germany, Australia and 14 states of the United States allow restricted use of medicinal marijuana and they, as well as Britain where the government is considering a similar move, will be carefully watching the Dutch experience.

ON THE WEB

Conferences and guidelines:

British 2003 HIV treatment guidelines

The British HIV Association (BHIVA) has published the 2003 UK treatment guidelines online in both html and pdf file format.

http://www.bhiva.org/

http://www.bhiva.org/pdf/2003/guides/BHIVA_2003_Guidelines.pdf

US Guidelines for the evaluation and management of dyslipidaemia

Guidelines for the Evaluation and Management of Dyslipidaemia in Human Immunodeficiency Virus (HIV)-Infected Adults Receiving Antiretroviral Therapy.

Download the 15-page pdf file of these guidelines, published in the 1 September 2003 issue of Clinical Infectious Disease.

http://www.natap.org/2003/sept/Guidelines.htm

The Body coverage of IAS conference

Extensive coverage from the 2nd IAS Conference in Paris, organised by subject, was produced by TheBody.com.

http://www.thebody.com/confs/ias2003/complete.html

Medscape articles:

New topic overviews from the 2nd IAS Conference and 5th lipodystrophy Workshop

http://www.medscape.com/viewprogram/2536

New antiretroviral drugs - Mark A. Wainberg

Treatment failure and antiretroviral management of treatment-experienced patients - Julio S.G. Montaner, Marianne Harris

Novel treatment strategies - Douglas J. Ward

Antiretroviral drug resistance and viral fitness - Stefano Vella

Advances in clinical pharmacology of antiretroviral therapy - Praphan Phanuphak

Etiology and management of morphologic changes associated with HIV infection and antiretroviral therapy (includes an update from the 5th International Workshop on Adverse Reactions and Lipodystrophy in HIV) - Graeme J. Moyle

Antiretroviral influences on atherosclerosis and fat metabolism (includes an update from the 5th International Workshop on Adverse Reactions and Lipodystrophy in HIV) - Mark A. Wainberg

Opportunistic infections: little attention to the big killers - Pedro Cahn

Virus and host factors in HIV pathogenesis - Jay A. Levy

HIV immunopathogenesis and correlates of protection - Bruce Walker

Treatment of HIV infection in children - Stephane Blanche

Journal articles available online:

The AIDS Reader

From Vol13 No7

http://www.medscape.com/viewpublication/93_toc?vol=13&iss=7

NNRTI choice: has 2NN changed our practice? - Graeme J. Moyle

Has 2NN settled any arguments? Did one of the drugs win?

Triple diagnosis: dual diagnosis and HIV disease, Part 1 - Antoine B. Douaihy and others

Substance use disorders and psychiatric illness commonly co-occur in what is known as dual diagnosis. With the spread of HIV infection in persons with dual diagnoses, the triple diagnosis has emerged as a clinically challenging condition for primary care physicians, addiction medicine specialists, and psychiatrists.

Patients who want to stop their medications: treatment interruption in HIV infection - Susan C. Ball

AIDS:

When should antiretroviral therapy be started for HIV infection? Interpreting the evidence from observational studies
Andrew Phillips and others. AIDS 2003; 17(13):1863-1869
http://www.natap.org/2003/sept?090203_2.htm

Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy
Dario Bruera and colleagues. AIDS 2003; 17(13):1917-1923
http://www.natap.org/2003/aug/082503_4.htm

Clinically relevant interpretation of genotype for resistance to abacavir
http://mp.medscape.com/cgi-bin1/DM/y/hdSX0EIgTL0D1N0FgT70AA
The authors present a new strategy for the analysis of correlation between genotype profile at baseline and virologic response.
AIDS 17(12) 2003

NEJM:

Structured treatment interruption in patients with multidrug-resistant HIV
Jody Lawrence and others
NEJM, Vol 349:837-846, Aug 28, 2003, Number 9
http://www.natap.org/2003/aug/082903_1.htm

JAIDS:

Effect of antioxidants on glucose metabolism and plasma lipids in HIV-infected subjects with lipoatrophy
Grace McComsey and others
JAIDS, Journal of AIDS 2003; 33(5):605-607
http://www.natap.org/2003/aug/081403_3.htm

HIV inSite: HIV Knowledge Database

New and updated chapters and antiretroviral updates.

Assays to detect host immune responses to HIV - by Helen Horton and M. Juliana McElrath
http://hivinsite.ucsf.edu/InSite.jsp?page=kb-02-02-04

Clinical characteristics of Kaposi Sarcoma - by Susan E. Krown
http://hivinsite.ucsf.edu/InSite.jsp?page=kb-06-02-03

Emtricitabine (Emtriva, FTC) - by Susa Coffey and Laurence Peiperl
Overview of this nucleoside analogue, now approved in the US.
http://hivinsite.ucsf.edu/InSite.jsp?page=ar-01-08

Dosing of antiretroviral drugs in renal insufficiency and hemodialysis by Rudolph A. Rodriguez and Ian R. McNicholl
http://hivinsite.ucsf.edu/InSite.jsp?page=md-rr-18

Options for once-daily dosing of antiretrovirals - by Susa Coffey
http://hivinsite.ucsf.edu/InSite?page=md-rr-19

Online medical lectures:

AIDS has a woman's face: gender and power: new strategies for HIV prevention

Lectures with RealAudio and slides from March 2003 meeting.

http://hivinsite.ucsf.edu/InSite.jsp?page=cfwghi-00-00

- **Women's choices: the struggle for gender equity**
- **Local perspectives on women and HIV and lessons learned from abroad**
- **HIV/AIDS and women**
- **Economic and social factors related to HIV risk**
- **Diaphragms: preventing HIV by protecting the cervix**

Newsletters and reports:

Hopkins report – September 2003

http://www.hopkins-aids.edu/publications/report/report_toc_03.html

ARV update from the 2nd IAS Conference - Joel E. Gallant

Pharmacology in Paris - Charles W. Flexner

Panel on clinical practices issues revised adult ART guidelines - John G. Bartlett

Basic lipids: NCEP made easy for HIV patients - Joseph Cofrancesco and Gail Berkenblit

Focusing on …prevention in positives - Emily J. Erbelding

RITA – Cancer and HIV

http://www.centerforaids.org/rita/0903/contents0903.htm

The summer 2003 issue of RITA! explores the latest epidemiological data on HIV/AIDS and cancer, the mechanisms of pathogenesis behind some of these malignancies, current philosophies of treatment, and available resources for research.

Forum for Collaborative HIV Research

New information posted to the website of the FCHR.

http://www.hivforum.org/

Cardiovascular risk in HIV infection and treatment: a roundtable discussion

This new report from an expert panel meeting held in May 2003 includes a review of studies looking at antiretroviral drugs and risk of cardiovascular disease.

Standardised data analysis plan and call for collaboration: initiatives for developing and comparing genotype and phenotype interpretation systems

Information source: description of HIV cohorts and databases

HIV and hepatitis coinfection:

High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C

Full test from Hepatology, September 2003, Volume 38, No 3

http://www.natap.org/2003/sept/090203_4.htm

Other websites:

Children's HIV Association of UK and Ireland (CHIVA)

http://www.bhiva.org/chiva/index.html

The Children' HIV Association of UK and Ireland (CHIVA) have just launched a new website with the British HIV Association website.

The site includes articles and protocols relating to care of children and adolescents living with HIV including information on testing, treatment, immunisation, adherence and pill swallowing.

It also contains patient factsheets for individual drugs used in paediatric care.

Websites for women living with HIV

The Well Project

http://www.thewellproject.com

A new website aimed to fulfill the need for an online, comprehensive, woman-specific HIV resource. The site offers the latest information on living with and managing HIV for HIV-positive women, health care providers, and advocates. This includes fact sheets, data sets, summary slides, a searchable clinical trials database, a resource directory and a physician network for expert discussion on treatment.

Additionally, members will be able to participate in confidential and secure discussion boards, read about real people living with and successfully managing HIV, download advocacy tools, and receive a regular e-mail newsletter highlighting the most up-to-date information about women and HIV.

The site is conceived, developed, and administered by HIV-positive women and those who work with them.

Women, children, and HIV

http://www.womenchildrenhiv.org/

This site contains a library of practically applicable materials on mother and child HIV infection including preventing mother-to-child HIV transmission (PMTCT), infant feeding, clinical care of women and children living with HIV infection, and the support of orphans. The goal of this site is to contribute to an improvement in the scale and quality of international HIV/AIDS prevention, care, and treatment programmes for women and children by increasing access to authoritative HIV/AIDS information

HIV InSite's site for young people

http://whatudo.org

The goal of this site is to provide straightforward, unbiased, nonjudgmental, accurate, and timely information about HIV/AIDS to young people who are searching for answers on the Web.

The site was developed by the faculty and staff of The Center for HIV Information (http://chi.ucsf.edu), which is based at the University of California San Francisco.

UK trials on-line

The Chelsea and Westminster Hospital, London has a new website listing their current studies, updated to September 2003.

http://www.hivgum.demon.co.uk/trials/index.html

The studies are divided into three sections:

- Treatment naive studies
- Treatment experienced studies
- Other studies including switch, intolerance, intensification, co-infection, opportunistic infection, observational and GUM.

Patient information and consent sheets are provided as pdf files for each study, together with contact details for research nurses responsible for each trial.

The Royal Free Hospital in London has a web page for studies run by their research department at the Ian Charleson Centre.

http://www.royalfree.nhs.uk/hivservices/icdckeepup2.htm

Each study listed links through to summary of the study provided on the aidsmap website.

These should help doctors and patients in the UK identify studies that may not be available at their own clinic. Arranging shared care in order to join these studies should be straight forward in the UK.

MEETING ANNOUNCEMENTS

UK Autumn meetings

10-11 October, 2003

7th Annual Resistance Meeting

Friday 10 October 2003

BHIVA Autumn Conference and Joint BHIVA/BASHH Ordinary General Meeting

Saturday 11 October 2003

Venue for both meetings is Kensington Town Hall, London

For programme and details:

http://www.bhiva.org/meetings/aut03/index.html

Community places and press registration are available.

For registration call 020 8446 8898, email: bhiva@bhiva.org

UK Resistance and PK Workshop

27-28 November 2003

An interactive educational workshop on resistance testing and pharmacological assessment in HIV, principally aimed at consultants and specialist registrars.

Training, including detailed case studies, will be provided by Professor Clive Loveday and Dr Stephen Taylor.

Places are limited to 25 per course and registration fee of £50 includes overnight accommodation in London, plus all meals.

Please contact Mediscript on 020 8446 8898 for further details.

READERSHIP SURVEY

Thank you, thank you

Everyone at HIV Treatment Bulletin would like to say a big thank you to all 204 of you – about 5% of our circulation by pdf and print – for completing and returning our readership survey. And we weren't offering any fancy prizes for doing so! We'd also like to thank you for making us blush with your many kind comments about HTB. This article sets out the main findings of the survey and some of the suggestions readers made as to how we could improve it.

One person identified themself as transgender, while 28% were women. While 13% were under 25 years of age, fully 43% were between 25 and 40, 37% between 41 and 55, and 7% were between 56 and 70. No-one ticked the box marked >70.

The majority of respondents were professionals. Twenty-seven per cent said they read HTB out of personal interest, although that statistic taken together with the fact that 38% were HIV-positive reminds us that it is foolish to try to divide people into 'positive' and 'professional' categories; many are obviously both. Interestingly, 17% were untested.

We were happy to see that 25% of those who responded have been readers for more than five years, and it was also encouraging that 10% had been reading HTB for less than six months, suggesting that we are adding to our readership while keeping existing readers.

Unsurprisingly, no one found HTB "not useful" (they would have stopped reading it if they did!) but while 25% said it was useful, 50% described it as very useful and 21% said it was essential.

We were surprised at how many people read each copy of HTB. Seventy-four per cent said they share their copy of HTB with others, including 10% who said they shared it with more than five others. (If you would like more, free copies, let us know).

We were also interested to learn that an overwhelming 96% find web links useful, with 56% either saying they were very useful or essential. Eighty-four per cent visit at least one referral website from each issue of HTB, which means HTB is an avenue to further research by readers. Many respondents use information technology to access HTB, with 7% reading it on the web and a further 37% reading emailed pdf files.

We are encouraged to carry on adding comments at the end of certain articles, after 27% said they were useful, 49% said very useful, and 18% said they were essential. About 90% said they also found other i-Base publications useful.

We asked you to tell us how we could improve HTB and many asked for single column format and hyperlinked titles in the pdf files, which we have done. There were also many requests for more information on HIV-HCV coinfection, HIV-TB coinfection and paediatrics. Of course, we already cover these topics, but will redouble our efforts to make sure they are well covered in the future.

Modesty prevents us from reproducing here many of the wonderful comments respondents made about what they found most important about HTB, but we can't resist ending with three:

1. "Crisp, up to date on all aspects of HIV. Just being there as a resource."

2. "The most important issues to come out of conferences and meetings are published in HTB with interpretation, something most people do not have the time to research themselves."

3. "Credible reporting. HTB is careful to deal with factual information and does not present opinions that they can't support. It is useful because it stands the test of time and can be relied upon."

Oh, please, stop it!

PUBLICATIONS AND SERVICES FROM i-BASE

Wolfgang Tillmans – limited edition print for i-Base

Photographer Wolfgang Tillmans, the subject of a retrospective currently at Tate Britain in London, has donated a limited edition of 30 photographs of his "Mohn" (German for poppies) for us to sell on behalf of HIV i-Base.

We have five prints left and the price is £750 each.

The prints are 480mm x 557mm and are numbered and signed on the back by the artist. If you are interested in purchasing one of the remaining prints please contact us on 020 7407 8488.

Although i-Base provides all publications free, including sending HTB to over 3,000 doctors and healthcare workers every month, and more than 20,000 treatment guides to clinics every year, we do not receive any statutory or health authority funding.

HIV i-Base is a registered charity no 3962064.

Updated 'Introduction to Combination Therapy' - October 2003

We have updated our essential, non-technical patient guide to treatment, 'Introduction to Combination Therapy', which is being distributed with this issue.

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

Changes made to this edition include:

• Updated section on choice of drugs and combinations.

• The drugs and dosing table includes several new drugs (T-20, atazanavir, FTC) and formulations (efavirenz, 3TC). It includes the most commonly used dual and boosted PI combinations.

• There is a new note on interactions between HIV medications and recreational drugs, street drugs, methadone and complementary treatment.

• We have included changes following the revisions in July 2003 to both the UK and US treatment guidelines. The main

changes to the 2003 UK BHIVA treatment guidelines include:

- d4T, unboosted-PIs or triple-nucleosides are no longer recommended for first-line treatment.
- Resistance testing is now recommended before you start treatment. It is also recommended for anyone with a new HIV diagnosis, whether or not you intend to start treatment straight away.
- NNRTIs are recommended over protease inhibitors for first line therapy.
- Treatment interruptions are not generally recommended except in a trial. However, people who started therapy several years ago with CD4 counts over 200-350 cells/mm3 may be able to stop.
- A section has been added on monitoring tests.

When starting therapy it is important that you choose a combination that is going to work for you. It must also be able to fit into your lifestyle. Getting as much information as possible before you start therapy is very important. It will help you make informed decisions about your therapy.

It is available at:

http://www.i-base.info/pub/guides/combo903/index.html

This guide has been translated into Portuguese, Latvian and Slovak, by HIV-positive support organisations in those countries. The Portuguese version is available to download as a pdf file and reprint from the i-Base website:

http://www.i-base.info/pdf/guides/nonuk/COMBO_PORTUGUESE_jan03.pdf

For Latvian and Slovak copies please contact the i-Base office.

Printed versions of this booklet are also available in English, French, Italian, Spanish, Chinese and Macedonian.

To order copies, see below.

Find HTB on AEGiS

AEGiS.com - the longest established and largest global resource of online HIV information - has added HTB to its list of regular journals that it puts online. You can find us at:

http://www.aegis.com/pubs/i-base/2003/

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

UK-Community Advisory Board (UK-CAB): new reports and presentations

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

The programme, reading material, reports and PowerPoint slides from the presentations from the sixth meeting, held on 8 August, are posted to the i-Base website.

The August meeting included:

Reports from the Resistance, Lipodystrophy and IAS Conferences and in the afternoon session the CAB met with GSK.

http://www.i-base.info/ukcab/aug03/index.html

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

Genetics, resistance and HIV - *Professor Clive Loveday*

Approaches to Salvage Therapy - *Dr Mike Youle*

Pregnancy, HIV and Women's Health - *Dr Karen Beckerman*

Fertility treatment and sperm-washing - *Dr Leila Frodsham*

Access to treatment for UK visitors, refugees and asylum seekers - *Linda McDonald*

TB and HIV coinfection - *Dr Anton Pozniak*

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

Treatment 'Passports'

These handy booklets for recording health and treatment history have proved so popular that we have distributed the entire 8,000 print run - but we have ordered more so you can still order them for your personal use or, in the case of professionals, for clients.

Treatment 'passports' are for HIV-positive people – whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Such a record is useful when talking to different health care workers, changing clinics or changing treatments.

Like all i-Base publications, it is available free as single copies or in bulk. Copies can be ordered using the form on the back page or by visiting our website (details below).

Guide to Changing Treatment

Our guide to second line and salvage therapy. Many factors contribute to whether a combination works and in salvage therapy it is important to look at all of these together. The section on treatment strategies includes an explanation of viral fitness and alternating treatment regimens. There is also information on expanded access and experimental treatments.

The guide also covers:

* T-20, which has reported clear benefits for people resistant to current drugs – and has received marketing approval in Europe.
* Atazanavir, which appears to increase cholesterol and triglycerides less than other protease inhibitors and is available in an expanded access programme for people with raised lipids on current PIs.
* Tipranavir, a PI with activity against currently resistant HIV, which will be available in a limited emergency access programme.

For additional free copies, including bulk orders see below

This guide has been translated into Greek by the Athens-based organisation Synthesis. You can download the pdf file from our website (see below). Further information in Greek is available at the Synthesis site:

http://www.hiv.gr

Guide to Avoiding and Managing Side Effects

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

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

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

The i-Base web site

Our web address is

http://www.i-Base.info

More than 500 people a day visit the site, where you can read all i-Base publications, fill in our readership survey, find details of the UK Community Advisory Boards (UK-CABs), learn about the organisation, our phone service and meetings, and access our archives and an incomparable range of links.

The site can also be used to order publications and regular subscriptions to be delivered by post or email (as pdf files).

Positive Treatment News (PTN)

The current issue of Positive Treatment News, our occasional 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.

HIV Treatment Bulletin (HTB)

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

http://www.i-Base.info

The printed version is available at most HIV clinics in the UK and is available free by post: see below for details.

Treatment information request service – 0808 800 6013

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

We can provide information and advice over the phone, and we can 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 Wednesday 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 them by email or by post; and you can order single copies or bulk deliveries by using the forms at:

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

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

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

HIV i-Base

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HIV Treatment 'Passports' - Booklets for patients to record their own medical history

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

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Introduction to Combination Therapy *(October 2003)*
IN ENGLISH

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Also available in several other languages - please state how many of each translation you require

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

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Positive Treatment News (PTN) *from Spring 2003*

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

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

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