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(hyperlinked)

EDITORIAL

This double issue of HTB features reports and research presented at the XV International AIDS Conference held in Bangkok in July.

There is always far more to report at every meeting that we can cover in this journal and we also include links to other sites, including those with webcasts of some of the sessions.

The social and political momentum to provide treatment for people in countries with only limited access to antiretroviral drugs is covered comprehensively by Graham McKerrow in the first article.

The conference also saw the issue of access to treatment for IV drug users achieve a much higher profile and we include an overview of these issues by Mauro Guanieri. We also include a transcript of the speech given by Paisan Suwannawong, who spoke movingly and passionately at both the opening and closing ceremonies, about the reality of HIV-positive drug users in Thailand, often with information that was in contrast to the official position given by Thailands Prime Minister at the same ceremony.

There was criticism that many of the scientific sessions presented results and conclusions based on only interim data and early results on small numbers of patients and early presentations risk skewing results of both these and subsequent studies.

We support seeing the early data from James McIntyre and colleagues however, showing the dramatic protection from resistance given to pregnant women who add Combivir for only 4 or 7 days to a single dose nevirapine on the onset of labour. These results are likely to quickly change the global recommendations for the healthcare of pregnant women in resource poor settings.

Additional reports from the meeting will also be included in the next issue of HTB, which will be a double issue for October/ November.

CONFERENCE REPORTS

XV International World AIDS Conference

11-16 July 2004, Bangkok

The biennial World AIDS Conference, which alternates hosting by countries in the Northern and Southern hemispheres, is the largest and broadest focused of the international HIV meetings. At this year's event close to 20,000 delegates met at a conference centre on the outskirts of Bangkok. Although basic and clinical science tracks are still important, they are now out-numbered by combined studies on social, prevention, community and access.

The meeting rightly continues to be a focus for access to treatment on a global scale, following advances made at the meeting in Durban in 2000, and in Barcelona two years ago which led to the launch of the 3x5 treatment initiative to treat three million people by 2005.

With only 440,000 people on treatment in July, the shortfall has been highlighted in previous issues of HTB, and is covered in detail in the access overview from the conference (below).

This meeting also saw IV drug user (IVDU) issues included as a priority on the agenda for access to treatment. Some of the largest recent epidemics have been mainly driven by this route of infection. Prevention and harm reduction programmes are often poorly funded, even if there is political will to support them. More often, as with treatment itself, this is very limited where it exists at all.

We include several important reports on this issue at the start of our coverage.

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

Searchable abstracts from the meeting are already online:

http://www.ias.se/ejias

Many of the lectures are available online, as are some slide sets for the webcast. Transcripts of some lectures are also available as pdf files,

http://www.kaisernetwork.org/aids2004

This meeting did not include a large amount of new clinical data – and there seems to be a consensus from both clinicians and advocates who attended the meeting. The most important studies are included here, but several good websites also cover other studies and presentations.

Specific reports are linked in the On The Web section of this issue of HTB, and particularly useful sites include:

http://www.thebody.com

http://www.natap.org

http://www.hivandhepatitis.com

http://www.medscape.com

Public statements, transcriptions, reports and pictures relating to community and activist demonstrations are online at:

http://www.actupny.org/reports/Bangkok/

We will also include additional reports in the next issue of HTB (October/November 2004).

BANGKOK: ACCESS TO TREATMENTS

Dollars, commerce, politics and prejudice all present obstacles to scaling up access to treatment in resource poor countries

Graham McKerrow, HIV i-Base

The question of how to scale up access to treatments in poor countries dominated the XV International AIDS Conference in Bangkok and it quickly became clear that different regions, different countries and different organisations would be pursuing their own ways of trying to treat as many people as possible. There is no one-size-fits-all solution to this enormous task because funding sources, local conditions, infrastructure, culture and needs all vary widely. What suits a middle-income democracy with a free-at-the-point-of-delivery public health service, like Brazil, would not suit a poor but stable country like Uganda, or a country like Cambodia, with political conflict and widespread corruption which make greater government involvement as undesirable as it would be ineffective.

Much of the focus of the conference was on the sharing of experiences of how poorer countries were already treating people. Many of the delegates I spoke to from developing countries were attending their first International AIDS Conference and reported that the information was invaluable. In contrast, delegates from rich nations, many of whom had been to previous conferences, said they found little of value to take home. This was in part because the plenary sessions that in the past have been used to give state of the art overviews of scientific and clinical information were replaced with single-country and single-project reports from the developing world. They didn't tell other countries how to scale up treatment provision but shared experiences so that individual governments, non-governmental organisations (NGOs) and projects could draw on a variety of experiences around the world.

Treatment activists and others criticised the American $15 billion President's Emergency Plan for HIV/AIDS Relief (PEPFAR) for being limited to just 15 countries regardless of need elsewhere, and for promoting a conservative morals agenda by emphasising abstinence and faithfulness before condom use in the so-called ABC policy (Abstinence, Be faithful, and "when appropriate" use Condoms). President George Bush has called this a "moral message" and has emphasised the primary importance of abstinence in his policy. Critics at the conference pointed out that abstinence was not an option for many women, some said most women, in the poorest regions. The conference heard particular criticism of the promotion of faithfulness as a prevention method because sexual fidelity to a partner who is positive or becomes positive offers no protection from the virus. Similarly, marriage can put a woman at risk in some regions marriage itself is a high risk factor for contracting HIV. President Bush has said PEPFAR will prioritise funding for faith-based groups. The 15 nations picked by the US are Botswana, Côte d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, and Zambia.

By comparison to PEPFAR, the Global Fund to Fight AIDS, TB and Malaria appeared to be the funding body that could do no wrong, and Fund The Fund, a loose group of activists from several rich nations, made their support clear throughout the week. However, several speakers from countries that have received money from PEPFAR expressed their thanks for the American money, and such gratitude is likely to grow as more of the $15 billion gets through to projects in the chosen countries. The US Global AIDS Coordinator, Randall Tobias, cancelled a speech and a press conference but did finally address the delegates although he made no new announcements. Tobias was dogged by mainly American protesters everywhere he went at the conference. When he did speak it was after a noisy protest and activists continued to hold up placards reading "He's lying".

The United States was widely criticised for limiting PEPFAR money to brand name drugs and for supporting the system of patent protection that prevents wider production and distribution of generic drugs.

Only a small audience attended Tobias's lecture in the main conference auditorium and the demonstrators stood up in front of the stage and broke into cries of "lie, lie" when Tobias played with statistics to claim: "America is the world's largest contributor to the [Global] Fund – making 36% of all pledges to date." This overlooked the fact that the US has slashed its support for the Global Fund from $546m this year to a promise of just $200m a year from next year, which is only slightly more than the $180m promised by France. The independent watchdog Aidspan says the US pledge represents just 18% of its equitable contribution according to the wealth of the nation.

Tobias also misled his audience when he claimed PEPFAR would fund the use of the cheapest, safest drugs regardless of who produced them: "These drugs may include brand name products, generics or copies of brand name products." In fact, the United States refuses to recognise the World Health Organisation system of approving ("prequalifying") safe generic drugs and has introduced new bureaucracy that will exclude most generic drugs in favour of more expensive brand name medicines. Critics point out that Tobias is a former Chief Executive Officer of Eli Lilly. In what seemed to be a reference to these new regulations, Tobias said: "America will not have one health standard for her own citizens and a lower standard of "good enough" for those suffering elsewhere. However, if the money is reserved for more expensive brand name drugs this can only result in fewer people being treated than could otherwise be the case.

America's "AIDS Ambassador" told the conference that PEPFAR would prioritise working with "indigenous organisations" that have the trust of local people. And he indicated his intention to prioritise faith-based organisations by adding: "The fact is that among those indigenous organisations, the Buddhist temples and monasteries, the churches, the mosques and the synagogues are among those who have gone where no one else would go."

The demonstrations that punctuated Tobias's lecture prompted both applause and boos from the audience. As he left the auditorium, the demonstrators stood and chanted "Shame. Shame".

Tobias ducked out of a scheduled presentation on the first day of the conference and his place was taken by Dr Mark Dybul, the Deputy Chief Medical Officer in Tobias's office, who made a very strong case for PEPFAR by quoting statistics about how much has been achieved with PEPFAR dollars. He, too, was greeted with cheers and boos from the audience. An activist from ACT-UP New York and Health GAP spoke at the delegates' microphone to criticise the US government for using the conference as a "PR platform". The speaker asked: "Why is the US government undermining generic drugs? Why has the US government reneged on Doha [the World Trade Organisation agreement that, among other things, allowed greater production of generic drugs]? Why has the US government drastically underfunded the Global Fund?"

Gregg Gonsalves, Director of Treatment and Prevention Advocacy at Gay Men's Health Crisis, New York, told the same session: "It has been the AIDS community that has been at the front of all progress in the field of AIDS … Professionals are still loath to see PWAs in positions of control; they would rather see us as patients, victims, carriers." Dybul said the answer was to protest in countries around the world to "mobilise PWAs and bring the community to the table." Sharonann Lynch from ACT-UP New York and Health GAP, said the key was to make the Country Co-ordinating Mechanisms (CCMs, committees that coordinate each country's grant applications to the Global Fund) involve PWAs, and to ensure that bilateral donors such as the United States through PEPFAR, use the CCMs.

Also on the first day of the conference, Médecins Sans Frontières (MSF) held a packed three and half hour session on Access to Affordable ARVs: Patents, Prices and Quality. Fernando Pascual, a pharmacist with MSF, said medicines for first line therapy cost 1.5 times more in developed countries than they do in developing countries. Second line drugs cost 26 times more because there is very little generic competition for new second line treatments. The so-called originator companies, those that invent and develop a drug, only cut the prices of their first line therapies after other companies have produced generic versions. Allowing generic competition is a key issue, said Pascual. A UNICEF worker from China emphasised that the key issue was generic production of second line drugs and asked what influence the Clinton Foundation, headed by the former US President Bill Clinton, was having. Pascual responded that Clinton was negotiating prices at country level, which would reduce prices in Rwanda and soon in Mozambique. A representative of the Nigerian Ministry of Health said that PEPFAR had assured Nigeria that they would be funded for buying generic drugs. Rachel Cohen, the US Director of MSF's campaign for Access to Essential Medicines, responded: "We have to be sceptical of assurances like that from the US government because they have said they will only fund drugs approved by the US government. In our experience, they will have to procure brand name medicines because of PEPFAR regulations. The prices mean that they could treat three times as many people if they were allowed to buy generics."

Pascale Boulet, of the MSF Campaign for Access to Essential Medicines, was keen to nail the myth that companies can hold international patents: patents are granted by National Patent Offices for each country to reward invention and facilitate the disclosure of the invention as a sharing of knowledge. A patent provides the holder with a monopoly in the country where it is granted and the World Trade Organisation (WTO) TRIPS (trade-related aspects of intellectual property rights) agreement ties signatories to making the monopoly last for a minimum of 20 years. One hundred and forty countries signed the TRIPS agreement.

Countries such as Brazil, Thailand and India did not grant patents before the TRIPS agreement so they have generic production of older, first line therapies, but TRIPS means that new drugs are likely to be patented which means that as more people are treated, and as virus develops resistance to the drugs, the world will become more dependent on brand name drugs

and producers of generics will be squeezed out of the market.

It should be remembered that the issue of patents can sometimes be a red herring because many of the biggest companies do not file patents in Africa. Equally, it is worth pointing out that manufacturers of generic drugs are not necessarily angels; The Mumbai, India-based company, Cipla, has patented Triomune (lamivudine, stavudine and nevirapine) in South Africa and is seeking patents on the product in 17 other African countries. Treatment activists have expressed outrage.

The good news is that the Doha declaration – a WTO agreement signed in Doha, Qatar – allows signatory countries to issue compulsory licences to protect public health and to "promote access to medicines for all". Thirty-two of the WTO's poorest member countries are classified as Least Developed Countries (LDCs) and they do not have to grant or respect patents on medicines until 2016. MSF is urging the countries to take full advantage of this clause in the next 12 years and to work to have it extended after the 2016 deadline.

Boulet explained to delegates how the national authority responsible for patents could issue authorisation to manufacture or import generics without permission of the owner of the patent. Examples of past uses include the UK Ministry of Health buying generic tetracycline from Italy in 1965, and more recently the Indian government importing Kaletra from Thailand.

Boulet highlighted the main concern for the future as being how to ensure sources of affordable medicines and how to tackle the cost of widely patented second line treatments. The main concern for the immediate future was the development of bilateral "free trade" agreements usually between the US and poor nations that threaten existing trade flexibilities by persuading countries to give up their rights to use generic medicines. Cohen cited the example of Uganda, which has been under sustained pressure from the US for several years to amend legislation to introduce respect for patents, even though as an LDC they don't have to.

Cohen and Pascual talked about how the United States government has rejected the WHO prequalification scheme that approves generic drugs as safe and effective. Instead, the US has published a draft document outlining regulations to approve drugs to qualify for PEPFAR funding. MSF has joined other observers in saying the regulations will make it easier for brand name drugs to get approval from the US authorities and difficult, slow and expensive for generic manufacturers to do the same for their products. Pascual commented: "The WHO prequalification is perfectly good and we don't need to duplicate approval in this way."

Dr Selina Lo, MSF's Medical Coordinator in China, spoke about their project in Nanning City where they have 100 people on ARVs. She said the only fixed dose combinations (FDCs) or combined pills available to them were Combivir and Trizivir but the MSF doctors wanted to be able to use FDCs containing combinations of other drugs. She said they didn't have access to any second line drugs. Kaletra is registered but not marketed. They want other combinations using 3TC, besides Combivir and Trizivir, and although GlaxoSmithKline has decided to preferentially price 3TC, that doesn't help provide FDCs for patients – "which is something we will continue to push for," said Lo. She pointed out the complexity of the problem involving patents when she said that 3TC has 51 patents on it in China alone.

A speaker from Egypt said that because that country officially had a low HIV prevalence most brand name drugs were not marketed there. Pascual said this was a common problem in countries with low prevalence and there was nothing they could do to make private companies market their drugs. He said the best thing to do was to press governments to issue compulsory licences, which allow the production and distribution of generic versions of patented brand name drugs.

Cohen said there was a problem procuring drugs at reasonable prices for middle income countries where lower prices, also known as differential pricing, announced by the major pharmaceutical companies, were often "virtual rather than real". Zahedal Islam, head of the MSF mission in Ukraine, said they had 1,000 mothers and children in their programme, and there were no patent barriers in the country which meant that generics (AZT, 3TC and nevirapine) were allowed there. However, because the drugs are not marketed in the country they have to be imported by MSF and shipping and customs costs take the cost of drugs up to the non-discounted rich nation price.

On the Tuesday morning of the conference, a demonstration by the Thai Positive People's Group demanding an end to the system of patents, greeted the start of a session in the main conference auditorium that asked: "Are Intellectual Property Rights a Barrier to Increased Access to ARVs?" In an appearance that surprised many observers, Hank McKinnell, Chairman and Chief Executive Officer of Pfizer, put the case for patents. He said intellectual property (IP) rights were what allowed companies like his to make enough money to sustain investment in technology. IP drives new research, which creates new treatments, which will help patients in the future, he argued. "We have to ask ourselves what is the balance of treating patients today and in the future." He said Pfizer would work with "any government anywhere" to give people access to Pfizer medicines, "but we will not negotiate with people whose purpose it is to appropriate our knowledge for sale by others at a profit."

Walden Bello, Professor of Sociology and Public Administration at the University of the Philippines, undermined McKinnell's main argument by pointing out that governments, universities and public bodies spend three times as much on research as do the pharmaceutical companies. He said that in the past big pharmaceutical companies - 'Big Pharma' in the jargon – doesn't develop new drugs, it buys them from smaller companies and other sources in order to market them. They spend more on marketing than on R&D. He called on TRIPS to distinguish between life saving medicines and drugs like Viagra "and other toys" which Pfizer should continue to be allowed to market as they do.

Bello said branded medicines retail at 20 to 100 times their manufacturing costs, that the pharmaceutical industry is the most profitable industry in the United States and he listed what the companies' CEOs were paid and – getting personal – he said McKinnell was highest paid of all on $28m annual pay plus $30m stock options. McKinnell told delegates these figures were inflated but he did not reveal what he was paid.

When discussion was opened to the floor, a French economics professor called for an independent task force to establish industry R&D costs.

Jonathan Berger of the Treatment Action Campaign and the AIDS Law Project at the University of Witwatersrand, South Africa, said it was necessary to amend the TRIPS agreement and to create incentives to develop new drugs while changing how patents were used. Countries should exploit the public health safeguards and flexibilities in the TRIPS agreement and the agreement needed amending so that a single compulsory licence would be enough to ensure production and distribution of generic drugs. He called on countries with manufacturing capabilities to lead the way but added that those without manufacturing capabilities should also have access to generics. The obstacles to scaling up access to treatment were that countries were failing to implement the Doha exemptions to their full extent, and bilateral and regional Free Trade Agreements (FTAs) were being negotiated "all round the world" that limit the possibilities for generic production and distribution. These retrograde bilateral and regional agreements are attracting little public attention, are often highly technical in nature, and are being negotiated in secret. They already affect the nations of the North American Free Trade Association, Caribbean Free Trade Association and the Southern Africa Customs Union, as well as Chile, Jordan, Morocco, Singapore and Australia.

A speaker from an NGO in India said that scaling up access to treatments was a lot more complicated than simply sidestepping patents because India had several thousand pharmaceutical companies including manufacturers of generic ARVs, but only 12,000 people, 1% of those who need treatment, were receiving ART. In countries like India where the basic delivery mechanism for any kind of drug is very weak, producing generics is only the first step towards treating people. Several speakers in other sessions also made the point that, India has 5.1 million people with HIV/AIDS, the largest number of any country other than South Africa, but despite the advantage of a developed domestic generics industry, the Indian government has failed to treat people. The appearance of Sonia Gandhi, head of the country's Congress party, on the last morning of the conference, suggests that the new government may take the problem more seriously than its predecessor. She acknowledged that "we need to do a great deal more" and added: "I would like to take this opportunity to categorically assert the determination and ability of the government and the people of India to meet this daunting challenge just as effectively as it did in the campaign to eradicate smallpox some decades ago."

There was considerable debate at the conference about how to decide who gets treatment in circumstances where need overwhelms supply. Laura McGough, an historian from Johns Hopkins University in the US, said there were already several rationing methods that controlled who got treatment; she said PEPFAR rations treatment to just 15 countries, the Global Fund rations by programme proposal, in some countries treatment is rationed to state employees, it is rationed by stigma or rationed to people with fixed addresses and family support. She and colleagues evaluated resource allocation decisions taken following four medical discoveries between 1922 and the present day. She told delegates that their recommendations were 1) to encourage public participation in establishing rationing criteria, 2) not to use social criteria as 'proxy' for adherence criteria, and 3) to act constitutionally. She concluded: "Each country needs to engage these questions and come to their own conclusions about inclusion criteria." [1]

Miriam Rabkin of Columbia University, New York, reported on the non-medical eligibility criteria used by different projects in the Columbia MTCT-Plus programme. This initiative provides care and support to women, children, and their family members at 12 MTCT-Plus sites in 8 countries. She said that first there were programmatic criteria that limited resources to women, children, partners and household members, then there were clinical/biological criteria to decide who would be treated and finally it was devolved to each site to decide how to define "households" and other criteria, using community boards to reach decisions. She reported to delegates that no one criterion was used by all sites; some demanded recipients be "within the neighbourhood", one insisted on a commitment to safer sex, one insisted on a fixed address, and one demanded participants be single or in monogamous relationships (although after discussion this requirement was dropped). Many criteria were abandoned within the first six months. Rabkin said: "Sites are at the ethical forefront of deciding on access criteria and community involvement is essential." [2]

There was also discussion about the best use of resources to identify and prioritise people who need treatment. Harmony Fusco of the Centre for Infectious Disease Research in Zambia – where fewer than 5,000 patients are on ARVs and the government target is to have 100,000 on treatment by the end of next year – said that to enrol one patient on ART they had to be willing to be tested, willing to undergo clinical and lab investigation and willing and ready to start treatment. She said they found they had to pre-test counsel 72 antenatal patients to enrol one on ART, but they had to pre-test counsel only 3 TB patients to enrol one on ART. "This dramatically cuts enrolment costs," she said, adding: "It is estimated that 80% to 90% of hospital in-patients are HIV-positive so there are high-yield – if you like to use that phrase – patient populations." [3]

The scale of the problem of identifying people suitable for treatment was illustrated by Chris Archibald of the Centre for Infectious Disease Prevention and Control, Canada, who said his research showed there are about 32 to 34 million

undiagnosed people with HIV. The success of the worldwide battle to combat HIV will rely on population coverage, not just treating people who present "and that requires steps to tackle stigma and prejudice". This also has implications for prevention because knowing one's status is the gateway to both prevention and care, he said. [4]

Among dozens of reports from individual projects in poor countries around the world, Frencesca Galletti of the WHO reported on the problem of individual healthcare projects having to care for people over large geographical areas and how this makes it difficult for people to consult their doctors about side effects and illness, to ensure they receive proper monitoring. She reported that in Uganda they are distributing blocked mobile phones that can only ring three numbers of healthcare workers so people can have long-distance consultations.

In a lunch break conversation, Peanh Sinal, Director of the Minority Organisation Development Economy in Kampong Thom, a province of northern Cambodia, described his work with racial minorities, mainly the Kouy people. MSF and other NGOs are treating about 7,500 people with ARVs in Cambodia and about another 20,000 people urgently need ART. Sinal was clear that the main problem in his country was government inaction due to political infighting and corruption, and he said the solution was for the Global Fund to finance the NGOs to increase the number of people being treated.

While MSF tackled the lack of generic versions of second line therapy, there needs to be emphasis on the dangers of treating people with multiple complications with only first line therapy. There will be treatment failure, people will get ill and die, and this could lead to demoralisation of patients and carers. We risk repeating the errors of the AZT monotherapy experience in the West a decade ago when information about treatment failure was kept from people for fear that it would take away hope; but leaving people with false hopes based on unrealistic expectations can only lead to disenchantment and future mistrust of treatment, healthcare workers and information providers. It is important that current FDC and MTCT programmes include information about adherence, resistance and side effects.

In one of the few presentations on human rights – a key part of so many aspects of the battle against HIV – Ronald Labwayii of Livelihood International in Kampala, Uganda, presented research that showed that there is a hidden epidemic throughout Africa among people who have homosexual sex. The research reveals huge levels of official and unofficial discrimination and violence against men who have sex with men (MSM) and women who have sex with women (WSW) throughout the continent with the exception of South Africa. They found high levels of rape in police stations, violence in correctional institutions, and sexual abuse of boys and girls. They also found that in Senegal, for example, the mean age of first sexual experience was 15 and one third of the sample said their first sexual partner was a member of the family. Condom use in all circumstances was very low. He concluded: "AIDS is fuelled by violence against MSM, and prejudice against MSM," and yet in most of Africa there are no education, prevention or care projects appealing to sexual minorities. A delegate speaking from the floor said the same problems affected MSM in eastern Europe.

If Africa made its presence felt four years ago at the Durban conference, this year at Bangkok it was noticeable that there were many more delegates from neighbouring Asian countries including China, as well as from central Asia, Eastern Europe and the Russian Federation. This reflects the growing concern about HIV in these countries and also demonstrates the importance of alternating the International AIDS Conference between developed and developing countries. Finally, there was a graffiti wall in Bangkok and among the jokes and anger, one anonymous delegate had written: "Where is the Middle East and North Africa in the fight against HIV/AIDS?" and very small writing in a different hand next to it had added: "I live there. AIDS crisis coming soon."

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Links:

Professor Walden Bello
http://www.zmag.org/bios/homepage.cfm?authorID=113

Jonathan Berger
http://www.alp.org.za/view.php?file=/about/bios/20020627_bergerj.xml

MSF
http://www.accessmed-msf.org/index.asp

Randall Tobias
http://www.state.gov/s/gac/rl/rm/2004/34366.htm

Gay Men's Health Crisis
http://www.gmhc.org/

Pfizer
http://www.pfizer.com/main.html

MTCT programmes in South Africa: nevirapine and the minister

Jonathan Berger and Nathan Geffen for HIV i-Base

Never one for passing up the opportunity to score a few cheap points, South Africa's Minister of Health used the opening of the South African Department of Health's exhibition at the XV International AIDS Conference in Bangkok on Sunday, 11 July 2004 to launch yet another unjustified attack on her most vocal and organised critic, the Treatment Action Campaign (TAC).

Claiming that new scientific evidence "vindicated" her original position on the use of nevirapine for the prevention of mother-to-child transmission of HIV (MTCT), Dr Manto Tshabala-Msimang sneeringly referred to the "pressure from some civil society organisations" that had caused the South African Constitutional Court to force the extension of the MTCT prevention "research programme".

The following day, South Africa's drug regulatory authority, the Medicines Control Council (MCC), issued a confusing press statement that referred to a 2 July 2004 meeting at which the MCC had recommended that nevirapine no longer be used as monotherapy for the prevention of MTCT. Failing to distinguish clearly between issues of resistance and efficacy, the MCC statement presented an inaccurate view of the risk of nevirapine resistance following its use for the prevenntion of MTCT. Most disturbingly, the MCC statement was silent on the implications of its recommendations for the public sector MTCT prevention programme that centres on the use of nevirapine monotherapy.

Shortly thereafter, TAC, Médecins Sans Frontières (MSF) and the AIDS Law Project called a public meeting in Bangkok to discuss the issue "from a scientific and human rights perspective." Attended by activists, scientists, researchers, government officials and representatives of UNAIDS and the World Health Organization, the meeting provided an important forum for constructive engagement. A day later, the Minister issued a press release confirming that the South African government's policy on the prevention of MTCT remained unchanged, with her department continuing to provide nevirapine as monotherapy "until new agreed upon treatment regimens are available."

A study presented in Bangkok shows how the use of AZT and lamivudine in combination, taken by the mother for at least four days after the single dose of nevirapine, significantly reduces levels of resistance *(see below in this issue of HTB for report on this study)*. But the best combination of medicines for reducing MTCT and avoiding resistance is triple-drug combination antiretroviral therapy, taken where this is medically indicated for the treatment of the mother herself and not simply for preventing MTCT.

With the introduction of treatment for AIDS into the South African public health service, it makes sense to keep as many antiretroviral drug options as possible open for pregnant HIV-positive women when they later develop AIDS. Therefore switching the MTCT protocol, wherever possible, to one that is more effective and results in less resistance, is rational, reasonable and in the interests of both mothers and the broader public.

So where does this take us? TAC's stance, as articulated in numerous media interviews as well as written statements, has consistently been that regimens other than the single-dose nevirapine can and should be introduced into the public sector wherever possible. Where there is a current lack of capacity in a clinic, the single-dose nevirapine regimen is the minimum acceptable regimen for the prevention of MTCT. At the same time, clinics must be given the resources they need to be able to provide better regimens. Also, where an HIV-positive woman presents late to an antenatal clinic (during labour, for example), single-dose nevirapine might be the only regimen available to her. We trust that the Minister will follow this sensible approach.

This leaves one question unanswered: does the evidence on resistance "vindicate" the South African government's original position on the use of nevirapine for the prevention of MTCT? Contrary to what the Minister asserted in her speech in Bangkok, the limited MTCT prevention programme adopted by government in late 2000 (prior to TAC's court action) did not seek "to interrogate the use of nevirapine as a monotherapy". Rather it sought to address certain operational issues, making no commitment to the universal rollout of the programme. Most disturbingly, the programme prohibited the prescription and use of nevirapine (or any other antiretrovirals) for the prevention of MTCT at any public health facility other than the 18 "pilot sites" at which the programme operated, regardless of the facility's ability to administer the drug safely and effectively. Indeed, by the time the TAC initiated court action, many of the pilot sites had still not begun the programme.

The Minister of Health suggested that the TAC forced government to adopt the single-dose nevirapine regimen. While it is true that the TAC forced government to implement a countrywide MTCT prevention programme by taking the Minister to court, it is incorrect for her to claim that the TAC forced government to adopt the single-dose nevirapine regimen. This regimen was the Department of Health's choice for its programme, despite knowing at the time that more effective regimens existed, usually

involving AZT. This was arguably a reasonable choice though; single-dose nevirapine is simple to administer and a good starting point for the rollout of a universal MTCT prevention programme.

In its judgment, the Constitutional Court found that "the Constitution require the government to devise and implement within its available resources a comprehensive and co-ordinated programme to realise progressively the rights of pregnant women and their newborn children to have access to health services to combat mother-to-child transmission of HIV." In particular, government was ordered, "without delay", to "remove the restrictions that prevent nevirapine from being made available for the purpose of reducing the risk of mother-to-child transmission of HIV at public hospitals and clinics that are not research and training sites."

The court also made it clear that the order relating to nevirapine does "not preclude government from adapting its policy in a manner consistent with the Constitution if equally appropriate or better methods become available to it for the prevention of mother-to-child transmission of HIV." In other words, the order is not restricted to nevirapine, but rather refers to a comprehensive programme to prevent MTCT.

Has the Minister been vindicated? Clearly not! Knowing what we know now, we would still have gone to court. Many lives have been saved as a result of the intervention. A comprehensive MTCT prevention programme is now in place. Government has adopted a comprehensive policy on antiretroviral treatment and has started to implement it in the public sector. None of this would have happened without the "pressure from some civil society organisations" that the Minister continues to deride.

Jonathan Berger is the Head of Law & Treatment Access Unit, AIDS Law Project
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BANGKOK: IVDU ISSUES

Urgency of global access to ARV treatment for IV drug users

Mauro Guarinieri, for HIV i-Base

A week-long conference is definitely a good thing in the fight against AIDS but it will count for almost nothing if it is not followed up by concrete measures and action. Since the last global AIDS gathering in Barcelona in 2002 6 million people have died and 10 million have been newly infected, so the question now is: "What will the follow up be?"

Months before the conference kicked off activists were saying that Bangkok had the potential to become a a real turning point in focusing the right kind of attention on drug use and HIV/AIDS issues. They were saying that discussion of HIV control in developing countries usually pays insufficient attention to injecting drug use (IDU). Yet half the population of the world lives in developing countries within a few hours flight from Bangkok, in a region where HIV infection is dominated by the sharing of injecting equipment.

UNAIDS estimates that injecting drug use accounts for 10% of annual HIV infections worldwide, as many as one in three new HIV infections outside Africa, and is the driving force behind the world's fastest growing epidemics. In Russia, as many as 1 million people have been infected with HIV in less than 10 years, with over 80% of infections being among injecting drug users (IDUs). All the countries of Central Asia and many in Southeast Asia and the Southern Cone of Latin America report that IDUs account for a majority of HIV infections or a rapidly growing share of total cases.

A high prevalence of HIV is now found among IDUs in Myanmar, Vietnam, China, Thailand, Malaysia, Indonesia, Nepal and Iran. In several of these countries, authorities are now reporting that over 60% of IDUs who have been tested are HIV positive. China alone is now estimated to have almost 900,000 injecting drug users, and more than 60% of the country's 1 million estimated infections are among IDUs. There are also large pockets of HIV infected IDUs in other populous Asian countries, such as India and Pakistan.

Fuelled by economic, social and political constraints, IDU continues to proliferate in this region as it does in many other parts of the world and what is more frightening is that HIV continues to spread among and from IDUs much more rapidly than the adoption and expansion of effective harm reduction interventions.

The major obstacle remains an entrenched commitment to an unbalanced drug policy heavily reliant on supply control, reinforced by a common but unwarranted fear that expansion of drug policies to include pragmatic harm reduction strategies will conflict with efforts to control the supply of and demand for illicit drugs.

Before the conference, activists from around the globe denounced the fact that drug users still represent a minority of those receiving ARV and called on the international community to ensure the inclusion of injecting drug users in the scale-up of antiretroviral therapy. More specifically, they called on the World Health Organisation (WHO) to ensure the inclusion of injecting drug users in its plan to treat 3 million people by 2005.

Following up a specific proposal made by over 200 drug users, people living with HIV/AIDS, and advocates from around the globe, to include methadone and buprenorphine into the List of Essential Drugs, Dr Andrew Ball, Manager of Regional and Country Support of the WHO HIV/AIDS Department, said during the conference: "The WHO fully recognises the overwhelming evidence that methadone and buprenorphine are highly effective treatments for drug dependence and prevention of HIV/AIDS, and has undertaken an extensive review of the effectiveness of methadone in HIV/AIDS prevention and care." He added: "An independent expert committee is considering including methadone on the WHO Essential Drugs List," during a press conference organised by the Open Society Institute, the European AIDS Treatment Group, the Russian Community of People Living with HIV/AIDS and the Thai Drug Users Network.

He said, however, it was not up to the agency to make drugs like methadone or buprenorphine widely available to the public. But the WHO supports the drugs being added to the Essential Drugs List, which is supervised by an independent committee.

The same statement was made by Dr Jim Kim, Director of the WHO's HIV/AIDS programme, at the end of a colourful demonstration comprising people living with HIV, drug users and sex workers, who called for action and accountability to stop the spread of AIDS before the conference opening. Kim emphasised that experience in many countries had shown that criminalisation of drug use only escalated the spread of AIDS.

Fearing the International Aids Conference was just another talk shop with empty promises, more than 1,500 people from all over the world joined the march, clutching banners and wearing various styles of slogan-bearing T-shirts to voice their demand to be included in the action plans. For Thais, the major demands - which were passed to Prime Minister Thaksin Shinawatra - included ensuring sustainable coverage for the cost of anti-retroviral therapy and the immediate end of Thaksin's all-out war on drugs, in which more than 2,500 drug users were killed under questionable circumstances.

An estimated 100,000 to 250,000 people in Thailand inject heroin, even though methamphetamine pills have overtaken heroin as the country's drug of choice. HIV prevalence among the country's heroin users has stood at 40% or more since the late 1980s, in contrast to the declining rates among others at high risk. Drug users face limited treatment options and regular abuse by police, including beatings, false arrest and forced confessions. The zero-tolerance Thai campaign's only effect was to drive intravenous drug users, who reportedly make up about 40 per cent of Thailand's Aids patients, underground.

The Thai government crackdown began in February 2003 for the official reason of curbing the trade in methamphetamine tablets. Within 3 months, an estimated 2,275 drug suspects were shot dead. Scores of alleged drug dealers were placed on poorly prepared government "blacklists" and ordered to report to the police and many were shot by unknown gunmen shortly after leaving the police station. In addition to almost 3,000 unexplained deaths, thousands had been forced into drug treatment in military-style boot camps.

Not surprisingly Prime Minister Thaksin Shinawatra's controversial war on drugs came back to haunt him during the opening ceremony. When Thaksin insisted in his speech that his government no longer treated drug users as criminals but as patients, demonstrators and hecklers reminded him of the controversial campaign that was condemned by the international community, including the United Nations. "Thaksin Lies" read one sign that went up in the packed auditorium. Activists reacted in uproar when their representative, Paisan Suwannawong, former heroin addict and chairman of the Thai Treatment Action Group, was designated as the last speaker at the opening ceremony of the Conference. By the time he reached the podium, Prime Minister Thaksin and UN Secretary General Kofi Annan, had already left the hall.

In contrast to claims made by conference organisers that people living with HIV/AIDS had been given wider access than ever before, activists said they continued to be ignored and even discriminated against by people in power. "What hypocrisy," said Paisan, also leader of the Thai Drug Users Network. "Thaksin said in his speech that he cares and wants to help drug users, so why didn't he stay to listen to me."

All through the conference, activists called for a worldwide reversal of public opinion on injecting drugs use. They said in many countries drug users have set up their own organisations that work to reduce the spread of infectious diseases, to decrease discrimination against drug users in society, and to improve medical treatment of all sorts for drug users.

At the eve of the conference, the International Harm Reduction Programme (IHRD) of the Open Society Institute released a report detailing successful efforts to offer drug users antiretroviral treatment (ARV) and the dangers of failing to do so. "The common assertion that drug users cannot comply with treatment represents a failure of vision by AIDS programme administrators, not a description of reality," said IHRD programme officer Konstantin Lezhentsev, noting that the report described successful efforts to offer ARVs to IDUs in Brazil, Argentina, and a number of urban settings in Western Europe and the US. "The question is whether governments and healthcare systems will step up to their responsibility to meet the specific needs of this group, or continue to simply deny treatment to drug-users based on the myths that are based more on prejudice and discrimination than on healthcare and human rights principles."

Activists underlined the importance of shifting both from the medical model - according to which IDUs are sick, they cannot adhere to treatment, and they have worse clinical outcomes - and the criminal model - by which they need to be charged and incarcerated, since they perpetuate a cycle of criminality that goes beyond just drug use. It is necessary to admit that when given proper access to healthcare, IDUs can adhere to treatment and have comparable clinical outcomes to other patient

populations. It is time to accept that criminality is not caused by drug use but by the same criminal system. Eliminating repressive drug laws and stopping widespread propaganda that blames IDUs for social and economic evils of all descriptions, and halting government-sponsored campaigns that murder them, can only support the functioning of IDUs in society.

Most importantly, they committed to establishing better and stronger links with drug users and harm reduction networks, noting that in most cases drug users' organisations also work for the decriminalisation of drug use. "What once was radical has to become common sense," said Paul Davis of Health Gap USA.

Harm reduction and HIV treatment activists have been building their capacity for the last year to arrive at this successful point. In spite of enormous challenges, involving legal, cultural, and moral dilemmas, a formidable and growing array of committed individuals and groups has now entered the battle.

They are trying to raise global awareness to the fact that no area more than drug use clearly demonstrates the bad consequences of abstinence based approaches, and that although in 7 out of the 10 UNAIDS regions (accounting for 90% of the global population) injecting drugs is considered among the most important risk factors for HIV, in many countries injecting drug users are still stigmatised, routinely excluded from treatment, and treated badly by various institutions along a continuum that has insults at one end and violent death at the other.

Unsurprisingly, exactly the same countries where discrimination creates the conditions of furtive drug injection using shared injection equipment are those where HIV prevalence among people who inject drugs is higher. This includes the United States. Despite the American impulse to tell other countries how to do it, the timing and scale of implementation of HIV prevention measures for IDUs in the USA has been anything but impressive, with at least 36% of new AIDS cases in the USA still directly or indirectly associated with injecting-drug use.

Although on 20 February, 1933, the US Congress acknowledged the failure of alcohol Prohibition, it seems that US officials have a strong incentive to maintain their faith in old paradigms even as the facts become increasingly difficult to explain within that paradigm, proving that attitudes toward drug users are often based on beliefs, misconception, moral certainty and "common sense", rather than on medical evidence.

Evidence tells us a very different story: that drug users can do as well as anybody else and that even the poor and the homeless can adhere to ARV**. T**heir exclusion from treatment and care has nothing to do with science. Rather, it has to do with a widespread discrimination toward active drug users.

So the only measure of both our success and our failure will be the number of lives that are saved, the adoption and implementation of evidence based policies to ensure comprehensive harm reduction approaches to prevention, care and treatment, the elimination of criminalisation, stigmatisation, and marginalisation of drug users, and a substantial reduction in the number of drug users sent to prisons.

AIDS reminds us that all transmissible diseases are rooted in social and economic life, and that respect for human rights and human dignity are paramount in responding to the epidemic. We have heard too many sad stories from Africa, where endless discussions were just an attempt to hide the real reason for not making treatment available, to let authorities do the same on injecting drug use.

Support from international organisations for equitable and comprehensive treatment for HIV-positive or at-risk drug users is growing dramatically as we can see from the UK Department for International Development, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, the World Health Organisation, and UNAIDS.

History will tell us whether their commitment to address the social, cultural, legal, and medical barriers that deprive IDUs of access to HIV treatment will result in effective changes in policies and laws. But while there are many declarations of positive intentions and good meetings taking place, it is up to us, the community, to speak out, advocate, and make our voice heard.

Mauro Guarinieri is Chair of European AIDS Treatment Group (EATG):
http://www.eatg.org

More information on acces for IDUs:
http://www.ceehrn.org/ARV4IDUs

Replace myths with evidence–based policies on IV drug use

Paisan Suwannawong
Director of the Thai AIDS Treatment Action Group

Speech to the Opening Ceremony, XV International AIDS Conference, Bangkok.

First I would like to say thank you to the people who supported my invitation to speak, and thank you to the International AIDS Society because it means a lot to me, to speak from the perspective of a drug user living with HIV.

I would like to tell you a little bit about myself. I grew up in one of Bangkok's biggest slums, not far from here. I saw many people

using drugs, but never imagined that I would become a drug user myself. The first time I smoked marijuana, it felt like a challenge because all the public campaigns said drugs were "bad" and "dangerous." I found it wasn't true, so I continued to smoke it. Then I started smoking heroin, and became addicted without realising it. I didn't have any money, I was feeling withdrawal symptoms, and my friend offered to share his heroin and inject me. Yes, it was scary the first time.

I got arrested at least 20 times. Most of the time, I did not have any drugs on me. The police would plant drugs on me and force me to confess, and beat me if I did not sign their document. I could not carry a needle around, because if the police arrested me, the charge would be more serious. I heard about the risk of getting HIV from sharing needles, but when you are craving heroin, you don't think about anything else. You just want to inject.

I was in prison twice. The conditions were terrible and we had to stay in our cells for more than 15 hours a day. For me, there is nothing worse than losing your rights and your freedom. I am not surprised that people use drugs and inject in prison, even if they never used or injected before. I believe that I got HIV in prison because I injected almost every day there.

Getting off drugs is not easy. Many times, I went into drug treatment just to please my family, to get away from the police, or to take a break because the amount of drugs I needed was getting expensive, not because I wanted to quit; and the attitudes of treatment staff only made me feel worse. Other times, I really did want to quit, but can you imagine how it feels to leave a treatment programme and go back home, with nothing to do? How difficult it is to find a job and explain where you've been? My own family would watch my every move; I could see in their eyes they did not trust me. I was too embarrassed to see my friends, whose lives seemed so successful. It was so lonely. I felt I had nothing at those times. The only thing I could think of was to go back to using drugs.

Finally, I got off drugs 13 years ago. I knew I really needed help. I decided to go to a "TC," or "therapeutic community." This is how I found out I had HIV. The test still is a requirement for entering the TC. There was no pre- or post-test counseling. In fact, my results were given to my sister, not me. Today, not much has changed. Drug users are still seen as morally weak and bad people. We face stigma and discrimination in society and in the health care setting. We experience constant police harassment and ineffective services. In Thailand, injecting drug users or "IDUs" are the only group whose 50% HIV prevalence has not changed in 15 years. One third of all new HIV infections are IDU-related, and this number is increasing. Yet there has been no effective response from the government.

In a recent war on drugs in Thailand, over 2,500 people were killed extra-judicially in the first three months of the campaign. More than 50,000 people were arrested, hundreds of thousands were forced into military-run rehabilitation centres, and drug users were forced underground and away from services that were already difficult to access. Last year, the Thai Drug Users' Network developed a proposal for a peer-driven HIV prevention, care and support intervention for injectors, and submitted it to the Global Fund. We had to bypass the country coordinating mechanism and lobby with the help of international AIDS activists to get political support for our proposal. In October, we were awarded a $1.3m grant, but we still haven't received the money. Even though the Thai government says its current policy is to treat drug users as "patients," not "criminals," it is still illegal to be a drug user. We continue to be arrested and offered the choice of prison or military-run rehabilitation centres. Is this harm reduction or harm production?

Every minute, a person is infected with HIV by using a dirty needle. Globally, 1 in 3 of all new HIV infections outside of Africa is IDU-related. In fact, contaminated needles account for the largest share of new infections in Eastern Europe and Asia. The WHO says drug users have an equal right to all levels of care, but in practice, we are denied access to ARV treatment, as well as basic prevention interventions like clean needles. Methadone is still illegal in many countries and should be on the WHO Essential Drug List. There are many harm reduction interventions, including clean needles and methadone, which have been proven to help IDUs stay free of HIV. We need these means of prevention in place now. And we need access to treatment now. Drug users, like other politically, socially, or economically marginalised groups, are easily abused by the government and others, who exploit them for money or services. We often do not enjoy even the most basic human rights. In Thailand, this is true for sex workers, MSM, migrant workers and undocumented citizens as well.

The world we live in today is not a world of sharing but of advantage-taking, profit-seeking, and competition to "get ahead." It is a world motivated by greed and controlled by corporations, which do not recognise the value of a human being. While an elite few amass enormous wealth, basic needs are denied to many millions. Today, many of our governments are run by this elite, who are more interested in protecting their personal investments than promoting public welfare. They invest public resources in projects whose profits go into the pockets of their friends instead of providing for the welfare of society. Governments privatise our public utilities, as well as our education and health care systems. Social welfare programmes and other forms of assistance become issues of charity, not rights or entitlement. As a result, our public hospitals are overloaded and under-funded, severely compromising the availability and quality of treatment and care offered. Of course, tackling AIDS isn't just about health care and ARV.

Prevention, harm reduction, poverty reduction and decent living standards are all part of the process; but governments, like the United States, or international organisations, like the WTO, make the task much more difficult. Market-driven policies and the emphasis on "abstinence-only" have already proved to be harmful or, at best, totally useless. It is outrageous that today, conservative groups, especially in the US, are advancing a moralistic ideology that contradicts scientific evidence about HIV prevention. Though condoms and clean needles are the most effective tool we have to prevent the transmission of HIV,

programmes that promote them are not funded, or are de-funded. Evidence shows that widespread access to ARV leads to huge improvements in health and quality of life, with significant reductions in health care and other costs, because of improved health and productivity among people living with HIV/AIDS and their families.

The most painful experience I can think of, after living with HIV for 13 years, is being poor and HIV-positive. Again and again, I watched many friends die in front of me, from terrible opportunistic infections, simply because they were poor and could not afford treatment. What kills us is not AIDS, but greed. Multi-national pharmaceutical companies inflate the prices of their drugs without thought for poor people. They use they wealth to influence US and European government policy to ensure that intellectual property rights are weighed in their favour. Other governments say they are too worried about adherence and drug resistance to offer treatment, when the truth is they don't want to pay or suffer repercussions from their trading partners by breaking patents. Four years ago, Thai people with HIV/AIDS asked the government to use a compulsory licence for ddI, but the government was too afraid of trade and other sanctions from the US. Ultimately, we took Bristol Myers-Squibb to court and won the right to produce tablet-form ddI, locally. In the final judgment, the Thai court ruled that, because patents can lead to high prices and limit access to medicines, patients have the right to sue the patent holder. This was a very important battle that we won. But the war is not over.

Recently, the Thai government entered Free Trade Agreement negotiations with the United States. We know the US unilaterally pushes for intellectual property protection that is stricter than what is agreed internationally. This means that Thailand, now producing generic ARV for most who need it, will no longer be able to sustain this important programme. We are demanding the Thai government refuse to trade away the health of its people by negotiating intellectual property protections for medicines.

The US government and its policies affect the ability of people all over the world to enjoy their basic rights and needs. Many poor countries cannot provide basic services like health care because they have to pay back enormous debt to the US and Western Banks. While thousands die of AIDS everyday from lack of funds, there is unlimited funding for war. Billions of dollars are freely available for the killing and destruction in Iraq, while the Global Fund is out of money. This is because of the broken promises of rich donor countries that refuse to pay their fair share. I have no simple solutions for achieving world peace, but I do know that the US government, led by that criminal, George Bush, wages war and occupies countries like Iraq in the name of peace. The US is too arrogant to listen to the UN, and the Thai government shows its loyalty to the US by sending Thai troops to Iraq.

Four years ago, at UNGASS, after activists demanded an urgent response to the global AIDS treatment crisis, Kofi Annan called on all the world's governments to develop what he described as a "war chest." This became the Global Fund. At the last International AIDS Conference, WHO launched its '3 by 5' initiative; yet, today, 6 million people are still waiting for their drugs. AIDS doesn't wait and neither do we. Faced with the abuse of power and greed of corporations, we cannot wait for our governments to act.

Governments and corporations hate activists because we know what they are up to, and we are pulling the masks of fake concern from their face to reveal their true nature. But to me, activists are to be honoured. Activists are my true friends. They stand by my side when I face discrimination and injustice. They have the courage to stand up to those in power who use their positions for their own benefit. They are the ones who can help provide a way forward to fight AIDS and injustice in this world. Access for all is the theme of this conference and the dream of many of us here. Yes, it's not easy to achieve in the world we live in today, but the world belongs to all of us to change.

Five years ago, doctors, nurses and many other people told me and my friends that ARV was an impossible dream. Recently, Thailand announced that it would provide ARV to all who need it, starting with 50,000 people by the end of this year. Today, I urge all of us to dream: of a day when our world will be filled with love, sharing and peace. And I believe that when we dream together, our dreams come true.

The webcast of this speech (which was also given at the closing ceremony) is available online:
http://www.kaisernetwork.org/health_cast/hcast_index.cfm?display=detail&hc=1185

Human Right Watch on Thailand:

http://www.hrw.org/campaigns/aids/2004/thai.htm

Thailand: Not enough graves: the war on drugs, HIV/AIDS, and violations of human rights. Human Rights Watch Report. Vol 16 No 8, June 2004:

http://www.hrw.org/reports/2004/thailand0704/thailand0704.pdf

CNN report on brutality of Thailands anti-drug policy:

http://www.cnn.com/2003/WORLD/asiapcf/southeast/05/07/thailand.drugs

Links to reports, pictures and transcript of activist groups at the conference:

http://www.actupny.org/reports/Bangkok/

BANGKOK: PREGNANCY AND MTCT

Adding Combivir to single dose nevirapine for reduction of MTCT significantly reduces resistance

Polly Clayden, HIV i-Base

Perhaps the most important data from this meeting was an interim analysis from the currently ongoing TOPS (Treatment Options Preservation Study, aka BI 1100.1413) presented as a late breaker by James McIntyre from the University of Witwatersrand, Johannesburg, South Africa. McIntyre described these preliminary findings as "causing quite a stir, certainly among the Africans." [1]

The study was originally planned to enrol 300 treatment naïve women and their infants and randomises mothers and babies to one of three arms. Arm1 involves single dose nevirapine given to mothers at onset of labour and single dose to the baby. Arm 2 involves single dose nevirapine to mother and baby plus 4 days twice daily Combivir (zidovudine/lamivudine combined pill) to mother and baby starting during labour and within 24-72 hours of birth respectively. Arm 3 involves single dose nevirapine to mother and baby plus 7 days twice daily Combivir. Enrolment and informed consent is at 34 weeks and women are randomised in labour.

The objective is to determine whether adding either 4 or 7 days Combivir can reduce the occurrence of nevirapine resistance in treatment naïve HIV-positive pregnant women, which would in turn preserve their future treatment options.

At the time of this interim analysis 156 women had entered the trial and six week resistance data was available for 61 (18, 20, 23 mothers in the single dose nevirapine, single dose nevirapine plus 4 days Combivir and single dose nevirapine plus 7 days Combivir arms respectively). The women in each study arm were well matched at baseline (see below). All women in this analysis had Clade-C HIV-1 infection.

Baseline characteristics (median) for 61 mothers in interim analysis:

	sdNVP	sdNVP+ CBV-4day	sdNVP CBV-7day
N	18	20	23
Age (years)	26.0	25.5	26.0
Prior live births	1.0	1.0	1.0
Baseline HIV RNA (log)	4.62	4.15	4.54
Baseline CD4 count	298	317	299
Resistance at 6 weeks	53%	5%	13% **
Resistance at any time	9/18 (50%)	1/20 (5.00%)	3/23 (13%)

** p=0.001 single-dose NVP to pooled CBV arms

The investigators reported that at 2 weeks, 57.1% of the mothers receiving single dose nevirapine had detectable nevirapine resistance vs 0% in either of the other two arms. At 6 weeks resistance was detected in 53.3%, 5.00% and 13.6% of mothers receiving single dose nevirapine, single dose nevirapine plus 4 days Combivir and single dose nevirapine plus 7 days Combivir respectively. They noted that 9/18 (50%), 1/20 (5%) and 3/23 (13%) of mothers from the three groups had detectable resistance at any time after baseline. Overall resistance was detected in 50% receiving single dose nevirapine and in 9.3% of those receiving nevirapine plus Combivir (p=0.001). The most frequently detected mutations at any time were the K103N and the Y181C. There was no resistance to either zidovudine or lamivudine.

Following these dramatic results, enrolment into the single dose nevirapine arm of the study was closed in June 2004. McIntyre explained: "The trial was originally powered expecting 20% resistance in the nevirapine arm but emerging data, notably Neil Martinson's Retrovirus report of 39%, suggest the real figure is much higher…" The trial is continuing with adjusted sample size (150 mothers in each arm) to compare 4 and 7 days of Combivir as the optimal duration of this supplementation is uncertain. [2]

The trial was not powered to look at efficacy but of the 68 evaluable infants, four were infected through intrauterine transmission and one peri- or post-partum in the single dose nevirapine alone group.

C O M M E N T

Prior to the presentation of these results, on 14 July, the WHO announced the publication of their new guidelines on preventing mother to child transmission of HIV [3]. Key recommendations include:

i) **Treatment for maternal disease if indicated**

ii) **Prophylaxis for MTCT if treatment not indicated or not available and described as follows:**

- **Zidovudine from 28 weeks of pregnancy plus single-dose nevirapine during labour and single-dose nevirapine and one-week zidovudine for the infant;**
- **Alternative regimens based on zidovudine alone, short-course zidovudine + lamivudine or single-dose nevirapine alone are also recommended.**

The guidelines also acknowledge the issue of resistance: "Drug resistance linked to short-course regimens to prevent mother to child transmission that do not fully suppress the virus has been known since early 2000…Since these women are all expected to eventually require treatment, potential resistance has become a far greater concern." Continuing: "New data being presented at the International AIDS Conference in Bangkok may offer a way of reducing resistance observed shortly after delivery and needs to be further assessed before any recommendation can be made to use this approach in programmes to prevent mother to child transmission."

Tim Farley, from the WHO Department of Reproductive Health and Research explained: "We now have access to the full (McIntyre) data, this will be reviewed by the panel and we expect to issue a statement to accompany the guidelines. This appears to be a promising approach but it may be premature to make recommendations based on these preliminary results. Results from a similar study are expected in the next few months – a sub-study of DITRAME Plus – that also covers the nevirapine tail with Combivir. Those data are currently being analysed."

Additionally the WHO will soon initiate their own study providing comprehensive care to HIV-positive pregnant women and assessing the safety and effectiveness of using combination antiretrovirals to reduce the risk of HIV transmission to the infant. The overall objective is to optimise the use of ARVs during pregnancy, delivery and the postpartum period in order to (a) preserve the health of the mother, (b) minimise the risk of MTCT, and (c) provide a safe alternative to replacement feeding.

Both the risk of MTCT and the risk of maternal AIDS or death are strongly associated with the maternal stage of HIV-disease. Transmission and progression risks are increased for women in advanced stages of HIV disease as measured by clinical stage, CD4+ cells count or viral load.

- **Over 500 CD4 cells/mm^3 the risk of maternal progression to AIDS is low, currently recommended short-course MTCT prophylaxis ARV regimens are highly effective and the risk of transmission during breastfeeding is very low. Therefore, a short-course MTCT prophylaxis ARV regimen and counselling on safer infant feeding practices appears sufficient for this group of women.**
- **By contrast, women with CD4 counts below 200 cells/mm^3 have a high risk of rapidly progressing to AIDS and death, and of transmitting HIV to their child despite the use of short-course MTCT-prophylaxis ARV regimens. WHO recommends that such women be treated with long-term Highly Active Antiretroviral Therapy (HAART) for their own health. Starting HAART during pregnancy or lactation is likely to substantially reduce the risk of MTCT.**
- **The situation for women with CD4 counts between 200 and 500 cells/mm^3 is much less clear: although triple-ARV combinations may help reduce MTCT rates, the well-known toxicity of antiretrovirals may offset their efficacy in MTCT reduction. Furthermore, a CD4 cell count of 200-500 cells/mm^3 is not currently an indication for HAART in developing countries. Further research is needed to define the best MTCT-prevention strategy for this group.**

The project divides women into three groups according to their disease stage assessed during late pregnancy.

- **Women with CD4 counts below 200 cells/mm^3 or who are clinically ill will be offered triple-ARV therapy for their own health and continued through pregnancy, delivery and as long as required.**
- **Women with CD4 counts above 500 cells/mm^3 will be offered a short-course regimen consisting of zidovudine starting form 34-36 weeks plus single-dose nevirapine during labour (and possibly cover the nevirapine tail following these data).**
- **Women with intermediate CD4 counts (in the range 200–500 cells/mm^3) will be randomised to receive the short-course or the triple-combination regimen which will be continued up to six months provided the mother chooses to breastfeed her infant.**

All infants will receive single-dose nevirapine within 72 hours of birth.

The health of all women will be carefully monitored and any mother whose health deteriorates and requires ARV treatment will be offered treatment during the project. In order to ensure sustainability of the programme beyond the life of the project, partnerships are being built with existing or developing access to treatment programmes so that long-term care of the participants and their families can be assured.

The project is a partnership between the local and national MTCT and ARV access programmes and international agencies working to improve maternal health and MTCT-prevention programmes. It is due to start shortly in three sites in Africa – Bobo Dioulasso (Burkina Faso), Mombasa (Kenya) and Nairobi (Kenya) –supported by grants from the French Agence Nationale de Recherche sur le SIDA (ANRS), the Belgian Technical Cooperation and WHO, and the USA Centers for Disease Control and Prevention and National Institutes of Health, and respectively. Additional funds are being sought by the project team in order to extend the project to Durban (South Africa), Kigali (Rwanda) and Moshi (Tanzania). When complete a total of 2400 women and their infants will have been treated by the programme.

The results from the project will be very important in determining how to balance the risk and benefits of combination ARVs in pregnant

women, and are expected to influence international and national guidelines, as well as being implemented in public sector and private sector maternal health and MTCT-prevention programmes.

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3. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings. WHO document. http://www.who.int/hiv/pub/mtct/guidelines/en/

Lopinavir/r levels reduced during pregnancy

Polly Clayden, HIV i-Base

Pregnancy can alter the pharmacokinetics (PK) of antiretrovirals and it is well known that optimal exposure during pregnancy is essential both for maternal health and preventing mother to child transmission. In an oral late breaker, Alice Stek presented preliminary findings from a small sub study of PACTG 1026 – an ongoing study of PK in HIV-infected women.

This study compared data from intensive PK profiles (over 12 hours) performed at 30-36 weeks gestation obtained from 12 women receiving lopinavir/ritonavir 400/100mg twice daily to non-pregnant controls and to post partum measurements at 6-12 weeks (available for 4 women). Maternal and cord blood samples were also obtained at delivery.

Target LPV AUC was >10th percentile (52mcg*hr/mL) and the investigators reported that 10 of the 12 women did not reach this target – the average antepartum LPV AUC was 44+- 17mcg*hr/mg (95%CI 34-54). Of the 4 women for which post partum evaluations were available 1/4 did not reach the target LPV AUC. Maternal and cord blood samples were available for 5 maternal infant pairs and these revealed an average foetal exposure of 23% of maternal LPV concentration indicating that only small amounts of LPV appear to cross the placenta.

Findings from this small study suggest lower LPV exposure during the third trimester of pregnancy compared to non-pregnant controls and to post partum exposure. Dr Stek explained that this ongoing study would be modified to enrol women in the second trimester to investigate increased dosing of LPV/r in pregnancy.

Ref: Stek A, Mirochnick M, Capparelli E et al. Reduced lopinavir exposure during pregnancy: preliminary pharmacokinetic results from PACTG 1026. XV Intl AIDS Conference, Bangkok. Abstract LbOrB08.

BANGKOK: ANTIRETROVIRALS

Another chance for 3TC in patients with M184V mutation?

Simon Collins, HIV i-Base

The continued use of 3TC to maintain 3TC-associated M184V mutation because of the theoretical impact on viral fitness is supported by several early and persuasive studies. However, no clinical benefit was found in the long-enrolling Colate study when results were eventually presented earlier this year at CROI. [1] Colate had randomised patients on failing 3TC-containing treatment to either stop or maintain 3TC in their subsequent regimen.

Castagna and colleagues from Vita-Salute San Raffaele University, Milan took a different approach. They randomised patients failing treatment (median VL approx 7,000, IQR 3,000 – 15,000) with relatively high CD4 counts (median > 600 cells/mm^3, IQR approx 560-750) to either discontinue treatment completely (arm A) or continue with 3TC monotherapy (arm B). The primary endpoint was progression to immunological failure defined as CD4 count failing to <350 cells/mm^3. [2]

Results were presented on 45/50 pts: 24 in arm A and 21 in arm B. Discontinuation occurred in 21 patients due to viral failure, one patient who withdrew consent and one patient with oesophageal thrush, and occurred more frequently in patients who discontinued all treatment 14/24 (58%) vs 9/21 (43%).

Although statistical significance analysis was not provided, the nine patients remaining on study taking 3TC showed a protective effect on both CD4 count and virological rebound.

Median (IQR) change in CD4 and viral load:

	Arm A (N=22; NoRx)		Arm B (N=18; 3TC mono)	
	Disc.	On Study	Disc.	On Study
N	14	8	9	9
Delta CD4	-169	-187	-111	+23
(IQR)	(-278/-110)	(-259/-9)	(-159/-93)	(-43/+38)
~ delta VL	91k	76k	15k	6.6k
(IQR)	(42-124k)	(58-160)	(13k-20k)	(1k18k)

The study concluded that these preliminary results support the hypothesis that 3TC monotherapy reduces the frequency of immunological failure and induces less viral rebound than therapy interruption.

C O M M E N T

These results are very interesting, despite low numbers (and lack of statistical analysis!). The interest in a beneficial effect of using 3TC is of course driven by its low toxicity. The cost of 3TC is likely to fall further once 3TC comes off-patent.

It is frustrating that from the tens of thousands of people either using 3TC or with 184V resistance that a larger set of supporting data for this simple approach has still not been assembled.

References:

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2. Castagna A, Danise A, Carini E et al. E-184V. Pilot study to evaluate immunological response to lamivudine monotherapy vs treatment interruption in failing HIV-1 infected subjects, harbouring the M184V mutation. XV Intl AIDS Conference, Bangkok. Abstract WeOrB1286. http://www.ias.se/ejias/show.asp?abstract_id=2175034

Kaletra monotherapy: small studies and early data

Simon Collins, HIV i-Base

At last year's IAS conference in Paris, several studies reported on ritonavir boosted PI monotherapy using either indinavir or lopinavir/r both as maintenance therapy and first-line therapy.

In an oral session, Joe Gathe presented 48-week results from lopinavir/r monotherapy in 30 treatment naive patients (28 male, 2 female) treated at a public hospital in Texas. It was emphasised that a large part of the rationale for this choice of treatment was the cost of standard therapy for these patients. [1]

18 patients were white, 6 black and 6 Hispanic. Mean age was 36 years, mean viral load was 262,000 copies/mL (17 subjects had viral load > 100,000 copies/mL) and mean CD4+ cell count, 170 cells/mm^3.

The 24-week results reported last year were generally maintained out to 48 weeks.

By intent-to-treat analysis, 20/30 patients (67%) achieved viral load < 400 copies/mL and 18 (60%) achieved viral load < 50 copies/mL. Mean increase in CD4 cell count was 317 cells/mm3. Ten subjects discontinued treatment: loss to follow-up 2; adverse events (GI related) 2; non-adherence 2; virologic failure 2; deportation from the US 1; hepatitis B 1.

Several case histories were provided for treatment that failed on various occasions, often due to interruption related to health insurance or cost of treatment, and universal treatment access is still clearly a major issue in the US.

Four patients received intensification with tenofovir/3TC/ and/or saquinavir, including 1 with hepatitis B who used tenofovir/3TC. Potential explanations for incomplete suppression to < 50 copies/mL on lopinavir/r alone included poor adherence, incomplete absorption/metabolisation/bioavailability of lopinavir/r and possible development of resistance not detected by assays used.

In conclusion, Gathe emphasised that this was not an approach that is ready for general clinical application but that it is should continue to be studied in clinical trials.

The interest in boosted monotherapy was shown by four (five??) other studies in the poster sessions with similar study designs.

Arribas and colleagues reported on a study carried out in four hospitals in Madrid, that randomised (1:1) 42 patients on maximally suppressed LPV/r-based treatment (50 copies/mL for at least six months) to either use lopinavir/r monotherapy or continue lopinavir/r with two background RTIs. [2]

Baseline characteristics were similar: median CD4 cells/mm3 (662 vs 585), CD4 nadir (146 vs 145), HIV log10 viraemia prior to HAART (5.11 vs 4.85) or months with HIV RNA < 50 c/mL (11 vs 9), in the mono and triple therapy arms respectively.

Results at 24-weeks:

	LPV/r mono	LPV/r + 2RTIs
% < 50 copies/mL (ITT, NC=F)	81%	100%
Treatment failures	3/21	0/21
Mean change in CD4	+50	+3

The three failures were: at week 12 (VL 3,600, after a 3-month period of 59% compliance; L63P present at rebound but also present in a pre-HAART sample, subsequently patient discontinued treatment), at week 24 (VL= 1,270, no mutations, results of reinduction pending) and week 24 (VL=564, no mutations, HIV-RNA < 50 copies/mL after 4 weeks of reinduction). Patients with viral rebound had shorter time with VL < 50 than patients without failure (218 vs 1095 days; P = .002).

One patient in each arm was on lipid lowering agents at the start of the study, and by week 24, this increased to two patients in the monotherapy arm and three in the triple arm. It was suggested in a separate poster analysing lipids changes in this study, that d4T discontinuation was a cofounding factor in lipid changes. [3]

Pierone and colleagues from AIDS Research and Treatment Center of the Treasure Coast, Ft. Pierce, United States, looked at LPV/r monotherapy as maintenance therapy for patients previous suppressed on an NNRTI + dual RTI combination. With only 18 patients and a mean follow-up of 18 weeks (range 4-24 weeks) this is too early to be presenting these results. [3]

Nevertheless, four patients have already discontinued (3 due to diarrhoea at or before week 8, one with virologic failure with viral load 1,067 at week 12).

Two patients with baseline impaired glucose tolerance developed diabetes mellitus. Both are controlled and continue on study and three patients have added lipid-lowering therapy on study.

Based on these preliminary results this writer would disagree with the researchers conclusion that 'this is one of the first prospective studies showing effectiveness and tolerability of simplification to LPV/r monotherapy'. In this instance, the intervention in a small group of patients on stable NNRTI-based therapy led to both virological failure and new toxicity.

Finally, Ruane and colleagues from private practice in Los Angeles, switched 18 patients with a history of viral suppression <50 copies/mL for at least nine months to lopinavir/r monotherapy. [5] An additional safety consideration in this study was to use therapeutic drug monitoring to ensure that all patients had sufficiently high trough levels (> 3.0 ug/mL) prior to the switch.

Percentages of patients with viral suppression using monotherapy with LPV/r:

	B/line	Wk4	Wk8	Wk 16	Wk 24
N	18	18	18	13	6
VL <400	100%	100%	100%	100%	100%
VL <50	100%	100%	93%*	92%^	67%#
CD4	623	651	718	682	671

* Pt 7-blip to 185, returned to <50 next visit; ^Pt 14-blip to 387, next visit 150;

#Pt 7- blip to 79, pt 10-blip to 327

Mild to moderate GI complaints were the most frequently reported adverse event. Although viral rebound is reported as 'blips' the long term significance of this has not been established. Only having six patients at week 24 must question the value of presenting this early data.

The lack of a control arm to evaluate frequency of blips in triple therapy will also make the results difficult to interpret.

C O M M E N T

Although there were several posters on use of lopinavir/r monotherapy, apart from the Gathe study, these were generally too small and short term to contribute much new insight into this approach.

If boosted-PI monotherapy can produce or maintain sustained viral suppression in a large group of patients, the additional contribution of nucleosides in traditional three-drug regimens needs to be understood. While issues of drug penetration and sanctuary sites cannot

be addressed in short studies, continued suppression <50 copies/mL after a year becomes very interesting. If this was a short term effect, and resistance developed in sanctuary sites, you would expect to see viral rebound in plasma RNA by 48 weeks.

Conflicting results have been reported looking at maximizing the slope of viral load reduction in the first days and weeks of treatment. Using more potent regimens to reduce viral load more quickly to <50 copies/mL, reducing also the potential exposure to the development of resistance, has scientific plausibility and was supported by early studies. Other research has suggested that viral dynamics may include a maximum rate limited reduction, and that recommended efavirenz- and lopinavir/r- based combinations provide this maximum potency.

The appeal of nucleoside-sparing regimens is largely to avoid side effects associated with nucleoside analogues associated with higher levels of mitochondrial dysfunction. This may be less of an issue with more recent approved drugs in this class. Tolerability of the boosted-PI approach is just as important to consider, shown by significant discontinuation rates in the some of these studies.

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   http://www.ias.se/ejias/show.asp?abstract_id=2174887

Lowering dose of d4T can maintain efficacy and reduce side effects

Simon Collins, HIV i-Base

As ARV programmes slowly increase access to treatment in resource-poor countries, it is important not to repeat the same mistakes made in patient management in the West. Prolonged use of d4T, in particular, left many patients with permanent and debilitating peripheral neuropathy or substantial lipoatrophy. The incidence of both these side effects is higher when treatment is started in more advanced disease, and this is often the case in access programmes.

Earlier this year, in reports from the 11th Retrovirus conference (CROI), we detailed several studies showing that the incidence of these side effects is similar to that seen in the West. More importantly several studies showed that using a lower dose of d4T provided similar efficacy and reduced toxicity. [1]

Several further studies at Bangkok provided further data on this approach.

In a retrospective analysis, Haslinger and colleagues from University Hospital of Duesseldorf, looked for CNS effect and side effects in 627 patients treated with different d4T doses in combination with another NRTI (3TC, TNF, ddI) plus either an NNRTI or protease inhibitor (PI) for CNS. [2]

444 HIV-1-positive patients treated with 80 mg d4T/day and 89 individuals treated with 60 mg/day were compared for CD4+-cell counts, plasma viral load (VL), nerve conduction velocity (NCV), amplitudes of peroneal and surale nerve action potentials (EMAP and SNAP) and motor speed - contraction time (CT) as well as reaction time (RT) - as parameters for brain affection with respect to effectivity (at least stable reaction and contraction times) and side effects (NCV, EMAP, SNAP) over a period of 6 months.

Other causes for peripheral nerve disease were excluded, before including data in the study.

Over six months there was no statistically significant difference between the high and the low dose group with respect to CD4+-cell count and motor speed parameters. Polyneuropathy was rarer in patients receiving 60 mg/day. Although viral load was significantly lower in patients receiving 80 mg/day this could be due to the other antiretroviral drugs applied in combination with d4T in these patients.

Siangphoe and colleagues presented 96-week results from a Thai study comparing half-dose to full dose d4T. [3] This study was started in February 2000 when dual-nucleoside therapy was the most advanced treatment available. The second RTI was

ddI. A third comparitor arm used AZT+ddI. Doses of d4T and ddI were adjusted by weight in people who weighed <60kg. Median body weight was 54.4 kgs.

Multivariate logistic regression showed the likelihood of VL <500 c/ml was significantly greater in both d4T groups compared to the AZT group; if baseline VL <10,000 c/ml; and baseline CD4 200 – 350 vs <200 /mm3. There was no significant difference between groups d4T half dose vs full dose.

Serious lactic acidosis was found in 3 patients in the full dose d4T group.

Although dual-therapy would not be recommended now, the use of more potent triple combinations that would improve response rate are likely to further reduce the importance of the d4T contribution to the regimen.

	Half dose d4T+ddI (d4T 30 or 40 mg/d)	Full dose d4T+ddI (d4T 60 or 80 mg/d)	AZT+ddI	
N	109	110	108	
B/line CD4	290	282	240	
range	(202.5 - 355)	(177.5 - 378.5)	(151 - 361.3)	
B/line VL	4.2 (3.8 - 4.5)	4.3 (3.7 - 4.6)	4.3 (3.9 - 4.6)	
CDC stage C	4.6% *	4.5% *	14.8%	
Week 96 results:				
pts VL <500	33%*	47.3%*	9.3%	
pts VL <50	5.5%	12.7%	2.8 %	
CD4 change	131*	126*	0	
range	(30 - 253)		(20.5 - 260.3)	(-37.5 - 95)

**group 1 or 2 vs 3, p < 0.01*

References:

1. Treatment with generics: tolerability, safety and resistance. HIV Treatment Bulletin, Vol 5 No 3, April 2004 http://www.i-base.info/pub/htb/v5/htb5-3/Treatment.html
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BANGKOK: SIDE EFFECTS

Three-year renal safety with tenofovir; cystatin may be a useful marker

Simon Collins, HIV i-Base

Tenofovir is now widely used in treatment naïve patents and 3-year data presented at the conference showed in several analysis from the 903 Study and numerous smaller studies continued to support its improved lipid profile and reduced peripheral lipoatrophy and neuropathy, when used with 3TC and efavirenz, and compared to d4T. [1]

Several posters also showed more surprisingly that the incidence of kidney-related side effects including increased creatinine, proteinuria and renal failure may not be higher in patients using tenofovir in their combination, or compared to patients not on treatment. In the 903 Study <1% in each arm (2/296 in each arm) developed serum creatinine >2.0 mg/dL and mean change from baseline in creatinine clearance (ml/min) was greater in the d4T than TDF arm (+7 vs +1). [2]

Stebbing and colleagues, in a case control anaylsis classified patients with creatinine ever >120 umol/l in a large clinic database by antiretroviral exposure and found a lower rate in patients on treatment including tenofovir, compared to those who were antiretroviral naïve (rate ratio versus no anti-ARV 0.22, 95% CI 0.07 to 0.69, p < 0.001). [3] Of the 1,058 individuals who were exposed tenofovir DF, 84 patients (8%) experienced a creatinine > 120 mmol/l subsequent to exposure. An alternative aetiology of renal dysfunction was found in 75 (90%) of these individuals.

Preexisting kidney dysfunction, or concomitant use of other nephrotoxic medications does appear to increase the risk of nephrotoxicity though. [4] For example, in a retrospective chart review from May 2002 to September 2003 of 507 patients

attending Jackson Memorial Hospital, Miami, Chin-Beckford and colleagues indentified six patients whose creatinine increased with tenofovir and normalised upon discontinuation. Mean age was 53 years and 5/6 subjects had either hypertension or diabetes or both. Most subjects did not have a renal dose adjustment for tenofovir.

Another study showed that cystatin levels may be more sensitive marker for tenofovir-associated kidney dysfunction. Mauss and colleagues measured serum and urine levels of creatinine, cystatin C and electrolytes over 24 hours in 74 patients using tenofovir and 84 patients who had never used tenofovir. Diabetes mellitus, hypertension, liver cirrhosis or known renal disease were exclusion criteria for the study. [5]

Results showed statistically significant differences in cystatin clearance (normal >80 ml/min) between the two groups, but no differences in electrolytes and creatinine were observed. No patient had a nephrotic or fanconi-like syndrome and proteinuria in three patients resolved on discontinuation of tenofovir.

	TDF	No-TDF	
N	74	84	
Mean cystatin clear. (ml/min)	87–21	96–20	(p<0.01)
Cystatin <80 ml/min	28 (38%)	21 (25%)	(p=0.08)
Mean protein in urine (mg/d)	118–114	96–58	(p<0.05)
Proteinuria (>130 mg/d)	26 (35%)	15 (18%)	(p<0.02)

(+/- mild glomerular damage)

Cystatin may therefore be a more sensitive marker than creatinine, that could be used in the future to help identify patients at risk from renal toxicity prior to using tenofovir, and in monitoring patients using this drug.

Appropriate tenofovir dosage adjustments for patients with renal dysfunction are included in the product characteristics and should be used appropriately. Renal function is especially important in patients with advancing age and co-morbidity factors including diabetes and hypertension.

References

All references are to the programme and abstracts of the XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand.

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http://www.ias.se/ejias/show.asp?abstract_id=2169665

2. Staszewski S, Gallant JE, Pozniak AL et al. Three-year analysis of the renal safety of tenofovir DF (TDF) versus stavudine (d4T) when used in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral-naïve patients. Abstract WePeB5917.
http://www.ias.se/ejias/show.asp?abstract_id=2176085

3. J Stebbing, M Nelson M et al - Renal dysfunction with tenofovir DF containing HAART regimens is not observed more frequently: a cohort and case control study. Abstract WePeB5893.
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3. Chin-Beckford N, Kaul S, Jayaweera DT -Comorbidities drive nephrotoxicity associated with tenofovir fumarate. A case series from Florida. Abstract WePeB5970
http://www.ias.se/ejias/show.asp?abstract_id=2167221

4. Mauss S, Berger F, Carls H et al - Tenofovir is associated with mild renal dysfunction. Abstract WePeB5941.
http://www.ias.se/ejias/show.asp?abstract_id=2168151

BANGKOK: PK AND DRUG INTERACTIONS

Fluconazole increases nevirapine levels and risk of serious hepatotoxicity

Simon Collins, HIV i-Base

A South African study from Geel and colleagues reported the new data on the potential effect of fluconazole to increase nevirapine plasma levels.

In a single-centre, open-label, single-arm trial the pharmacokinetic parameters of fluconazole were measured alone and in combination with nevirapine in 24 patients on a stable regimen of three nucleoside analogue antiretrovirals.

The nevirapine effect on fluconazole pharmacokinetic parameters was minimal. However, the clearance of nevirapine was halved during concomitant administration of fluconazole resulting in an approximate doubling of nevirapine Cmin, Cmax and AUC.

95% of drug-related adverse events occurred during the period of co-administration of nevirapine and fluconazole.

During this phase 25% (CI 7-43%) of patients developed serious hepatotoxicity including two cases of clinical hepatitis (8.3%) and four cases of transient grade-4 transaminase elevation (16.7%).

The incidence of serious hepatotoxicity with the combination (25.0%) was much higher than reported in other studies using nevirapine alone (8.8%).

The authors concluded that because of pharmacokinetic interaction and the apparent increased incidence of toxicity, the combination of nevirapine and fluconazole should be used with caution.

Reference: Geel J, Pitt J, Orrell CJ et al. The effect of fluconazole on nevirapine pharmacokinetics. XV Intl AIDS Conference, Bangkok. Abstract TuPeB4606.
http://www.ias.se/ejias/show.asp?abstract_id=2170472

C O M M E N T

These results need to be confirmed. This study lacked an interpatient comparison, and only compared treated patients with historical controls of nevirapine used without fluconazole, who are likely to have different patient characteristics.

If both drugs are used together, additional monitoring for nevirapine toxicity should be included.

Itraconazole may be a safer option for treating non-CNS fungal infections and perhaps should be the agent of choice for non-invasive candidiasis in patients on nevaripine.

Efavirenz interaction with rifampin may not require dose adjustment in patients with low body weight

Simon Collins, HIV i-Base

Treatment guidelines for patient requiring treatment for both HIV and TB currently recommend increasing the dose of efavirenz from 600mg to 800mg daily in patients using rifampin-based TB regimens. This has difficult logistic and cost implications especially for treatment in patients using WHO-recommended fixed-dose combinations that include efavirenz. These recommendations are based on pharmacokinetic interaction studies.

Manosuthi and colleagues from Mahidol University, Bangkok presented results from the first clinical trial comparing 600mg to 800mg efavirenz (with d4T and 3TC) in patients on stable rifamicin treatment. Plasma efavirenz level was measured (at 12 hours after dosing, on day 14) by HPLC. CD4 and HIV RNA were assessed at 16, 24, 36, and 48 weeks.

Preliminary results of 70 patients (37 in group A and 33 in group B) were presented. The follow-up period ranged from 16 to 36 weeks. The groups were evenly balanced on all important baseline characteristics. Mean body weight and BMI was about 50 kg and 19 kg/m^2. Median baseline CD4 counts were 29 (range; 1, 224) cells/mm^3 and 46 (0, 384) cells/mm^3 in group A and B, respectively. Median efavirenz levels were 3.97 mg/L (0.07, 12.21) and 3.39 mg/L (1.03, 21.31) in group A and B, respectively. Three patients in group A, but no patient in group B, had efavirenz level <1 mg/L ($p = 0.347$). Median time to virological success (HIV RNA <50 copies/mL) was 16 weeks in group A and 19 weeks in group B ($p = 0.960$). Median CD4 increase from baseline to week 16 was around +898 cells/mm^3 in each arm.

CNS toxicity was found in 13 and 11 patients in groups A and B, respectively ($p = 0.675$). One patient in group A had to discontinue efavirenz.

Ref: Manosuthi W, Sungkanuparph S, Vibhagood A, et al. A randomised controlled trial of efavirenz 600 mg/day versus 800 mg/day in HIV-infected patients with tuberculosis to study plasma efavirenz level, virological and immunological outcomes: a preliminary result. XV Intl AIDS Conference, Bangkok. Abstract MoOrB1013.
http://www.ias.se/ejias/show.asp?abstract_id=2171015

C O M M E N T

Although median efavirenz levels were similar in each group, the range varied considerably. There is an obvious concern for the three patients in arm A with very low levels. As weight is referred to in the study it will be interesting to see any correlation between weight and drug levels in the final analysis. This is clearly a factor in Asia and often in Africa.

Tipranavir significantly lowers doses of saquinavir, amprenavir and lopinavir/r

Simon Collins, HIV i-Base

Interaction data were presented again from the BI 1182.51 study using tipranavir with additional protease inhibitors in extensively PI-experienced patients. [1] Although management of treatment-experienced patients has often included multiple-PI and boosted-PI regimens, the negative interaction of tipranavir in reducing levels of saquinavir, amprenavir and lopinavir/r must be remembered.

HTB reported this data in full when it was presented at the pharmacology workshop earlier this year, and no new data was added to the analysis in Bangkok. [2]

Tipranavir is available in the UK on an expanded access programme.

References

1. Walmsley S, Leith J, Katlama C et al. Pharmacokinetics and safety of tipranavir/ritonavir (TPV/r) alone or in combination with saquinavir (SQV), amprenavir (APV), or lopinavir (LPV): interim analysis of BI1182.51. XV Intl AIDS Conference, Bangkok. Abstract WeOrB1236. http://www.ias.se/ejias/show.asp?abstract_id=2166920
2. See HTB Vol 5 No 4, May 2004. http://www.i-base.info/pub/htb/v5/htb5-4/Large.html

BANGKOK: HEPATITIS COINFECTION

Responses to hepatitis vaccinations: an optimum window for protection?

Simon Collins, HIV i-Base

HIV-positive people often belong to groups associated with high risk for hepatitis infection, and guidelines therefore recommend screening HIV patients for hepatitis A, B and C when diagnosed with HIV, and subsequent vaccination for hepatitis A and B when antibodies for either virus is not present.

However, the effectiveness of vaccinations is reduced even with relatively low reductions of CD4 levels. CD4 increases following HAART have previously been reported not to return to earlier response levels with all vaccines, so there is may be only a short window period to obtain protection for many HIV-positive individuals.

Several interesting poster presentations contributed to understanding determinants of vaccine response, and one study suggested that this could be safely increased by doubling the dose of vaccine used in HIV patients.

HBV vaccine, CD4 count and increasing response with double-dose

Veiga and colleagues from Brazil reported response rate by CD4 count to hepatitis B vaccination in 55 HIV-positive patients and 20 HIV-negative controls, who had received 3 doses (0, 30 and 180 days) of recombinant DNA hepatitis B vaccine. [1]

The overall HBV vaccine seroconversion rate was 59% (32/55) for HIV+ group, and 100% the 20 controls. Response rate by CD4 count at the time of vaccination were 81%, 65% and 25% in patients with >500, 200-499 and <200 cells/mm3 respectively.

The median CD4+ count at the time of vaccination among responders was 452 cell/mm^3, significantly higher than in non-responders (359 cells/mm^3, 20%, p=.03). Memory T CD4+ cells were also significantly (p=.04) higher in responders (255 cells/mm^3) than in non-responders (178 cells/mm^3). In addition, viral load at the time of immunisation was significantly (p=.03) higher in non-responders (3.63 log^{10}) than in responders (2.86 log^{10}). Seven HIV-1-infected patients experienced a significant viral load increase, transient in five cases.

Response to HBV vaccine by CD4 count at vaccination (anti-HBs>10 UI/L):

CD4 count (cells/mm^3)	Response rate
>500	81%
200-499	65%
<200	25%

However, a larger study from Overton and colleagues at the Washington University School of Medicine, did not find a link with vaccine response and CD4 count. [2]

Of 342 recipients of regular 3-dose HBV vaccination programme, 149 subjects had complete data for evaluation; 35.6% were male, with a mean age of 34.3 years and baseline CD4 + T cell counts 429 cells/mm^3.

In this cohort, only 18 patients (12.1%) developed protective HBsAb (> 10mIU/mL).

Baseline characteristics and timing of vaccine administration were not statistically different among responders and non-

responders. Factors associated with a protective antibody response included male gender (p=0.001), older age (p=0.002), and an HIV plasma RNA level < 400 copies/mL at time of vaccination (p<0.001). Neither the CD4 cell counts at time of vaccine nor preceding CD4 cell nadir was predictive of successful response.

A strategy to improve response rates was suggested in a study by Fonseca and colleagues from University Medical School of Sao Paulo. This group randomised 210 patients to use either standard (20ug) or double dose (40ug) (given at 0, 1, 6 months, IM) to see whether this would increase response rates. [3]

Response rate (anti-HBs >10mIU/mL) was 47% for the double dose and 34% for the standard dose. A logistic regression model, showed a statistically significant higher seroconversion rate with the double dose, a history of HIV heterosexual exposure, CD4 cell counts >= 350 and HIV viral load < 10,000 copies/mL.

This study concluded that the best current strategy for a HBV vaccine response in HIV patients would be to use a double dose as a primary series when the viral load is likely to be low and when there is likely to be an adequate immune response. This might be early in the course of infection or following successful HAART.

A second study from Brazil, reported response rate of 47% using the double-dose strategy, and that responders had significantly higher CD4 counts than non-responders. However the study abstract contained no further breakdown by CD4 levels. [4]

References:

1. Veiga APR, Casseb J, Duarte AJS - Efficacy to hepatitis B vaccination and its relationship with T CD45RA+ (naive) and CD45RO+ (memory) subsets in HIV-1-infected subjects. XV Intl AIDS Conference, Bangkok. Abstract B10392.
   http://www.ias.se/ejias/show.asp?abstract_id=2170874
2. Overton ET, Sungkanupargh S, Seyfried W et al. Protective immunity after hepatitis B vaccination in HIV-infected persons: Does an undetectable HIV RNA level predict success? XV Intl AIDS Conference, Bangkok. Abstract MoPeB3284.
   http://www.ias.se/ejias/show.asp?abstract_id=2171751
3. Fonseca MO, Pang LW, 2, Cavalheiro NP et al. Randomised trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. XV Intl AIDS Conference, Bangkok. Abstract MoPeB3312.
   http://www.ias.se/ejias/show.asp?abstract_id=2175659
4. Conference Góngora DVN, Góngora-Rubio F, Onishi E et al. Serological responses to hepatitis B vaccination in HIV infected patients. XV Intl AIDS Conference, Bangkok. Abstract B10109.
   http://www.ias.se/ejias/show.asp?abstract_id=2169929

Response to Hepatitis A (HAV) vaccine determined by CD4 count

Rimland and colleagues from the VA Medical Center, Atlanta, Georgia analysed responses to hepatitis A vaccine in 214 patients who were vaccinated between 1996 and 2003 (standard dose and schedule).

Overall, 130 of 214 vaccinated individuals developed HAV antibody (61%). Response rate by CD4 count at time of vaccination were 83%, 62%, 39%, 27% and 8% in patients with CD4 >500, 201-500, 101-200, 51-100 and <50 cells/mm^3 respectively (p<0.0001).

In a multivariate analysis, only CD4 at time of vaccination (and not CD4 nadir) was associated with absence of response (p<0.0001). HCV infection was not associated with response.

The study concluded that determination of hepatitis A antibody after vaccination should be considered in all HIV patients receiving HAV vaccine. CD4 at time of vaccination is the critical determinant of response to HAV vaccine. Also, that the absence of a multivariate association with nadir CD4 suggested that patients may respond to HAV vaccine after immunologic reconstitution in response to HAART.

Response to HA vaccine by CD4 count at time of vaccination:

CD4 count (cells/mm^3)	Response rate
>500	83%
201-500	62%
101-200	39%
51-100	27%
<50	8%

Reference: Rimland D, Guest JL. Response to hepatitis A vaccine in HIV patients in the HAART era. XV Intl AIDS Conference, Bangkok. Abstract MoPeB3299 (this report based on revised abstract in poster).

http://www.ias.se/ejias/show.asp?abstract_id=2174521

C O M M E N T

These two sets of studies underpin the importance of early consideration of Hepatitis A and B vaccination in HIV-infected patients and

in particular patients co-infected with HCV.

Overall, CD4 counts at time of vaccination, rather than nadir CD4 counts, seem to be an important factor in determining response to hepatitis A (as judged by appearance of antibodies in HAV). Therefore, early use of vaccination is optimum, but as demonstrated by Rimland et al, there is a 60% or more response for HAV vaccine with CD4 counts over 200 cells/mm^3.

The use of double-dose vaccination in hepatitis B is a strategy already adapted by renal physicians for patients on dialysis, and Fonseca and colleagues provide evidence that this may be applicable in HIV-infected patients as well.

BANGKOK: PAEDIATRICS

Inventive ways to explain HAART and adherence to children

Simon Collins, HIV i-Base

Inventive ways to explain complicated ideas behind HAART allow people of any age to have greater understanding and control over their treatment. Most healthcare workers and advocates have probably developed their own examples, but amid 100s of adherence-related posters one study from South Africa shared several creative ways to explain the importance of continued treatment and maintaining viral suppressions to children.

The first idea is to pour some pepper in a bowl of water. If you rub your finger with soap and put it in the middle of the floating pepper, the pepper immediately moves to the edge of the bowl. When you take it out it comes back again (though fairly slowly when this writer tried it). The pepper represents the virus and your soapy finger is the medicine. You need to always have the medicine present to reduce viral load.

A second idea is to use a tennis ball sized stress ball to represent the virus and your hand to represent the medicine. It is hard work to keep the stress ball compressed and hidden in your hand - but this shows that the medicine is powerful. If you relax or lift a finger though - ie if you miss a dose - then the virus comes back very quickly.

A third idea is to use a spinning top to represent treatment that is working - and that you need to regularly respin the top to keep it upright, just as you need to repeat doses of HIV medications at regular intervals to keep the treatment working.

Ref: Gous H, Moultrie HJA, Meyers TM for Wits Paediatric HIV working group, Johannesburg - Adherence interventions in children on anti-retroviral therapy at Harriet Shezi HIV Clinic, Chris Hani Baragwanath Hospital, South Africa. XV Intl AIDS Conference, Bangkok. Abstract WePeB5789.

Isoniazid has early and unexpected benefit in reducing childhood mortality

Polly Clayden, HIV i-Base

A South African oral late breaker presented by Martin Cotton evaluated the impact of isoniazid (INH) on mortality in a group of young HIV positive children.

This prospective double blind study conducted at two centres in Cape Town compared INH to placebo given in addition to co-trimoxazole (TMP-SMX) - either daily or three times a week - to a group of 278 HIV positive children with a median age of 23.5 months (range 3 to 123 months). Children in Cape Town have a 4% chance of developing active TB. The study was powered to look at the effect of isoniazid primarily on mortality and secondly on developing active TB.

The children received the INH in accordance with the TMP-SMX schedule. The majority (80%) of the children where symptomatic with HIV and 7% of the children receiving INH and 6% of children receiving placebo were receiving HAART.

Between the initiation of the study – which began enrolment in January 2003 – until May of this year, the investigators reported a total of 32 deaths: 20 in the placebo and 12 in the INH groups – an overall reduction of 53% in the INH groups.

They also noted that the survival benefit appeared early – within 50 days and occurred in all CDC disease stages and age groups although mortality risk was greatest in children less than 8 months old.

Although there was a higher instance of active TB in the children that received placebo -14 cases in placebo and 5 in the INX groups – this was not statistically significant.

Considering these findings the data safety monitoring board discontinued the placebo arm of the study. The study will continue to compare the daily and three times a week TB interventions.

Ref: Zar H, Cotton M, Lambard C et al. Early and unexpected benefit of isoniazid in reducing mortality in HIV-infected children in an area of high tuberculosis presence. XV Intl AIDS Conference, Bangkok. Abstract LbOrB12.

BANGKOK: TRANSMISSION

Lack of keratin overlaying inner foreskin may explain lower HIV infection rates in circumcised men

Simon Collins, HIV i-Base

McCoombe and colleagues from University of Melbourne presented results of a study designed to determine where HIV enters the penis, hoping to understand the reported lower incidence of circumcised men in many African countries.

They studied the distribution of target cells in the glans penis, frenulum, foreskin and urethral meatus from five uncircumcised penises obtained at autopsy and measured the thickness of the overlying layer of keratin. Keratin potentially prevents HIV gaining access to these penile receptors.

Langerhans cells, dendritic cells, macrophages and T-cells and keratin thickness were studied using histochemical staining techniques and microscopy.

HIV target cells expressing CD4 and CCR5 were found in the inner and outer foreskin, frenulum and glans penis, but at lower levels in the urethral meatus and penile urethra. Dendritic cells, macrophages and T cells expressing these receptors were observed in high densities in the dermis of all regions of the penis except the urethra. HIV susceptible Langerhans cells in the inner foreskin and frenulum were closer to the epithelial surface, but less frequent than in the outer foreskin and glans.

There was little if any protective covering of keratin overlying the inner foreskin and frenulum (Langerhans cells were within 4.5um of the epithelial surface), in contrast to the glans penis and outer foreskin which were heavily keratinized and (rarely coming with 20um of the epithelial surface), thus protecting them from viral entry.

The study concluded that HIV is likely to enter the penis of uncircumcised men via superficial Langerhans cells on the inner aspect of the foreskin and frenulum since these sites are not keratinised. These two area are also highly vascular and most prone to trauma. The major protective effect of male circumcision can best be explained by the removal of most HIV receptor sites in the foreskin and frenulum.

Ref: McCoombe SG, Cameron PU, Short RV - How HIV enters the human penis. XV Intl AIDS Conference, Bangkok. Abstract MoPeA3048.

TREATMENT ACCESS

A round-up of news about access to treatments with links to sources

Graham McKerrow, HIV i-Base

Effects of generic FDC similar to other HAART regimens, says study

A clinical trial in field conditions of a fixed dose combination (FDC) of generic versions of nevirapine, stavudine and lamivudine – called Triomune and increasingly commonly prescribed in the developing world – shows that its effectiveness and tolerability are similar to that reported with other HAART regimens in patients with comparable baseline HIV disease status.

This research is of vital importance because although generic FDCs are widely accepted as assisting adherence and have been prequalified by the World Health Organisation for use in poor countries and are widely used, they are not accepted by some of the major donor agencies owing to scarcity of clinical data on effectiveness, safety and quality.

Researchers from France, Cameroon and Médecins Sans Frontières, followed 60 patients in an open label, 24-week multicentre trial in Cameroon. The patients received one tablet of the FDC twice daily. The primary outcome measure was the proportion of patients with viral load less than 400 copies/mL at the end of the study period.

At baseline, 92% of patients (n=55) had AIDS; median CD4 count was 118 cells/mm^3 (IQR 78-167) and median plasma HIV-1 RNA was 104,000 copies/mL (~41,000-243,000). The proportion of patients with undetectable viral load (<400 copies/mL) after 24 weeks of treatment was 80% (95% CI 68-89). Median (IQR) changes in viral load and CD4 counts were -3·1 log^{10} copies per mL (-2·5 to -3·6) and +83 cells/mm^3 (40-178) respectively. The probability of remaining alive or free of new AIDS-defining events was 0·85 (95% CI 0·73-0·92).

The researchers tested the seven batches of Triomune, produced by Cipla in India, and noted that the unit dose of every component was as claimed

The researchers write: “Our findings lend support to use and funding of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine as first-line antiretroviral treatment in developing countries.”

Ref: Laurent C, Kouanfack C, Koulla-Shiro S,et al. Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial. *Lancet 2004,* Vol 364,No 9428*29-34*

Tenofovir price reduced in Africa and LDCs – but not Latin America and Caribbean

Gilead has announced that tenofovir (Viread) will be available to private and public programmes in every country in Africa and in 15 additional least developed countries for $24.71 for a 30-days supply, one-third lower than its current 'non-profit' price.

The company intends to make the fixed-dose combination of tenofovir and FTC (emtricitabine) available through the programme now that it has received US regulatory approval. However, apart from Haiti, Latin America and the Caribbean are excluded from this programme -only Argentina is mentioned separately as a country where tenofovir is marketed. Despite having much weaker economies these countries must pay the full US price plus distribution and shipping.

Request forms can be submitted via the internet or by email, mail or fax. The company is prepared to ship tenofovir to qualifying programmes as soon as request forms are reviewed and approved.

Complete programme information and request forms are available at:
http://www.gileadaccess.org
Source: Gilead press release
http://www.aegis.org/news/bw/2004/BW040704.html

WHO removes three Ranbaxy generics from its prequalification list

The World Health Organisation has removed three generic antiretroviral medicines from its list of prequalified medicines following an inspection of a contracted laboratory that had carried out bioequivalence studies of the drugs. The laboratory was found to be "non-compliant with international standards of good clinical and laboratory practice". The drugs will be removed from the list of approved drugs until the manufacturer, Ranbaxy, can submit data from new studies proving the products' bioequivalence with the originator brand name medicines.

The three medicines affected are combinations pills: two containing lamivudine, stavudine and nevirapine in two different strengths, and one containing lamivudine and zidovudine (AZT). Ranbaxy will resubmit the medicines for new tests at a different laboratory. If and when the laboratory and the products are approved the WHO will reinstate them on the list of prequalified medicines.

A similar inspection in May of a laboratory contracted to Cipla resulted in the removal from the prequalified medicines list of two of Cipla's products: Lamivudine and a combination of lamivudine and zidovudine.

The full WHO announcement is at:
http://www.who.int/mediacentre/releases/2004/pr53/en/

Ranbaxy to seek FDA approval for its generic ARVs

The generic drug manufacturer Ranbaxy Laboratories Limited of New Delhi will file its antiretroviral drugs with the US Food and Drug Administration under the expedited review process of the US FDA for the US President's Emergency Plan for AIDS Relief (PEPFAR). The first filing is likely to take place before the end of the year. The first study for bio-equivalence is being planned at a contracted laboratory in North America. Only FDA approved drugs can be bought with the $15bn being made available through PEPFAR to tackle HIV in 15 countries.

Full company announcement:
http://www.ranbaxy.com/newsroom/pressrelease_det.asp?sno=166

South Africa withdraws approval of Cipla's Duovir

The South African Medicines Control Council (MCC) has declared the use of the antiretroviral Duovir "undesirable" and has enforced a recall of all stocks of the medicine. Duovir combines zidovudine (AZT) and lamivudine in a combination similar to Combivir manufactured by GlaxoSmithKline.

Duovir has been withdrawn from the market because the MCC has concerns regarding the quality of the bioequivalence studies that formed the basis of the medicine's registration. The problems around these studies do not imply that Duovir is not bioequivalent, but the onus is on Cipla to prove bioequivalence in order for the MCC to approve Duovir.

The Treatment Action Campaign and Médecins Sans Frontières have issued a joint statement calling on Cipla to act speedily to address the MCC's concerns/

Source: TAC-MSF joint statement

ANTIRETROVIRALS

US FDA approves Glaxo and Gilead drug combinations

The US Food and Drug Administration has approved two antiretroviral drug combinations made by GlaxoSmithKline and Gilead Sciences for use in the United States and in developing countries. Truvada, the Gilead medicine, contains emtricitabine and tenofovir. Epzicom, the Glaxo combination, contains lamivudine and abacavir.

The speedy approval time - only four months for Truvada - confirms speculation that US regulations would facilitate rapid approval for brand name drugs so they can be bought with PEPFAR (the $15 billion President's Emergency Plan for AIDS Relief) dollars in developing countries. Observers are waiting to see if generic drugs are approved as quickly or if, as is expected, they will be held up by the American bureaucracy in order to favour the multinational pharmaceutical companies.

The US price for Truvada is $650.83 and Epzicom is $621.60 for 30-day supplies.

Source: FDA press release

http://www.fda.gov/bbs/topics/news/2004/NEW01099.html

Link (free registration required):

http://www.medscape.com/viewarticle/484763?src=mp

Abbott applies for once-daily license for lopinavir/r

Abbott Laboratories has submitted a supplemental New Drug Application to both the US Food and Drug Administration (FDA) and a Marketing Authorisation variation to the European Medicines Agency (EMA), seeking approval of once-daily dosing for its protease inhibitor (PI) Kaletra (lopinavir/ritonavir).

The submission package includes data from a clinical study in which once-daily Kaletra had comparable efficacy to twice-daily Kaletra, both dosed in a regimen containing tenofovir and emtricitabine, in treatment-naïve patients.

Among patients who participated in the study submitted, Kaletra was generally well tolerated. In the 48-week study comparing a Kaletra once-daily vs. twice-daily based antiretroviral regimen, the most frequent drug-related adverse events of moderate or greater intensity reported were diarrhoea and nausea.

Diarrhoea was reported more frequently in patients on once-daily therapy (16%) versus patients on twice-daily therapy (5%).

Source: Abbott press release

AIDS activists respond to NIH decision on overriding HIV drug patent

AIDS activists in the US expressed disappointment with a recent decision of the National Institutes of Health (NIH) regarding the patent for ritonavir (Norvir), made by Abbott Laboratories. In an official statement released yesterday, Dr Elias A Zerhouni, NIH Director, stated the NIH's official decision not to override the patent on ritonavir. The NIH held a public hearing on 25 May as a result of a petition claiming that a 400% increase in the drug's price in December 2003, which was developed in part with government funding, adversely affected reasonable consumer access to the drug.

The petition was filed under the Bayh-Dole Act, which allows the government to exercise "march-in" rights on a patented agent thereby allowing the drug to be produced by generic competitors. This authority has never been exercised since the Act was passed in 1980. The petition was filed by Essential Innovations Inc, a nonprofit corporation, with the support of healthcare providers, some members of Congress, and patient advocacy groups such as the AIDS Treatment Activists Coalition (ATAC).

Robert Huff, of Gay Men's Health Crisis (GMHC) in New York, said, "It's disappointing that the NIH rejected this petition without an on-the-record examination of the issues." Huff testified during the hearing last May in Bethesda, Maryland.

Transcripts form the hearing and the final NIH report:
http://www.atac-usa.org/Abbottpricehike.html

PERIPHERAL NEUROPATHY

Efficacy of acetyl-l-carnitine for antiretroviral toxic neuropathy

Leighton Davies MD, for HIV i-Base

The results of a recently published trial by Andrew Hart and colleagues from Blond McIndoe Centre, Manchester, and the Royal Free Hospital in London, provide confirmatory evidence for the use of acetyl-l-carnitine as a pathogenesis-based treatment for antiretroviral-associated toxic neuropathy (ATN). [1] ATN is the commonest cause of distal symmetrical neuropathy affecting between 11% and 66 % of individuals on antiretroviral therapy and is usually associated with the dideoxynucleoside analogue drugs ddC, d4Tand ddI (the 'd-drugs').

Currently available therapies - analgesics +/- adjuvant therapies (tricyclic antidepressants, anticonvulsants, mexiletine and peptide T) offer little in the way of symptom amelioration.

The proposed mechanism of ATN is impairment of neuronal mitochondrial oxidative metabolism (mediated by RTI inhibition of DNA-gamma-polymerase, upon which mitochondrial DNA replication is dependent). This results in reduced metabolic function in the long peripheral axons, producing a dieback effect that is responsible for the glove and stocking distribution of symptoms. Abnormal sweating patterns (night sweats) have also been described, suggestive of an autonomic neuropathy.

Acetyl L-Carnitine (LAC), which is crucial for normal mitochondrial function, is also thought to potentiate nerve growth factor actions, promote peripheral nerve regeneration and is thought to be generally neuroprotective, based on animal studies of diabetic neuropathy.

This elegant study provides 33-month data on the efficacy of LAC at 1500mg twice daily in a cohort of 21 HIV-positive individuals with established stable dysaesthetic neuropathic symptoms (of grade 2-4 severity). Skin biopsies were taken from the legs of patients before LAC treatment and at 6-12 month intervals thereafter alongside five HIV-negative non-neuropathic control volunteers. The degree of neuronal re-growth was then assessed by means of immunohistochemical staining of the biopsies with nerve-fibre specific antibodies directed towards PGP (protein gene product 9.5) as a non-specific indicator of re-growth, CGRP (calcitonin gene-related product) as specific for C and A-delta (small sensory) fibres. Sections were then examined by fluorescence microscopy and a fractional area of immunostaining calculated as a representation of neuronal re-growth, which was then used for statistical comparisons. The results of the study showed that immunological parameters remained stable throughout the study. Median baseline CD4 count and viral load were 286 cells/mm3 and <400 copies/mL respectively and median neuropathy duration prior to the study was 11 months (range 2-41 months).

Morphologically, patients with established ATN exhibited reduced total innervation of epidermis, dermis and most markedly, sweat glands prior to commencing treatment. There was a statistically significant increase in neuronal regeneration during the course of LAC treatment. The increase in small sensory fibres (epidermis 100%, $p=0.006$; dermis 133%, $p<0.05$) was more than that for all fibre types (epidermis 16%, $p= 0.04$; dermis 49%, $p<0.05$; sweat glands 60%, $p< 0.001$) or for sympathetic sudomotor fibres (sweat glands 41%, $p<0.0003$). The benefits continued to improve after 24 months treatment while re-innervation of sweat glands stabilised. This correlated with an improvement in grade of neuropathic symptoms in 15 of 21 patients (76%). The temporal pattern of improvement accounts for the slow resolution of symptoms on starting LAC therapy.

This study reported that LAC treatment is associated with an improvement in neurological symptoms in 76% patients and remained unchanged in 19%. A randomised controlled clinical trial is now underway which will use a validated visual analogue pain scale to establish symptomatic benefit conclusively. Traditionally peripheral neuropathy has been the principal complication limiting the use of certain NRTIs, for which LAC many now offer an effective management approach.

COMMENT

First results from this study in six patients from 2000 were reported over four years ago in HTB Vol 1 No 2. (May 2000).

http://www.i-base.info/pub/htb/vol1/htb2/htb2.html#L-Acetyl

These results should in a larger number of patients should now make LAC easier to prescribe in the UK.

Ref: Hart AM, Wilson ADH, Youle M et al. Acetyl-l-carnitine: a pathogenesis based treatment for HIV-associated antiretroviral toxic neuropathy. AIDS. 18(11):1549-1560, July 23, 2004.

HEPATITIS COINFECTION

Chiron relaxes patent licences for hepatitis C

Chiron Corp plans a change in the licensing policy on its patents covering the genetic makeup of the hepatitis C virus, a move that they say could lead to the development of new drugs to fight the disease.

Scientists at Chiron were the first to identify hepatitis C virus in 1987, and the company has more than 100 patents on the virus' genome, many of which still have over 10 years to run. Tight control of these patents and high licensing fees have often been claimed to limit research into new therapeutic treatments, including in a report by the National Academy of Sciences on intellectual property rights.

Chiron has now decided to no longer demand that licensors pay upfront fees and make annual payments to obtain rights to the hepatitis C patents.

Chiron, which is working on a vaccine and drug for hepatitis C, has licensed its patents to 15 other companies. Chiron had revenue of $1.8 billion last year, of which $312.2 million was royalties, mostly from licences on hepatitis C, HIV and a drug used to treat multiple sclerosis,

Source: Denise Gellene, LA Times 22 June, 2004

OTHER NEWS

Activists arrested in Nepal in homophobic atmosphere

Graham McKerrow, HIV i-Base

On the night of 9 August at about 10.30pm, 39 members of Blue Diamond Society (BDS), a gay rights and HIV prevention organisation in Nepal, were arrested and taken to Hanuman Dhoka Police Station in the centre of Kathmandu. First reports as HTB went to press said they were being detained without food and had been treated inhumanly. Sunil Pant, Director of BDS issued a statement saying: "We are very concerned. They were arrested along with other people from different occupations and this is against the human rights. The inhuman behaviour by the police is not only in arresting but also brutally beating up the arrested MSMs [men who have sex with men], which is against any principles.

"Thus, we request His Majesty's Government of Nepal to release our captured members without any conditions. Basically, Blue Diamond Society is involved in purely promoting human rights and HIV awareness among sexual minorities in Nepal without causing harm to anyone, thus we request HMG of Nepal and the other related organisations not to cause any harm which may affect our members' basic human rights and not to repeat this kind of any activity in the future."

Nepal has an appalling record of official and unofficial homophobia. A fundamentalist has recently brought proceedings in the Supreme Court of Nepal against the government calling on it to close down BDS as illegal and immoral. Observers don't know if the arrests were inspired by that writ.

Mauro Guarinieri, Chair of the European AIDS Treatment Group, has circulated a statement to activists in several countries saying: "Please notify Amnesty International and Human Rights Watch in your country. Please take what steps you can to put pressure on the government of Nepal to make sure these people are released safe and sound."

C O M M E N T

As we went to press we heard that the 39 members of Blue Diamond Society have now been released on bail.

CORRESPONDENCE

SMART study examines the long term benefit risk of interruptions versus continued use of ART

The following letter was received from Jens D Lundgren and others

In the July issue of HTB, Simon Collins raised concerns regarding the potential of emergence of resistance in patients discontinuing an NNRTI-based ART regimen, and he was asking for guidelines for how to diminish the risk of this in the SMART study.

The SMART protocol team shares the concerns being expressed in the article. Immediately after the data were first presented at CROI, we drafted a set of guidelines on strategies to diminish this risk.

The preferred strategy is to switch to a PI-based regimen 3 weeks before discontinuation to allow for complete removal of the NNRTI when ART is discontinued. Although this strategy is not based on formal clinical studies, it is the best advice available at the present time. We plan to update the guidelines as new information emerges.

The SMART study plans to enrol and randomise 6,000 patients to one of two strategies of using ART:

i) the viral suppression strategy where ART is used at all times to suppress HIV replication to the largest extent possible (current state-of-the-art);

ii) the drug conservation strategy where ART is only used intermittently to maintain a CD4 count in the range of 200-350 cells/mm3.

The study will proceed for the next 5-7 years and hence allow for a profound understanding of the longer-term implications of the two treatment strategies to be compared. A present, 2,050 of the 6,000 patients have been enrolled, and we expect that a large number of patients from across Europe will enrol in the study over the next year.

Yours sincerely, Jens D. Lundgren & Ulrik B Dragsted (Copenhagen coordinating centre), Adrian Palfreeman, Abdel Babiker & Janet Darbyshire (London coordinating centre).

COMMENT

The SMART study addresses important and compelling questions over long term management of treatment and has been developed with strong community input and support.

The study protocol for stopping treatment provides current best practice for any patient considering stopping an NNRTI or 3TC-based treatment. As such the guidance is also worth considering for patients stopping treatment for any reason, whether or not they are in this study.

ON THE WEB

Conference abstracts and reports:

XV World AIDS Conference: reports and links

Numerous sites include coverage from this conference.

Webcasts from the meeting are available at:

http://www.kaisernetwork.org/aids2004/kffsyndication.asp?show=guide.html

Other sites with particularly useful original coverage include:

http://www.thebody.com
http://www.natap.org
http://www.hivandhepatitis.com
http://www.medscape.com

Treatment guidelines:

European Paediatric guidelines

The PENTA Guidelines for the use of antiretroviral therapy in paediatric HIV infection are now available to download as a pdf file from the PENTA website:

http://www.pentatrials.org

Driect link:

http://www.ctu.mrc.ac.uk/penta/guidelin.pdf

They are also published in HIV Medicine, July 2004 (Volume 5, Supplement 2).

The Guidelines were written by members of the PENTA Steering Committee: Guido Castelli-Gattinara from Rome, José Ramos Amador from Madrid, Stephane Blanche from Paris and Mike Sharland and Diana Gibb from London. New guidelines will be produced in 2006, but drug dosing information will be updated in the interim.

Comments are welcomed by email to:

Mike Sharland <msharlan@sghsm.ac.uk>

Treatment Access:

UNAIDS 2004 Report on the global AIDS epidemic

http://www.unaids.org/bangkok2004/GAR2004_html/ExecSummary_en/ExecSumm_00_en.htm

NGO Perspectives on the Global Fund

ICASO report entitled "NGO Perspectives on the Global Fund." This publication examines the role of civil society involvement at the Global Fund Board, the Secretariat and at country level CCMs. It affirms that since the Global Fund was formed in late 2001, many successes have been achieved. Nevertheless, the report outlines several issues of concern from ICASO's perspective. An Adobe .pdf version is available in French, Spanish and English at

www.icaso.org/gfatm.htm

Online treatment journals and newsletters:

New PRN Reports

Diagnosis and management of HPV-associated anogenital dysplasia in HIV-infection - Joel Palefsky MD
http://www.prn.org/prn_nb_cntnt/vol9/num2/palefsky_frm.htm
Excellent and comprehensive overview of the pathogenesis, management and treatment of anal and cervical HPV-related dysplasia from the leading researcher in this field.

Novel viral markers predict HIV disease progression - Eric S Daar, MD

http://www.prn.org/prn_nb_cntnt/vol9/num3/daar_frm.htm?notify04-207
Article covering range of CD4 and virological reponses to HIV, including discordant responses and the role of long-term slow progressors.

GMHC Treatment Issues – May/June 2004

http://www.gmhc.org/health/treatment/ti/ti1805.html

May/June 2000 include:

- **Demanding Gender Equality: Stephen Lewis issues a challenge**
- **ARV Progress in India: Interview with Khousalya Periaswamy**
- **Immunology Report: Gareth Hardy on the Keystone Conference**
- **Abbott's Bad Medicine: How the ritonavir price increase will hurt innovation**

- **Drug News: Updates on drugs in and out of the pipeline**
- **Scramble for Africa: Gregg Gonsalves on the future of NIH's AIDS research network**

TAG coinfection report

http://www.aidsinfonyc.org/tag/coinf/hcv2004/index.html

The Treatment Action Group (TAG), a New York-based AIDS research and treatment advocacy group, today released a comprehensive review of research on hepatitis C and HIV/HCV coinfection, accompanied by recommendations for research and policy.

MEETINGS

'Unique Conference to be held in London'

23-24 September 2004, Royal College of Physicians, London

The International Association of Physician in AIDS Care (IAPAC) announces the first-ever IAPAC Sessions—Europe,23-24 September 2004 at London's Royal College of Physicians.

Accommodation and most meals in London will be provided by IAPAC.

For the past three years, IAPAC-hosted symposia in the United States have provided HIV-treating physicians an opportunity to discuss and debate the latest issues of HIV clinical management.

The association is pleased to bring this unique gathering to Europe.

Please forward this information to any doctors you think may be interested. For more information and the programme see:

http://www.iapac.org/home.asp?pid=59

For more information or to register, contact Nicole Burnham at:

nburnham@iapac.org

TRAINING COURSES

A three-day course on methodological and statistical issues in clinical HIV research

Tuesday 23 – Thursday 25 November 2004

Sheila Sherlock Centre, Royal Free Campus, London NW3

This three day workshop will be run by the HIV Epidemiology and Statistics Group, Royal Free Centre for HIV Medicine, Royal Free and University College Medical School.

The course is for healthcare professionals and those working in the pharmaceutical industry who have an interest in HIV. It is aimed at those with little or no prior statistical knowledge and will include:

- Introduction to statistical techniques and hypothesis testing
- The use of survival analysis in studies of HIV infection
- The design and analysis of randomised controlled trials for antiretroviral therapy
- The role of observational studies in HIV infection
- The analysis of HIV RNA data and the use of surrogate marker endpoints in HIV clinical trials

Course tutors will include: Andrew Phillips, Caroline Sabin, Amanda Mocroft and Fiona Lampe. The course will be interactive and informal. Therefore, in order to maintain a low participant to tutor ratio numbers will be limited.

Price excluding VAT:

Pharmaceutical Industry	£ 1000
NHS / academic / community	£ 400

For further information please contact:

Elaine Harris Tel: 020 7830 2478 email: e.harris@pcps.ucl.ac.uk

PUBLICATIONS AND SERVICES FROM i-BASE

NEW: UK-Community Advisory Board: reports and presentations

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

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

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

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

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

World CAB Report: focus on international drug pricing

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

Available to download as pdf file (108kb)/

The i-Base website

Our web address is:

http://www.i-Base.info

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

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

Introduction to Combination Therapy

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

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

Guide to HIV, pregnancy & women's health

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

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

Guide to changing treatment: second-line and salvage therapy

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

Guide to avoiding & managing side effects

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

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

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

Italian treatment guides

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

Treatment 'Passports'

These popular booklets are for HIV-positive people – whether newly diagnosed or positive for a long time - to keep a record of health and treatment history.

Like all i-Base publications, they are available free as single copies, or in bulk.

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

HIV Treatment Bulletin (HTB)

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

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

Treatment information request service – 0808 800 6013

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

We can provide information and advice over the phone, and we can mail or email copies of the latest research studies relevant to the caller.

For details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm.

All calls are in confidence and are free within the UK.

Find HTB on AEGiS

AEGiS.com - the longest established and largest global resource of online HIV information - includes HTB in the regular journals that it puts online. You can find us at:

http://www.aegis.com/pubs/i-base/2004

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

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

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

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

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

h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website:
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Editor in Chief: Paul Blanchard
Editor: Simon Collins
Associate Editor: Graham McKerrow
Commissioning Editor: Polly Clayden

HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

Some articles are reproduced from other respected sources and copyright for these articles remains with the original authors and sources, as indicated at the end of each article.

We thank those organisations for recognising the importance of providing widely distributed free access to information both to people living with HIV and to the healthcare professionals involved in their care. We also thank them for permission to distribute their excellent work and we encourage HTB readers to visit the source websites for further access to their coverage of HIV treatment.

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

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