

THAI ME UP, THAI ME DOWN — THE XV IAS CONFERENCE IN BANGKOK

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A strong Rand, June heat, a beautiful country, and a fun and vibrant city — it doesn't get much better. Nearly 20 000 delegates attended the 15th International Aids Society (IAS) Conference in Thailand. They came to hear the latest updates from the scientists, activists and policy-makers, network with collaborators, sample the local Asian cuisine, and try to get 'One Night in Bangkok' out of their heads.

Bangkok is hot, bustling and polluted, with traffic from hell; it's also fun, vibrant, friendly and safe, with everything from glorious developed-world infrastructure, to a strong sense of culture and vast shopping plazas. Huge numbers of Southern African government health officials, researchers and HIV programme implementers descended on the city, desperately seeking refuge from an African winter.

This review of the conference doesn't do justice to its full depth or breadth, with around 15 different interest streams operating concurrently, but I hope it captures a few of the highlights, especially where southern African researchers contributed significantly to the programme, or where research directly informs our situation.

THE GLOBAL SUPERSTARS

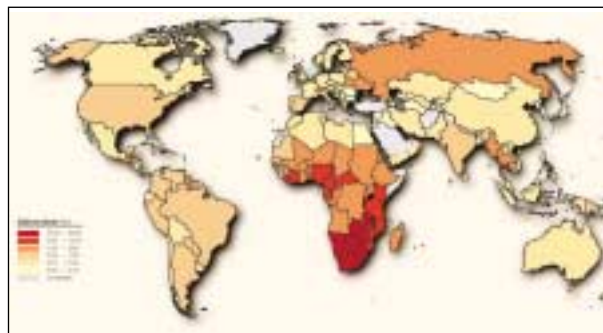
Richard Gere is an unlikely figure to preach safe sex, but that's what he did. The *American Gigolo* star shared a platform with Miss Universe 2004 (Australian Jennifer Hawkins in case you don't follow these things), significantly undermining controversial abstinence programmes, according to many slightly breathless onlookers. Add Ashley Judd, Dionne Warwick and Rupert Everett, and we had a mini-Oscars event.

AIDS conference veteran Madiba, attending his third consecutive conference, laid down the gauntlet, emphasising that he had retired but could not rest until he felt AIDS was being addressed with the urgency it deserved. 'Please let me enjoy my retirement', he pleaded with

delegates, 2 days before his 86th birthday. His wife Graca Machel played an extremely active part throughout the programme, much to the delight of celebrity watchers.

Peter Piot, the charismatic leader of USAIDS, and Richard Feacham, head of the ambitious Global Fund, made upbeat presentations, listing strong, new and novel programmes and partners, and stressing renewed commitment from governments and treatment partners. However, the UNAIDS data were worrying (<http://www.unaids.org/bangkok2004/report.html>), confirming previous data showing limited impact of prevention programmes on a regional level in sub-Saharan Africa, and the disastrous increase in new infections in Asia and Russia. There was also a strong indication that prevention programmes were failing in high-risk groups in developed countries, along with a steady increase in viral resistance to drugs.

No AIDS conference is complete without a nevirapine (NVP) public relations crisis imported from South Africa. The Minister of Health, popping in to open the South African stall at the Conference, was reported as announcing the deregistration of NVP for mother-to-child transmission (MTCT), with a pointed jibe at activists that this confirmed her previous view that the drug should never have been used for MTCT. NVP resistance post-MTCT was the focus of a large part of the Conference, and the spat attracted plenty of international media and research interest. A hastily convened press conference chaired by a visibly



UNAIDS figures revealed little to celebrate, with big increases in Asian and Russian numbers.

wear Zackie Achmat from the Treatment Action Campaign (TAC), recently nominated for a Nobel Peace Prize, provided a vibrant debate on the NVP issue, as well as the status of the national antiretroviral (ARV) roll-out. Many senior government health representatives attended the session, and participated in the discussion. Eventually, it was clarified that there was no plan to deregister the drug, and that the Medicines Control Council (MCC) was simply recommending against monotherapy with NVP for MTCT, a position no one could argue with. Dr Precious Matsotso, the hard-working head of the MCC, clarified the issue of deregistration calmly, saying that it was the MCC's responsibility and not that of the minister to deregister the drug. Other government officials also reassured the audience that there was no plan to stop the NVP MTCT implementation programme. The ideal treatment for MTCT is highly active antiretroviral therapy (HAART) – NVP monotherapy acknowledges that we do not have the human resources or infrastructure to provide HAART to all pregnant women with HIV in southern Africa.

CONFERENCE ACTIVISM

The Conference played host to a huge variety of interest groups, and international governments, pharmaceutical companies and donors were attacked at many levels for not doing enough, doing it wrong, or not doing it in a co-ordinated fashion. The USA in particular provided a lightning rod for many perceived wrongs in the HIV world. One senior journalist bemoaned the fact that he had to keep apologising for being American: 'I feel like a white South African in the 1980s!' A diverse group of activists, researchers and community groups attacked PEPFAR (the Presidential Emergency Program for AIDS Relief), the huge HIV relief fund initiated by President George Bush, with allegations of American protection of multinational pharmacy patent rights, criticism of the focus on abstinence and monogamy, and perceptions of a challenge to the efficacy of condoms. Some issues raised by activists that were not US-related were straight from the headlines, while other activist issues seemed curious to African observers – the demand for access to obscure ARVs, the perceived ethical problems with using tenofovir for prevention of HIV in sex workers highlighted by Paris ACTUP, and the strong focus on intravenous drug abusers. Ugandan President Yoweri Museveni did not help clarify things, in a peculiar plenary speech that seemed to undermine condom use and promote a very old-fashioned view of morality. The head of PEPFAR, Randall Tobias, bravely faced a loud group of protestors, and strongly defended the PEPFAR goals, pointing out that the USA gave more to AIDS than all the other donor nations combined. He defended the allocation of one-third of the PEPFAR

prevention budget to abstinence programmes, pointing out that this approach was successful in Uganda. He said that he knew condoms prevented HIV, which he had been reported as questioning in the past. The National Institute of Health (NIH)'s Tony Fauci, who walks on water among HIV researchers, said that he thought the USA's approach was 'good housekeeping'. This did not stop senior officials, including UN Secretary General Kofi Annan, French president Jacques Chirac and Stephen Lewis, special UN envoy on AIDS in Africa, from criticising the USA on various fronts, including the fact that PEPFAR limits its support to only a few affected countries.

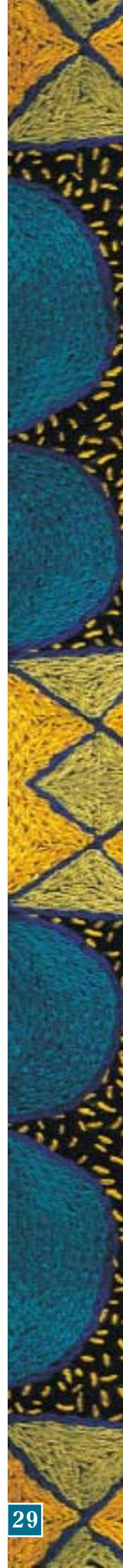
For those interested in the political aspects of HIV, it was a feast. Other attendees grumpily maintained that the science was being undermined by the 'soft' issues. HIV continues to be a showcase for the world's inequalities and social challenges, and solutions to these are not immediately forthcoming. Science purists may have to give future conferences a miss. It's a messy disease to manage, and no organiser was going to please the dozens of interest groups attending.

WHO LET THE DOGS OUT?

Developing-world public health workers breathed a huge sigh of relief as a diminutive investigator (who was later given an award for excellence at the closing ceremony) compared the World Health Organisation (WHO)'s 3 by 5 Initiative-recommended drugs with other regimens used in California (Abstract MoOrB1082). The WHO recommends combinations, using nucleoside backbones of stavudine (d4T) or zidovudine (AZT), with lamivudine (3TC), with either efavirenz or nevirapine. The study demonstrated that the WHO's choices were the best performers, significantly outperforming alternative regimens using other nucleosides and protease inhibitors (PIs) in terms of survival. South African adult treaters sat feeling particularly smug, as the regimen selected for South Africa's roll-out as first-line therapy, d4T/3TC and efavirenz, received the accolade of 'best on test!' However, Harry Moultrie, Baragwanth Hospital's paediatric doyen, correctly pointed out that there was a period where clinicians started patients who were more ill on PIs, which may actually explain the survival difference. The WHO will have to move fast to achieve its goal of treating 3 million people with ARVs in the next 18 months, good drug choices or not, as Jim Kim, head of the WHO's team tasked with this, admitted.

MOTHER-TO-CHILD-TRANSMISSION (MTCT) TAKES CENTRE STAGE

The South African Health Minister initiated the MTCT debate, but hard scientists quickly took centre stage. The



WHO released new and widely welcomed guidelines at the Conference (<http://www.who.int/mediacentre/releases/2004/pr50/en/>). Lynn Morris, from the National Institute for Communicable Diseases and South Africa's leading resistance expert, presented the first long-term data showing that resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) persisted for up to 6 months in women exposed to NVP single dose (sdNVP), particularly those with high viral loads and low CD4 counts (Abstract ThOrB1353). At the end of the talk she stressed that this was not a reason to avoid using the drug, and that the clinical implications of the resistance mutations were yet to be fully documented. The much-quoted Thai trials, showing efficacy of NNRTI-containing regimens in mothers exposed to NVP MTCT (presented at the Conference on Retroviruses and Opportunistic Infections in February 2004) were discussed in a plenary session, and the results appeared to be less alarming than previously thought. James McIntyre showed fascinating data in a late breaker session, demonstrating that adding AZT/3TC for a limited time after NVP monotherapy could reduce the chances of NNRTI resistance (Abstract LBOB09). Prevention of maternal transmission began to launch into the downright peculiar, as breast-feeding grandmothers graced the late breaker presentation as a way of avoiding exposure to infected mom's milk.

As a separate review of the state of MTCT will be published in this issue, it will not be covered further here.

KALETRA, LAMIVUDINE AND MONOTHERAPY/ DUAL THERAPY HERESIES

The quest for simpler and safer regimens continued, with exciting and novel approaches to treatments emerging, challenging the holy grail of 'triple therapy'.

Kaletra (lopinavir/ritonavir – the ritonavir is used in low doses (with minimal antiviral effect) to 'boost' the blood levels of the lopinavir) had the sort of glowing reviews we last saw for efavirenz a year ago at the Paris IAS Conference. Kaletra has a resistance barrier that drug developers dream of. Data presented at the Conference showed no resistance to the drug after 5 years of treatment – patients on regimens containing Kaletra developed resistance to the other drugs in their regimens, but not to Kaletra (Abstract WeOrB129). This is unique in the antiviral world, where all other drugs exhibit distinct resistance profiles. But even resistance to the other drugs was rare in this study. As if things couldn't get any better, it now appears that we may be able to use the drug once daily, and the company has applied internationally for QD registration. The remaining major concerns with Kaletra are its ability to cause lipodystrophy, and the fact that it melts in African heat.

But a Texan dramatically upped the ante (Abstract MoOrB1057). In a fascinating and frankly scary presentation, Dr Gathe from Houston challenged a decade-long heresy – monotherapy for infected patients. He treated 30 patients with Kaletra monotherapy, with CD4 counts from 7 cells/ μ l to over 400 (average 169 cells/ μ l), and many with high viral loads. Ten fell off for reasons of toxicity, non-adherence, etc., but 20 had viral loads of below 400 copies/ μ l after 48 weeks of treatment. Eighteen of these had viral loads below 50. Commentators flocked to urge caution, but a new can of worms has been opened forever. His 24-week data had been greeted at a previous conference with a 'wait and see' attitude. Now may be the time to design the big trials that may change the way we do the business of ARVs.

Other presentations looked at 'deintensification', a treatment concept similar to that used in oncology, where you use aggressive treatment at the start to contain the virus, and then once the viral load is low and viral resistance presumably unlikely, the regimen is simplified to a single drug. Patients with undetectable viral loads on ARVs were randomised to dual therapy with tenofovir/efavirenz or to the same two drugs plus 3TC. No difference between the two arms has yet been seen (Abstract TuPeB4493), although the trial has not been completed. Another used the redoubtable Kaletra as monotherapy in patients on successful ARVs, with excellent results (Abstract TuPeB4577).

The meek and mild 3TC still has not had its role as a viral 'weaker' clarified. The unusual M184V mutation associated with the drug causes the virus to be less 'fit', suggesting a role in deliberately inducing the mutation, by giving 3TC monotherapy, in a bid to decrease the destructive power of the virus. A small Italian study of patients failing conventional ARVs showed that people given monotherapy had slower decreases in CD4 and lower viral loads than those not given it (Abstract WeOrB1286).

But the bottom line remains – this is an exciting but completely unconfirmed area. Do not try this at home! Several clinicians have used Kaletra as monotherapy locally, and the evidence to do this is still very dicey – currently it should not be done outside of a research environment. Several case reports, the first of which came from Johannesburg,² have reported resistance to Kaletra, and particularly worrying is the occurrence of naturally resistant mutations in subtype C virus, the most common clade in southern Africa.

Efavirenz was not to be denied as the ARV poster-child. Data up to 4 years showed it to be a remarkably effective as part of a HAART regimen, even in people with high viral loads, and with very little toxicity (Abstract TuPeB4547).

Despite its low resistance barrier, it continues to be an excellent clinician and patient first choice as part of their ARV regimen.

NEW AND OLD DRUGS, OLD PROBLEMS

It is difficult not to be cynical about the development of new drugs. Every HIV conference seems to have dozens of new candidates paraded, only for them to disappear quietly off the scene when newly recognised toxicity or poor efficacy is realised. However, there were a few interesting developments.

Reverset (D-D4FC), a new nucleoside, shows excellent antiviral activity in a presentation given by Midwestern's Rob Murphy, with potential to be used in patients with resistance, and no side-effects in initial studies. It is now poised to go to phase 2b studies (MoOrB1056). Another PI, fos-amprenavir, showed good efficacy in people with multi-drug resistant (MDR) HIV (MoOrB1055). The much-awaited chemokine receptor-5 (CCR) blockers had a very low-key conference (Abstract WePeB5725).

The new PI, atazanavir, continued its cardiovascular darling status among PIs, with further data that the metabolic concerns afflicting other PIs are less of an issue with this drug (Abstracts ThOrB1355, ThOrB1356). Interestingly, there were still no data showing that metabolic consequences translate into clinical events, although one study showed increased atherosclerosis with PIs compared with NNRTI-containing regimens (ThOrB1355). It has become increasingly apparent that it is not only the PIs that can cause metabolic problems, and a study (Abstract ThOrB1360) demonstrated that the (now rarely used) combination of d4T/didanosine (ddl) causes significant lipodystrophy and metabolic changes previously thought to be specific to the PIs. An alarming study showed that length of time on ARVs correlated with the risk of eclampsia and fetal death, though reassuringly among the over 400 women studied there was no MTCT (ThOrB1359). ARVs seem to spare no organ, and bone came in for a pasting in a study (Abstract ThOrB1358) demonstrating convincingly in a multivariate analysis that length of time on ARVs strongly correlated with the incidence of osteonecrosis. Some commentators have noted that HIV-infected people get a peculiar form of accelerated aging, as part of their clinical profile – strokes, heart attacks and crumbly bones are a concern, although still not yet a clinical reality.

Once-daily dosing of ARVs seems to be the way to go for the developed world, with much attention being given to a regimen of combined tenofovir and emtricitabine taken with efavirenz. HAART delivered by 2 pills taken once daily was the stuff of dreams 5 years ago, but the surrounding

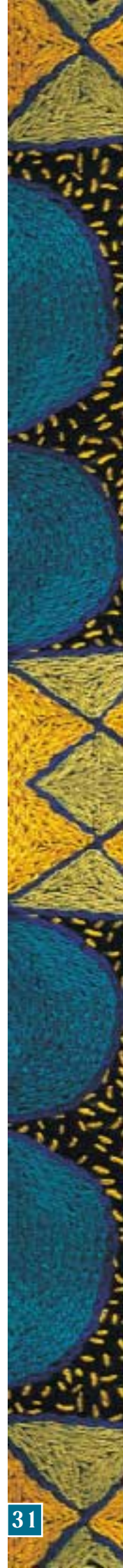
hype seemed slightly unreal given the ARV access issues in Africa.

Resistance continued its bogeyman status, with disturbing data showing resistance occurring in people on ARVs in three-quarters of patients with viral loads below 1 000 copies/ml (Abstract WeOrB1293.). But it is unclear how much clinical panic this should generate, as the gap between viral resistance and clinical outcomes appears to be more complex than previously thought. Studies treading the boundaries of resistance, using off-on approaches to ARVs, had variable results, with one trial having to be stopped because of major resistance.

CLINICAL PROBLEMS AND OPPORTUNISTIC ILLNESSES

This area continues its orphan status in the international HIV conference circuit. Few presentations dealt with African experiences of these diseases, although there was further confirmation that efavirenz 600 mg can be used in conjunction with conventional rifampicin-containing tuberculosis (TB) regimens (Abstract MoOrB1013). Some clinicians have previously used 800 mg, as some studies have suggested that efavirenz levels are decreased in association with rifampicin, but this study showed no difference in blood levels of efavirenz at the different doses, and excellent 38-week viral outcomes. Unfortunately, the study was done in Thais, who are smaller than people in most other nations, with an average weight of 50 kg in the study. Efavirenz's reputation as a 'TB-friendly' ARV continues, although stronger evidence for this and for the use of other drugs would be welcome to people working in high TB prevalence areas.

The thorny issue of smear-negative TB, a huge headache for clinicians in countries where diagnostic resources are lacking, was tackled in a poster looking at using a 'syndromic approach', using clinical and simple laboratory criteria to identify patients with probable TB (Abstract MoPeB3229). The model proved robust, confirming the approach many clinicians are guiltily using – treat patients with symptoms suggestive of TB and see if they get better, before breaking out the expensive or invasive diagnostics. The model may help to formalise this. The prolific Gavin Churchyard, from Aurum Research in South Africa, provided several interesting studies on TB, including one that showed a 5% incidence of TB among mine workers after starting ARVs, despite prescreening (MoPeB3213). Another study from his group showed that oral thrush was a strong predictive factor for immediate severe HIV-related illnesses (MoPeC3392), and that perhaps making it a WHO-4 staging event may be merited.



An interesting study showed that HAART decreases the incidence of opportunistic infections, independent of the CD4 count, suggesting that the CD4 count may not be as robust a marker of immune recovery as it is of immune deficiency (Abstract TuPeC4719).

A remarkably high level of immune reconstitution inflammatory syndrome (IRIS) was seen in a cohort of Thai children commencing ARVs, confirming early anecdotal reports from paediatricians working in South Africa's ARV roll-out (Abstract TuPeB4404). Twenty-four children developed the syndrome out of 95 starting ARVs. The syndrome appeared early (within 3 weeks), and included cases of mycobacteria, herpes and, curiously, cryptococcus, which is reported to be rare in children. Four children died as a result of the syndrome. As expected, the lower the CD4 count, the higher the risk of IRIS.

As has been shown in many cohorts, 'late presenters' (CD4 < 50 cells/ μ l) are still common even in the developed world. A study from the UK showed that these patients place a huge strain on hospital resources in the first 3 months when compared with people presenting earlier, but still did very well on ARVs (Abstract MoPeB3356). The message for us is obviously to redouble efforts to get people tested early and referred quickly to an ARV access point, before they hit the 'late presenter stage'.

Lymphoma treatment for HIV-infected people is much better in the era of ARVs (Abstract ThOrB1403). Patients on ARVs showed a dramatic drop in risk of lymphoma. Those who had lymphomas survived much longer than those who were not previously given ARVs. The thorny question of which drugs to start first (the oncology drugs or the ARV drugs) and what sequencing of treatment should be given, remains a thorny everyday question for clinicians.

A South African study showed increased NVP levels when given with fluconazole, with an increase in hepatotoxicity (Abstract WeOrB1239). This problematic interaction is of concern to southern African clinicians, where use of fluconazole is high. A study comparing amphotericin B with or without an azole (fluconazole or itraconazole) found no benefit in terms of cerebrospinal clearance of cryptococcus or in clinical outcomes (MoPeB3232).

The difficult issue of ARV rationing in Africa was tackled in Abstract MoOrE1072. A distinction was made between explicit rationing (e.g. focusing on specified groups such as skilled workers, students, mothers, households) and the much more problematic implicit rationing currently in force (e.g. 'first come, first served', queuing, not providing transport to distant ARV sites). Implicit rationing creates situations where the elite can queue-jump, undermining efficiency and equity. The need for public debate was

emphasised – the topic will be comprehensively discussed in the *Lancet* later this year.

PREVENTION STRATEGIES

The prospect of a vaccine seemed about as hopeful as the cure for old age. Candidate vaccine corpses have littered the prevention landscape over the last year, and the news that we are years and possibly decades from an effective one was very sobering. Médecines Sans Frontières and a group of scientists headed by the acerbic Robert Gallo, called for the scrapping of the huge Thai vaccine trial currently underway, calling it an expensive flop. Trials of the diaphragm, with and without vaginal microbicides, vaccines, and male circumcision are all interesting but distant public health interventions. Treatment of HSV-2 as an HIV preventive strategy seems very exciting, especially in the light of recent publications suggesting that herpes may be the most significant co-factor driving transmission, with early work starting in South Africa on acyclovir.

CONCLUSIONS

The Conference was frustrating, especially if you don't like the politics or big crowds. More frustrating for us were the surprisingly large number of 'data-empty' presentations, where presenters spoke of their anecdotal experiences rather than presenting analysis of raw data. It does seem that a more rigorous assessment of abstracts is needed, as the good stuff often seems lost in a sea of mediocre presentations, leading frustrated observers to write off the Conference as a waste of time. This would be a pity – this Conference has fundamentally challenged the way we do clinical business. The exciting prospect of simpler and safer ARV therapy seems only a few years away. The next Conference is in 2006 in Toronto. It may not have the buzz of Bangkok, but it will certainly attract the AIDS conference crowd in droves. Here's hoping we won't be discussing NVP this time.

All abstracts, and selected webcasts, are freely available at the IAS website, <http://www.ias.se/>

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