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HIV Treatment Bulletin (HTB) supplement

i-Base report: 10 key areas of research:
non-technical summary of studies and presentations from Mexico

This supplement is a non-technical overview of some of the most interesting studies presented at the International AIDS Conference held in Mexico City from 3-8 August 2008. Technical reports from the conference are published in HIV Treatment Bulletin, available online and to order in print from the i-Base website (www.i-Base.info).

Hyperlinks in this PDF file link directly to each abstract or session.
All abstracts are on the conference website (www.aids2008.org).

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1. Introduction

The International AIDS Conferences are held every two years, and alternate between a developed and a developing country. Approximately 25,000 people attend and over 4,500 research studies are presented.

This year the conference had very few new scientific advances in terms of new drugs or treatment strategies, but it did have a few controversial studies. These large conferences focus more on epidemiology, prevention, policy, access to treatment and issues relating to social exclusion (drug users, sex workers, MSM, gay men, young people, sexual violence, women's rights, etc). These issues are covered in tracks C, D and E of the programme. Tracks A and B cover basic science and clinical science respectively.

Conference abstracts (reduced summaries of each study) are all available online, as are many of the powerpoint slides, web casts, transcriptions and daily 'rapporteur' summaries. Abstracts are accessed via the online conference programme. At the bottom of each daily programme (you need to scroll right down to find the abstract session) is a link to the searchable database.

As it is difficult to find, the direct URL for the posters is:

http://www.aids2008.org/Pag/PosterExhibition.aspx?presType=PE&D=04&S=621

The link for the programme is:

http://www.aids2008.org/Pag/PAG.aspx

This i-Base report includes references to a range of studies – from major presentations and large studies, to overview summaries and to examples of single posters. It is not meant to cover everything that happened, but to give an overview of some of the key themes.

Hyperlinks are either directly to the abstracts or to appropriate programme pages that include further links to abstracts, powerpoint slides or webcasts and abstracts.

2. HIV-positive activists: five talks

Many sessions included key talks from HIV-positive speakers who focused on experiences of people in very different parts of the world.

Some of the speeches were particularly strong and are worth watching as webcasts or downloading transcriptions or podcasts (from the webcast pages).

These activists have all contributed to the ways that governments and scientists approach HIV and they made world-class presentations.

Try to get to a broadband internet connection when you have an hour or two free and be inspired.

"Those of us who are living with HIV and have come to terms with that diagnosis […] in terms of our own ability to survive the traumas of our diagnosis and daily fight for our rights to existence.

Each and every one of you who live and breathe HIV is a leader, people with other health conditions look up to us for inspiration […] Do not give up, when life knocks you flat on your face get on your knees. Stand to your feet, hold your head high, and keep on going. "

Greater involvement of people living with HIV in healthcare - Rolake Odetoyinbo, Nigeria

From 'Advances in ART' plenary session on Thursday:

http://www.aids2008.org/Pag/PSession.aspx?s=37

"We must seek a cure and a vaccine, because lifelong triple drug therapy for the currently infected will already require 990 million patient years of HAART to be administered over the next 30 years. And if UNAIDS is right that 2.7 million new infections are going to occur every year in the next 20, 30 years, then we will need another 81 million people who will need 30 years of HAART which would be 2.43 billion patient years of HAART."

"Now, that is starting to be a lot of tons of molecules, and it is going to be very hard to deliver it. So we need massive investment on a cure, not just lip service and not just reinserting it into our talks at meetings. And we need better prevention methods and combination prevention methods to end the epidemic."

"We must continue to accelerate current scale up and we must scale up faster. We are still way behind the epidemic."

The future of AIDS advocacy - Mark Harrington,US

from the 'Looking to the Future' session on Wednesday:

http://www.aids2008.org/Pag/PSession.aspx?s=49

"I was very disturbed by this conference by not addressing TB as a priority by only having one session on TB on Sunday. The whole eight days there is no mention on TB while I come from a region where TB is one of the number one killers. And I am mentioning that because people live with HIV. There is only one percent of people with HIV who are diagnosed early of TB."

"Our workforce in South Africa is dying of multidrug resistant TB, so for me I do not see a future if we do not start stepping up diagnosis and better treatment for TB today."

The future of AIDS advocacy - Vuyiseka Dubula, South Africa

from the 'Looking to the Future' session on Wednesday:

http://www.aids2008.org/Pag/PSession.aspx?s=49

"Unfortunately, the current campaign for universal access was built without global targets because UNAIDS, DFID, and the US government refuse to accept them. I was at those meetings, I heard them speak."

"At the same time, the definition of universal access is so now irresponsibly vague. Just take a look at the latest UNAIDS report which contains more twists and turns than an Olympic gymnast to avoid any concrete commitments."

"The decision not to include global targets and to step back from specificity is a political one taken by organisations and agencies that are political to a large, if not complete degree, but that is really a poor and pathetic excuse, and one with potentially devastating public health consequences. Unless we have clear targets with clear timelines, we will never reach our goal of universal access."

ART scale up - Gregg Gonsalves, US

From 'Advances in ART' plenary session on Thursday:

http://www.aids2008.org/Pag/PSession.aspx?s=37

See also South Africa's HIV-positive Justice Edwin Cameron talk on Criminal Statutes and Criminal Prosecutions in the Friday plenary.

http://www.aids2008.org/Pag/PSession.aspx?s=38

3. IDU-related studies

This conference included many studies relating to injecting drug users (IDUs), who in general are socially marginalised and denied access to harm reduction health initiatives, substitution therapy and ARV treatment despite extensive evidence on the effectiveness of all these measures.

Many studies highlighted how HIV-positive drugs users are at significantly increased risk of mortality compared to HIV-negative drug users, including a poster from Vietnam that showed approximate 20% mortality over one year for HIV-positive people vs 2-3% for HIV-negative. (see Monday posters 0247 for Vietnam, 0244 for India and 0253 for Canada).

http://www.aids2008.org/Pag/Abstracts.aspx?AID=9931

http://www.aids2008.org/Pag/Abstracts.aspx?AID=8338

http://www.aids2008.org/Pag/Abstracts.aspx?AID=7351

For a powerful overview of all the issues involved watch the web cast of the lecture given on Tuesday that packed the vast Session Hall 1. This focused on the importance of IDU-related issues being seen as health-related rather than legal and law enforcement programmes – current spending give 2% to the former and 70% to the latter.

Substance use and harm reduction - Adeeba Kamarulzaman

http://www.aids2008.org/Pag/PSession.aspx?s=32

4. New drugs

Information on new drugs was presented in several sessions that include webcasts and slides.

"Newer ARV Agents" on Tuesday 5 August.

http://www.aids2008.org/Pag/PSession.aspx?s=256

And the second **"Track B late-breaker"** session on Thursday 7 August.

http://www.aids2008.org/Pag/PSession.aspx?s=287

In summary we saw more information about the integrase inhibitor raltegravir and a new NNRTI called rilpivirine (TMC278), both in people using treatment for the first time ('treatment-naïve' patients).

Two small studies presented first results in HIV-positive people of two other NNRTIs that are in early stages of development.

The need for alternative NNRTIs to efavirenz and nevirapine depends not just on how active they are, but on whether they are easier to take – ie having fewer side effect, drug interactions or cautions in pregnancy.

Studies of new formulations included a version of ritonavir that doesn't need to be stored in the fridge and several new paediatric formulations.

- **Two year results of raltegravir vs efavirenz in treatment-naïve patients**

This presentation was important to see extended results from this early (Phase 2) dose-finding study. After one year everyone receiving raltegravir (n=160 people) switched to the 400mg twice-daily dose and 38 patients continued with efavirenz. Background nukes were tenofovir+FTC.

Viral load results at 96 weeks were similar to after one year - with 84% patients achieving undetectable viral load (less than 50 copies/mL) and an average drop of -2.3 logs. CD4 counts, which increased by 150 cells/mm3 over the first year, continued to increase by another 70 cells/mm3 over the second year in each group.

Side effects were similar in the raltegravir and efavirenz groups, but twice as many patients reported neuropsychiatric side effects with efavirenz (32% vs 16%). Raltegravir had no negative impact on lipid levels. Some laboratory markers were higher in the raltegravir group (ie creatine kinase) which showed the importance of results from the larger Phase 3 study that is currently ongoing.

Virological failure was generally rare, but was associated with either integrase or NNTRI mutations when it did occur, depending on which treatment patients were taking.

- **TMC-278 (rilpivirine) – two year results on a new NNRTI: a potential alternative to efavirenz**

Results from another Phase 2 study compared 3 doses of a new once-daily NNRTI called rilpivirine, to efavirenz, both with background tenofovir + FTC. After two years

70-75% patients in all groups had undetectable viral load <50 copies/mL.

Side effects were either similar in both arms, or occurred less frequently with rilpivirine (ie rash 9% vs 21%, nervous system disorders 31% vs 48%; psychiatric disorders 16 vs 21%) and lipid increases were lower with rilpivirine.

Some of these side effects may be dose related, and the lowest rilpivirine dose (25mg rather than 75mg or 150mg) is going forward into larger studies (Phase 3) which are needed for a drug to be approved.

Virological failure was similar in each group, and included similar levels of NNRTI resistance.

- **Apricitabine (a new RTI that is active against some nuke-resistant HIV)**

One-year safety results were presented on this new RTI: 6 months on one of three apricitabine doses and a further 6 months with all patients on 800mg. Previous studies showed a -0.7 to -0.9 log reduction in viral load after 3 weeks compared to 3TC in treatment experienced patients (CROI 2008, Abs 793).

Side effects reported in this study were generally similar to 3TC, which is one of the drugs least associated with side effects. There were no reports of peripheral neuropathy, myelotoxicity, hyperlactaemia, lipidaemia, hyperlipasaemia, pancreatitis, rash, hypersensitivity or liver or kidney toxicity from apricitabine.

- **Other new NNRTIs**

Short term (7-14 days monotherapy) results from two other new NNRTIs were presented in the second Track B late-breaker oral session.

http://www.aids2008.org/Pag/PSession.aspx?s=287

IDX899 (abstract THAB0402) – previously reported at the Resistance workshop in June - and **RDEA806** (abstract THAB0403) – from a study at the Chelsea and Westminster Hospital.

Both compounds produced close to -2.0 log reductions after 7 days at all doses (which makes them more potent than rilpivirine) with no short-term side effects, including CNS efavirenz-like side-effects (which would have been expected in a short study). Longer studies are needed to look for rash, lipids, lipodystrophy etc.

- **Non-refrigerated formulation of ritonavir**

Equivalent results for a new heat-stable film-coated formulation of ritonavir (ie one that doesn't need to be stored in the fridge), compared to the current gel capsule formulation were shown in a study in HIV-negative adults. This has the potential to improve quality of life, through easier storage and extending treatment choice, especially in hotter countries.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=16161

5. Abacavir: risk of heart attack and efficacy compared to tenofovir

Two different sets of studies, both relating to abacavir, probably caused the most controversial discussions. Abacavir is widely prescribed and recommended as a first-line combination in developed countries, though far less widely used in other settings due to caution about hypersensitivity reactions and low access to the genetic B-5701 test.

These studied two areas:

i) Does abacavir increase risk of heart attack and other cardiovascular problems?

ii) Is abacavir less effective in people who start treatment with a viral load over 100,000 copies/mL, especially when compared to tenofovir?

Both questions were highlighted by independent researchers and countered by studies from GSK, who manufacture and market abacavir.

- **Abacavir and heart disease: SMART study supports links found by D:A:D study**

In February 2008 at the Retrovirus conference (CROI), the D:A:D researchers reported finding that current or recent abacavir use approximately doubled the risk of having a heart attack compared to other nukes. This was most pronounced in real terms in people who already had high risk of heart disease.

Even though D:A:D was the largest study ever designed to look at heart disease and HIV treatment (over 33,000 people were followed for over seven years), many people wanted confirmation of these results in other studies before they would believe them.

In Mexico, we heard that the large randomised SMART study found similar results (seeing 2 to 4-fold increases in risk) when they looked at abacavir use by patients in their database. This risk was increased however heart disease was defined (ie strictly by having a heart attack, or more broadly including other aspects of heart disease).

They found the risk was most significant in people with high cardiovascular risk (those with 5 or more other risk factors) and that this was seen whether abacavir was compared to all other nukes, or just to tenofovir. They also reported that baseline inflammatory markers (IL-6 and hsCRP were higher in people on abacavir and that this could explain the higher risk, although the design of these studies can only report the association and not show that abacavir caused this. See also the HEAT study below).

Whenever a safety signal is found in a licensed drug, the manufacturer has to investigate. Earlier in the conference, GSK had presented the results from their own database of clinical trials, where they couldn't find a link to heart disease. However, this doesn't balance the findings from D:A:D and SMART for several reasons.

Firstly, patients in GSK studies were generally younger and healthier and people with higher cardiovascular risk are usually screed out from taking part in new drug studies. Age increases cardiovascular risk and GSK patients were around 10 years younger. The GSK database was not designed to look for or record cardiovascular disease, and most importantly, it was not powered to be able to see any link to abacavir use – whether or not they saw anything, there were too few events to make this statistically meaningful.

In summary, HIV-positive people need to check their risk of heart disease using online Framingham calculators. If it is high (20% risk of heart attack in the next 10 year), then use an alternative drug to abacavir, and look at other lifestyle changes that could reduce this risk (exercise, diet, stopping smoking etc).

SMART study (THAB0305):
http://www.aids2008.org/Pag/PSession.aspx?s=291

GSK analysis (WEAB0106):
http://www.aids2008.org/Pag/PSession.aspx?s=264

- **Is abacavir/3TC (Kivexa) less effective than tenofovir/FTC (Truvada)?**

The second abacavir controversy in Mexico realted to whther Kivexa is less effective than Truvada at high viral loads. This was raised by an independent US study called ACTG A5205 that randomised 1800 patients to either abacavir/3TC or tenofovir/FTC. Earlier this year the study was changed after a safety analysis showed a higher rate of treatment failure in almost 800 patients who started treatment with a viral load that was higher than 100.000 copies/mL. Other drugs in the study were either efavirenz or atazanavir/r, but results from use of these drugs are not yet available.

GSK responded to these findings with results from the HEAT study and a combined analysis (called a meta analysis) from six abacavir studies.

The HEAT study is the first randomised study comparing abacavir/3TC to tenofovir/FTC and an analysis by baseline viral load showed no differences after 2 years in terms of risk of virological failure or tolerability – although it is a smaller study (with under 700 patients, with only around 150 patients in each group with baseline viral load higher than 100,000 copies/mL).

Interestingly, the HEAT study found that IL-2 and hsCRP inflammatory markers both dropped significantly during the first year of treatment, but that this occurred in both the abacavir and tenofovir groups at a similar rate.

The meta analysis was not able to measure outcomes in exactly the same way as ACTG A5205 and wasn't comparing abacavir to tenofovir, but reported similar response rates at higher and lower viral load levels.

Nevertheless, both European (EACS) and UK (BHIVA) guidelines have thought these results important enough for tenofovir to be either preferred as a first-line regimen or preferred in patients with higher baseline viral loads.

Both studies were presented at the late-breaker oral presentations on Thursday:

http://www.aids2008.org/Pag/PSession.aspx?s=291

HEAT study: (late breaker poster)

http://www.aids2008.org/Pag/Abstracts.aspx?AID=15873

6. Treatment access

Three themes relating to treatment access focused on roll out and funding, side effects (mainly to d4T) and resistance.

- **Roll out funding and sustainability**

How to maintain existing programmes and how to expand these to the growing numbers of people who are still not accessing care;

A poster on Monday showed the projected figures for Russia, where over 400,000 people are already diagnosed in 2007 (from less than 2000 in 1997), with 37,000 people on treatment in 2007 compared to 85.000 people in need of treatment. (Monday poster 0168). In this study the limiting step to increasing the numbers of people on-treatment was due to low numbers of healthcare workers. Several other presentations talked about 'task shifting' which is where, for example, nurses could be trained to prescribe first-line HIV treatment.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=11847

- **Side effects**

The risk of serious side effects limits the benefits from first-line d4T-based combinations which are still taken by over 70% of HIV-positive people globally. There is little access to second line treatment. Many of these discussions involved access to tenofovir and PIs, and at affordable prices.

For example the Thai study in the poster discussant on Monday showed almost 30% on d4T-based regimens had lipoatrophy that was significant enough to switch treatment.

http://www.aids2008.org/Pag/Abstracts.aspx?SID=220&AID=10927

- **Resistance**

Resistance is also a concern from d4T-based treatment, particularly when viral load monitoring is not available to know when treatment has failed. A study of 101 people with non-B sub-type HIV, failing first-line treatment in Malawi, showed very high rates (up to 50%) of nucleoside cross-resistance, including K65R (which is cross resistant to tenofovir and ddI).

http://www.aids2008.org/Pag/PSession.aspx?s=256

7. Prevention

In many ways some of the most significant advances reported at the conference related to the science underlying prevention of transmission.

- **ARV treatment as prevention**

Viral load drives and changes the risk of infection associated with any specific risk. It increases all risks during seroconversion, and more controversially, recent Swiss guidelines have argued that in people with viral load suppression to less than 50 copies/mL for at least 6 months, any sexual exposure may be low to zero risk.

See the web cast on "HIV transmission under ART" – Sunday for an excellent debate on many aspects of the recent Swiss guidelines on transmission.

http://www.aids2008.org/Pag/PSession.aspx?s=485

Tthe Swiss guidelines study was Monday poster 0202.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=6151

See also Monday poster 0046 on the HPTN 052 study enrolling 1750 sero-different couple and following them for 5 years to see where randomizing half the HIV-positive people to treatment will have a knock on effect of reducing transmission. International – Asia, Africa, Latin America – only 2% gay couples.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=12810

- **Pre- and Post-Exposure Prophylaxis (PEP/PrEP)**

Macaque studies with tenofovir/FTC still provide the most promising data in support of using oral HIV drugs to prevent infection – whether taken before (Pre-) or after (Post-) exposure to HIV.

A study presented to the 3rd International Workshop on HIV Transmission, that was held in Mexico two days before the IAS meeting, reported that three schedules of intermittent dosing offered a similar level of protection to PrEP/PEP taken every day.

ie: 2 hours before and 22 hours after

22 hours before and 2 hours after

3 days before and 2 hours after

Practical issues relating to how PrEP/PEP might be used were looked at in several studies.

For example, a Thai late breaker poster (Mon LBPE1164) - showing once or twice a week is possible for most people and making cost implications, if successful, a bit easier.

Roughly a third of MSM interviewed either had sex once that week or not at all, with only 15% having sex twice, indicating how much PrEP/PEP could be saved in practice if it is possible to dose when you want to have sex, rather than needing to dose every day.

Please remember that all PrEP is only theoretical until proven in studies.

- **Microbicides**

A study of tenofovir/FTC gel used as a microbicide protected 6/6 female macaques from SIV infection after 20 exposures ('challenges'). In contrast, 7/8 control macaques (5/6 placebo; 2/2 no gel) became infected after a median of 3.5 challenges (range = 2-11). Low levels of both ARVs were consistently detected in the plasma of all macaques 30 min after vaginal application.

This is the first successful proof-of-concept study of an effective microbicide in macaques and should fast-track human pilot studies.

As with the initial macaque oral PREP/PEP studies with tenofovir, and later tenofovir/FTC this is exciting and compelling data that needs human studies.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=15936

- **Circumcision**

The success on reducing transmission on a population level (rather than individual level) from circumcision is dependent on setting – ie background risk has to be high, but also on other factors.

In high prevalence heterosexual settings, male circumcision of young adult continued to reduce the risk of catching HIV by over 60% from previous reports at two years out to 42 months.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=16237

The mechanism for this protection has been linked to a thinner keratin layer in the inner compared to the outer foreskin and higher concentration. A laboratory model for this was constructed and reported in one of the presentations.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=5036

Importantly, circumcision can reduce risk of other infections for both male and female partners, including high-risk Human Papilloma Virus (HPV), by approximately 50%.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=15881

As with studies from Peru and Australia last year, a UK study presented in Mexico showed that circumcision seems to have no benefit for gay men on a population level.

A late breaker poster from the UK showed no statistically significant difference in rates of HIV infection in ~16,000 MSM from 5 different ethnicities relating to whether or not they were circumcised. (LBPE1163).

An explanation may be that circumcision status is likely to only protect MSM who are exclusively active, and that this is likely to represent a small proportion of MSM in any survey.

8. Other clinical studies

- **Atazanavir improved lipids but not lipdystrophy**

Switching a twice-daily ritonavir boosted protease inhibitor to once-daily atazanavir/r didn't result in any reduction in central fat accumulation, though lipids improved, in a study from the Chelsea and Westminster Hospital.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=4171

- **Safety of switching from T-20 to raltegravir if you have an undetectable viral load**

Switching from T-20 to raltegravir in 50 treatment-experienced patients with undetectable viral load – easy and safe with only one very low level blip (63 copies/mL). What you would hope, but useful to see the data.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=3930

See also similar results from a smaller study.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=14684

Another T-20 switch study suggested that there may be a previously unrecognised interaction between raltegravir and tipranavir that resulted in liver complications.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=7276

- **Treatment-experienced patients getting undetectable viral load with newest drugs**

High rate of virologial suppression in 103 treatment-experienced patients using raltegravir + darunavir/r + etravirine. French independent investigator study with 90% patients seeing viral load suppressed to less than 50 copies/mL after 24 weeks and 95% suppressed to less than 400 copies/mL.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=16101

- **Responses to treatment by race and gender**

Analysis of race and gender responses in several drug trials (lopinavir/r; darunavir, etravirine) were interesting to see and it is important that companies are now taking this seriously, although, generally, few differences were seen.
Darunavir (by gender, age, race and subtype)

http://www.aids2008.org/Pag/Abstracts.aspx?AID=12495

http://www.aids2008.org/Pag/Abstracts.aspx?AID=11221

Etravirine (PK by age, sex and race)

http://www.aids2008.org/Pag/Abstracts.aspx?AID=8430

Atazanavir/r vs lopinavir/r (some viral load and CD4 differences by race)

http://www.aids2008.org/Pag/Abstracts.aspx?AID=4835

Lopinavir/r (by gender and race)

http://www.aids2008.org/Pag/Abstracts.aspx?AID=4835

http://www.aids2008.org/Pag/Abstracts.aspx?AID=12835

The darunavir/r GRACE study, enrolling mainly non-Caucasian women, had a 25% a drop out rate not linked to viral failure, showing the importance of other issues.

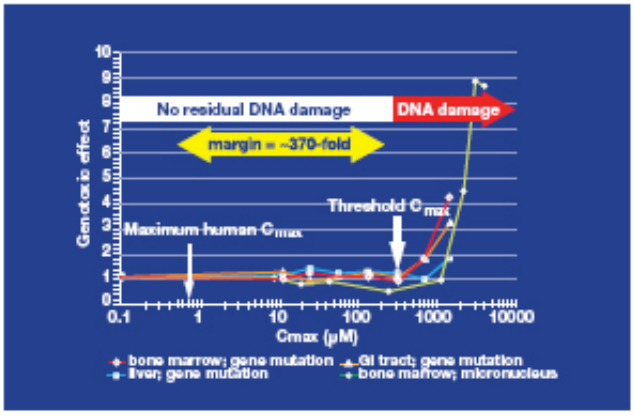
http://www.aids2008.org/Pag/Abstracts.aspx?AID=11972).

9. Nelfinavir contamination and safety recall

Just prior to the conference, the EMEA issued a statement that they are not looking to pursue follow-up registries for people exposed to EMS that caused nelfinavir to be withdrawn last year.

The summary slide shows that based on animal studies the maximum exposure anyone could have been exposed to is 370-times lower that the concentration at which predicted toxicity could occur.

Figure 8. Risk assessment for Viracept patients calculated using Cmax (measure of peak exposure)



The EMEA has interpreted these results to mean that safety registries do not need to be established.

http://www.aids2008.org/Pag/Abstracts.aspx?AID=16184

10. Children and treatment

The number of children on ARV treatment has increased from 75,000 in 2005 to around 200,000 in 2007. Treating children is as effective as treating adults but many children still don't receive treatment and mortality is still high.

The CHER study showed the importance of treating all children aged less than 12 months irrespective of CD4 count, CD4% or clinical stage. This is only possbile with access to viral load testing. For example, only 6 out of 24 countries in Asia pacific region have access to PCR (viral load) technology. Currently, most children are diagnosed in hospital when they much older and already ill.

Posters on peadiatric forumulations included AZT/3TC/nevirapine, etravirine, d4T/3TC, a scored Combivir tablet, and tipranavir oral solution (posters MOPE0183-0186).

....PS... the cure

Finally, although a talk by top research head Tony Fauci referred optimistically to a cure, reading between the lines this meant being treated within weeks of infection - not one for most of us. Still, optimism is always worth checking:

http://www.aids2008.org/Pag/PSession.aspx?s=49

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