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SUMMARY

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List of abbreviations

3TC	Lamivudine
ABC	Abacavir
ARV	Antiretroviral
ATV	Atazanavir
AUC	Area under the curve
AZT	Zidovudine
BID	Twice daily
BMD	Bone mass density
CAF	Cell-associated factor
CMV	Cytomegalovirus
Combivir	AZT plus 3TC
CSF	Cerebrospital fluid
CTL	Cellular T-cell toxicity
ddI	Didanosine
DOT	Directly observed therapy
EFV	Efavirenz
FAQ	Frequently asked question
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
IAC	International AIDS Conference
IDU	Drug user
IDV	Indinavir
IDV/r	Indinavir boosted with small doses of ritonavir
IFN	Interferon
IL	Interleukin
LDCs	Less developed countries
LDL	Low density lipoprotein
LTNP	Long-term non-progressor
LTR	Long terminal repeat
MRC	Medical Research Council
MTCT	Mother-to-child transmission
NNRTI	Non-nucleosidic inhibitor of reverse transcriptase
NRTI	Nuleoside inhbitor of reverse transcriptase
OI	Opportunistic infection
OR	Odds ratio
PASS	Pediatric AIDS Severity Score
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PK	Pharmacokinetics
RTI	Reverse transcriptase inhibitor
RTV	Ritonavir
SIV	Simian immune deficiency virus
SQV	Saquinavir
TDF	Tenofovir
TNF	Tumor necrosis factor
TPV	Tipranavir
TT	Tetanus toxoid
VL	Viral load

1. Elephants, Oon, and Frequently Asked Questions

Hirschel- What's it like to organize an AIDS conference? You prepare for years, go to never-ending committee meetings, pore over budgets, fight with organizations that are very important but you didn't know existed beforehand, carefully select the right topics, the right speakers, get buried under an avalanche of abstracts, emerge in time to worry some more over budgets, get into more arguments on program and speakers, drink beer with representatives of organizations that now you'll never forget, until finally, arrives the Opening Ceremony which invariably runs over time. The five days pass in a blur, you have no time to go to any sessions, until arrives the Closing Ceremony which invariably runs over time.

And the 15000 or so delegates, what will they first remember when they think about your conference? Well, one will always remember that his computer wouldn't recognize his memory stick anymore and how he spent a frantic hour on the phone home until his secretary sent him the PowerPoint file by Email. Another will remember the rude waiter at the restaurant in Berlin, the sunset on Lake of Geneva, the heat in Yokohama… nothing the organizer can influence.

So what will I remember about the 15th World AIDS Conference in Bangkok, from July 11 to 16 2004? The elephants. There were thousands of them, on posters all over Bangkok, small, large, and gigantic. A dozen or so milled about the conference center, where they contributed to the opening ceremony. Nearby there is an elevated highway, under which were living some poor laborers in a lean-to, tending a small garden and drinking. One 55 year old man pulled the tail of an elephant who happened to pass by. The elephant was not amused, stomped on him and killed him.

The victim's friends accused "Absolutely Handsome", a male of 22 years, but this was contested by the chief mahout, who vouched for "Absolutely Handsome"'s irreproachable character, and denied the journalists' speculations to the effect that "Absolutely Handsome" was moody and had strong sexual urges. He said the misdeed was the work of a stray elephant. How a stray elephant made it to downtown Bangkok was not further explained. On Friday the newspaper reported that a veterinarian and a forensic expert had examined "Absolutely Handsome", and had found no human remains on his toes or his incisors.

Then our plane left. Stay tuned for the denouement of the elephant mystery – at the 16th World Aids Conference, in Toronto, 2006.

I'll also remember Oon, born congenitally HIV-infected in 1987. In 1996, a retired Swiss physician living in Pattaya (140 km South of Bangkok) told me about her: very immuno-suppressed, weighing only 17 kg, with tuberculosis, living in an orphanage founded by a priest named Giovanni Contarin in Rayong. We rummaged in drawers and cupboards for leftover Indinavir, 3TC, and zidovudine, and managed the TB/HIV co-infection with the help of Thai colleagues, Email, and good luck.

Oon miraculously reappeared on screen before the Opening Ceremony, in a video prepared by the International AIDS Society. She is now 17 and looks healthy and robust, the oldest known survivor of congenitally acquired HIV infection in Thailand. For more on Oon, see www.**camillianrayong**.8k.com, or www.fides.org/eng/approfondire/aids_b_11.html

FAQs:

1. *Why is this summary in English, and not in French and German as were all previous editions since 1990?* I (BH) was the "chief rapporteur" for track B (Clinical Care), which means that I presented a summary of the Conference at the closing ceremony. During the conference, I received daily summaries from my rapporteur team (Zala, Pett, McNally, Koulla, and Eron) - in English. I'd appreciate feedback from readers: Is it worth it to spend time and effort for translation, or are you happy with the English version?
2. *How many people attended ?* 17000, the Bangkok Post said, more than in Geneva (13800), Durban (10000), and Barcelona (15000)
3. *In what ways did this IAC differ from its predecessors?*

   One important difference: In Thailand, the government organized it, through the Ministry of Health. Hence, resources were employed which were not available elsewhere. For instance, the city was almost papered over with publicity for the conference. Schools had a week off to lighten traffic. The Thai government invited politicians from other countries to attend.
4. *What was this thing called the "Leadership Track"?*

   An attempt to have politicians and public health officials discuss priorities in the fight against HIV, during the conference. I'm not sure that this was un unqualified success: "Leadership" sessions were poorly attended, and many leaders were in the program who did not attend.
5. *How about the demonstrations and the riots?* No riots – the TV reports in Europe and the US may have given the wrong impression. As usual, some of the pharma booths were trashed, but with forewarning so that anything breakable could be removed beforehand. Also as usual, US officials were copiously insulted. There seems to be a pattern: Insult the Americans, they come up with cash, insult them some more, they come up with more cash, etc. In the meantime, the Europeans give next to nothing, particularly Switzerland, whose contribution to International AIDS Programs amounts to approximately 1 US$ per person, compared to the USA's 17 $ per person.
6. *Was it humid and hot?* Yes, except indoors: Hotels and the Conference Center were air-conditioned down to long-sleeves-and-sweater temperatures.
7. *Was the traffic bad?* Not so bad, it helped that schools were off. It took only 30 to 40 minutes to get from the hotels to the Impact Conference Center, approximately 25 km away and close to the airport.

8. *Did you see Richard Gere?* Yes, and I can prove it because I took a picture for my daughters (13 and 15). They said: "Wasn't there anybody younger?"

And with that, let's turn to serious matters:

2. HIV Biology

Hirschel: As everyone knows by now, this is emphatically **not** a basic science conference. Track A's demise has been forecast for many years, but it survives, just barely, for instance by putting subjects which at CROI would be in track B (such as drugs in pre-clinical stages) into track A. Here is an interesting abstract that I can't put anywhere else:

> **OrA1012 HIV-1 group M isolates are significantly more fit than group O or HIV-2 strains: Ex vivo fitness matches prevalence in the epidemic.** ***E. Arts,G. Vanham. et al. Case Western Reserve University, Cleveland, United States***

After testing all known subtypes with head-to-head dual infection/competition experiments, three main classes separate: HIV-1 group O (least fit), HIV-2, and HIV-1 group M (most fit). Within group M, subtype C is least fit (but maybe most frequently transmitted because of slower disease progression?)

3. Immunology

3.1 Humoral Immunity

HIV immunology swings

> **Sy146: Vicky Polonis ,** ***The Henry M. Jackson Fnd., Rockville, MD, United States;***

Pett- HIV immunology swings: from cellular to humoral to innate and back again. Five years ago, it was all cellular - and indeed, the cellular immune response is still thought to play a predominant role in predicting the success, if any, of candidate vaccines – but interest in the humoral immune response has now re-emerged from a 15 year eclipse, fueled, perhaps, by the realization that practically all successful vaccines elicit neutralizing antibodies. However there are major hurdles in the HIV arena: the correlates of neutralizing protection are poorly understood and replication of assays in the lab are not standardized. A consortium, established since 2000, is actively pursuing these issues in an endeavour to overcome some of the problems.

3.2. Cellular Immunity

> **Sy148: Julie McElrath,** ***Fred Hutchinson Cancer Research Center, Seattle, United States***

The anti-HIV immune response is inefficient: Why?

Pett, Hirschel- What determines viral setpoint ? In this study neither the magnitude of IFN-gamma production by CD8+ T-cells, nor the number of epitopes recognized, nor functional avidity correlate with the set-point. CD8+ T-cell responses were initially narrow (n=2.3) and broadened over time to all HIV proteins, with regulatory and later structural proteins recognized. The host's HLA type influences the speed of HIV progression, but the mechanisms through which this happens are still unclear.

And why does the cytotoxic lymphocyte response (CTL) fail to control virus? There are many explanations for which there is some experimental evidence (which is another way of saying that nobody really knows): down regulation of class I HLA

antigens by the product of the viral nef gene, loss of CD4+ T-cell help, upregulation of Fas-ligand on CD8+ cells followed by apoptosis, thymus damage and viral escape.

Mallal (Sy274) presented data on the evolution of viral escape. The evolution of viral escape necessitates repeated sequencing of virus and correlation with recognition of epitopes: months and years and hundreds of thousands of $s per patient! In one such closely followed individual, the earliest changes in the virus were in *Tat* and *Vpr*, with escape unrelated to the magnitude of avidity of immune response. Escape appears to be occurring within the epitopes, but also in flanking amino acids and through amino acid insertions.

Immune responses are HLA restricted and as HLA is invariant during the life of the host, this has implications for both immune control of the virus and the selection pressure exerted on the virus to develop certain changes in epitopes. During evolution of the human species, certain HLAs provide better protection against some pathogens than others; therefore different HLA are selected in different populations in different geographical locations. By analogy, it appears likely that prevalent HLA types have influenced the evolution of HIV pseudospecies in different populations.

CTL responses to the virus are not immediate following infection but evolve over weeks and months. Innate immunity predominates initially. Allelic variants in the HLA exert pressure on the virus to develop escape mutations but at a cost to the replication capacity (RC) of the virus. If such a virus is now transferred into someone lacking that HLA allele e.g. from a HLA B57-positive to a HLA B57-negative person, it will revert to wild-type.

- Vaccines will have to induce rapid responsiveness, activity at site of transmission, avoid escape, maintain durable anti-viral activity. As vaccines will undoubtedly exert pressure to escape, they may need to be designed to evoke immune responses against escape virus as well, and as these escape viruses are likely to be influenced by the HLA of the host this is potentially an enormous task.
- Apart from escape, other mechanisms may contribute to lack of control of HIV. CD8 dysfunction was described in LTNP and progressors, who had low perforin production, and non-proliferation of CD8+ after exposure to HIV antigens. Appears to be a maturation block, with an inability of cells to proliferate best described as replicative senescence secondary to high antigen burden.

Gamma-interferon Elispots don't correlate with cytotoxicity

Hirschel: One big problem in investigating CTL: Measuring the actual cytotoxic activity is expensive and time-consuming; it also necessitates cell culture which brings its own artifacts. Therefore, IFN-gamma production by lymphocytes, in response to HIV antigen, is used as a substitute for cytotoxic potential, but how well does it correlate with cytotoxicity?

OrA1051 The cytotoxic activity of HIV-1-specific CD8+ T cells is preferentially mediated by the subset of cells secreting both interferon-g and TNF-a following viral stimulation. ***M. Lichterfeld, M. Altfeld. et al. Partners AIDS Research Center, Massachusetts General Hospital, Boston, United States.***

Lichterfeld et al. from Bruce Walker's group at the MGH, used a novel cytotoxicity assay base on caspase 3 substrates as indicators of target cell death. Then, they correlated results in this assay with IFN-gamma and TNF-alpha secretion. They found no significant correlation between IFN-gamma secretion and cytotoxicity. The correlation was only evident with cells which secreted both IFN-gamma and TNF-alpha.

3.3. Innate Immunity

Sy145: Jay Levy. ***University of California San Francisco, San Francisco, United States***

IFN- α producing dendritic cells, and CAF

Pett- Jay Levy summarized data on the innate immune system.

- The plasmacytoid type-1 interferon-α producing dendritic cell (PDC) responds to HIV-infected CD4+ T-cells. This interaction leads to reduced production of virus by that cell, with the interaction blocked by CD4+ antibodies, gp120 neutralising antibodies and inhibitors of endocytosis, e.g. chloroquine. PDC are productively infected with HIV, but have poor replicative capacity. In long term non progressors (LTNP) even with very low CD4+ T-cells (n=4, with 2 with CD4+ <4 cells/μL), PDC levels were in the normal range (0.26% of peripheral white cells). In other patients an inverse relationship between high VL and low PDC exists. Immune based strategies that appear to increase PDC and therefore might have future clinical application include the use of GCSF, FLT3 Ligand and Thrombopoietin.
- He then described the anti-viral activity of CD8+ T-cells, which was neither class I/II restricted and was mediated by a secretory cytokine, CD8+ T-cell antiviral factor (CAF), which appears to block viral transcription of both RNA and protein. LTNP appear to have high CD8+ T-cell anti-HIV activity. This activity declines over time and is increased by IL-2 and -15, IFN-alpha and anti-CD3. But what is "CAF"? After 15 years of research, this is still not clear.

  Hirschel (From a chat in the bus with David Ho): Alpha-defensins have antiviral activity and were thought to be a candidate (Science, October 2002). However, it has since then become clear that defensins are produced by neutrophils and then absorbed by CD8+ T lymphocytes. When all beta-chemokines are eliminated, more than 80 percent of CAF disappears. So DH's guess is that CAF corresponds to beta-chomokines, but an individual molecule "responsible" for CAF may never be identified.

3.4. Varia

Three types of immune response, with their proper cytokines

Sy147: Giuseppe Pantaleo. Laboratory of AIDS Immuno-pathogenesis, Division of Immunology and Allergy, CHUV, Lausanne, Switzerland

Pett- GP reported on cytokine production of memory CD4+ T-cells in the setting of 3 different models of antigen burden:

- cleared antigen (e.g. tetanus toxoid (TT)). IL-2 is the dominant cytokine
- protracted low level antigen load (eg chronic CMV/HSV): Both IL-2 and interferon gamma
- high ag burden (e.g. untreated HIV), where IFN-gamma is the predominant cytokine.

This issue has implications for the monitoring of vaccine responsiveness which is focused on IFN-gamma responses. In those re-exposed to TT, the dominant IL-2 response was followed by an IFN-gamma response. In structured treatment interruption of treated HIV, a polyfunctional response predominated which differed from the response when ART was used, with a predominantly IL-2 response.

GP proposed a model to explain the differing functionality of CD4+ T-cells in the setting of different antigen burden with an increasingly IFN-gamma response in response to high chronic HIV burden, which shifted to a mixed cytokine response with ART. All patients studied in this group had high CD4+; it is unlikely that the IL-2 production of CD4+ T-cells will be restored when the CD4 count at ART commencement is low.

4. Epidemiology

OrA1139. Detecting HIV-1 dual infections in a high-risk cohort in Tanzania. ***S Piyasirisilp, F McCutchan et al. Henry M. Jackson Foundation, Rockville, MD, United States***

Follow-up of a high-risk cohort in Tanzania every three months to determine the incidence of co-infection and superinfection. 71 percent had a single infection and an astonishing 28 percent a dual infection, with a mix of the three subtypes (A, C, and D) prevalent in Tanzania. In one patient who was followed in detail, recombination was observed "while it occurred" (Hirschel)

OrA1141. Breakthrough HIV-1 infection in long-term exposed seronegative individuals. ***T. Zhu, J. McElrath. et al. University of Washington, Seattle, United States***

It's not who you think it is

These were homosexuals in discordant couples. Inevitably, during longer follow-up, some get infected (Long term exposed seroconverters, LSC). However, contrary to expectations, the infecting virus is only rarely the partner's. Rather, it comes from other sexual contacts. Indeed, the genetic distance between the infecting virus and the partner's virus is much greater than would be expected by chance. This suggests that LSC have a partner virus-specific immunity. (Hirschel).

5. Vaccines

Tricks to increase immunogenicity of vector-based DNA vaccines

Hirschel- We did not cover vaccine sessions very well, but the sessions we saw were disappointing in that there was not much new. Exceptions:

> **OrA1344 Novel forms of DNA vaccines decrease viremia in juvenile and neonatal macaques upon SIVmac251 challenge.** ***B K Felber, G N Pavlakis et al. National Cancer Institute at Frederick, Frederick, United States.***

DNA vaccines may become more immunogenic if vaccine vectors produce secreted, or intracellularly degraded antigens. Viral protein genes were fused either to the secreted chemokine MCP-3 (targeting the viral proteins to the secretory pathway); or to a beta-catenin peptide (targeting the viral proteins to the proteasomal degradation pathway). These vaccines were then used in macaques. Upon challenge with SIV, infection was not prevented, but viral loads remained lower than those of controls for 12 to 30 weeks.

> **A5680. Control of viremia after antiretroviral treatment and therapeutic vaccination with novel forms of DNA vaccines in chronically SIV-infected macaques.** ***B K Felber, G N Pavlakis et al. National Cancer Institute at Frederick, Frederick, United States***

In another experiment, infected macaques were treated with ART, and vaccinated while treated. ART was then stopped, and macaques controlled viremia for up to 18 months. Control correlated with measures of *in vitro* SIV-specific immune response.

However, in several other instances where macaques were protected against infection, or had a lower viremia than expected, measures of specific IR did not correlate with protection, suggesting a role for the innate immune system.

6. Antiretroviral treatment

6.1. Introduction

What's the best HIV treatment – Avoid the perfume fallacy !

Hirschel- It is the 64 thousand dollar question – or should we say, in view of the stakes, the 640 million dollar question – and nobody has an answer. Nonetheless, a few courageous souls have tried; thus the title of presentation[1]: "Which antiretroviral regimens yield the best odds of survival in San Francisco?", by S.Y. Chen. She examined patients who had AIDS before 1997, and were treated with HAART from the start. Some had died by the end of 2002, others had lived. The statistical analysis is complicated, but the essentials are easily grasped: An effective treatment would be more frequent in the living, an ineffective treatment more frequent in the dead.

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[1] **OrC1082. Which antiretroviral regimens yield the best odds of survival in San Francisco?** ***S Y Chen, W McFarland et al. Johns Hopkins Bloomberg School of Public Health, Baltimore, United States***

Chen compared the so-called 3 by 5[2] regimens recommended by the World Health Organization (i.e. combinations of either nevirapine or efavirenz, with stavudine and lamivudine, or with zidovudine and lamivudine) with other drug combinations. It turns out that the odds of survival in San Francisco are better when HAART started with a WHO-approved combination, than when using other combinations. In conclusion: Avoid the Perfume Fallacy ! (the belief that what's more expensive is necessarily better). Patients in poor countries who have to rely on the WHO-approved drugs for reasons of cost can take heart: The limited evidence available suggests that they are at the least not less effective than more expensive alternatives.

Caveats for Chen et al.:

- retrospective, non-randomised. Although cases and controls were matched carefully, un-detected bias is still possible (for instance, if sicker-looking patients received PIs rather than NNRTIs)
- the study was done in a setting where alternative treatments (after failure or intolerance of "3 x 5" regimens) were available.

Pett- One approach to the management ART was summarized by Havlir (Plenary session):

- the first regimen should be focused on control of viral load, with early switch for first failure
- the second on CD4+ and viral load, with later switches in case of failure
- and the third on CD4+ T-cell count, with the use of other strategies including IL-2 to preserve CD4+. Soriano went onto emphasize that it is viral load over 10,000 that appear most associated with CD4+ T-cell loss (see The Lancet 2004; 364:51-62)

When to Start, What to Start With

Zala- (Session B03) A variety of clinical settings were considered. Although population-based studies conducted in the developed world validated the 200 CD4 T cell threshold for initiation of therapy, little information has been available for special groups of patients and PWA from resource limited settings. To better define the best time for initiation of HAART, a probabilistic computer simulation was constructed with data from a cohort of 6000 HIV infected individuals in the US (Braithwaite [3]). In this model, initiation of ARV at 200 CD4 cells rather than at 350, decreased survival by 1.0 year and treatment duration by 1.5 years in a referenced 40 y/o individual with 100.000 cps/mL at baseline. However, a survival benefit from early initiation of therapy was reduced by many other variables including

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[2] The expression refers to WHO's goal of treating 3 million people in developing countries by ART at the end of 2005

[3] **OrB1079 Estimating the optimal threshold for initiating antiretroviral therapy in HIV disease** ***R.S. Braithwaite, A.C. Justice. University of Pittsburgh, Pittsburgh, United States***

older age, poor adherence to HAART and drug related toxicity, indicating the need for clinicians to carefully balance determinants of clinical outcomes at initiation of HAART.

A more difficult situation is faced by patients and providers in undeveloped areas of the world with limited access to monitor surrogate markers of disease progression. The correlation between CD4 T cell counts and the WHO clinical staging was established within a cohort of 339 patients at a Hospital in Phnom Pehn (Chel[4]). In this analysis, clinical criteria identified 94 % of patients in need of HAART, indicating the late stage at which HIV infected patients seek care in this region.

In summary, the optimal threshold for initiation of antiretroviral therapy remains uncertain, and seems to depend on patient characteristics, endemic opportunistic infections and health care systems in different areas of the world. In resource limited settings, the high proportion of patients presenting with advance HIV disease emphasizes the need to strengthen voluntary counseling and testing programs for timely identification of patients eligible to receive antiretroviral therapy.

HAART is getting better all the time, or at least the lab results are.

OrC1157. Prognosis up to five years after initiating HAART: Collaborative analysis of prospective studies ***M. Egger. On behalf of the ART Cohort Collaboration; University of Bern, Bern, Switzerland***

Pett- Egger reports from the ART collaboration. This collaboration was established in 2000 by pooling 12 cohorts in Europe and North America, to model prognosis in ART-naïve patients starting ART.

5 year results: mean age 37.5 years, 20,379 patients, 24% female, 23% AIDS at starting HAART. Median year of starting HAART 1999, 70% started with PI-based regimen and 12% started with 4+ drugs. 62,000 years of follow-up

Factors considered in the model included: age (<50 or >50 years), IVDU, clinical stage at time of HAART (Aids Defining Infection vs. no ADI), CD4+ T-cell count (5 strata), HIV VL (<100'000). Five time points considered at years 1, 2, 3, 4 and 5. At 5 years of follow-up AIDS or death risk was 6.5-74%. Full results are posted on the www.art-cohort.collaboration.org.

There is an ongoing debate regarding clinical outcome depending on when ART initiated. In those with VL <100,000, AIDS free and CD4+ <350 or above 350, there was approximately 1% risk of ADI or death i.e. *no difference in outcome despite starting HAART at a lower CD4 count*. However, these results need to be treated with caution as this is not a randomized controlled study.

Baseline characteristic over time: The median CD4 count at the start of HAART was 164 in 1996, rose to 260 in 1998, and fell again to 199 in 2003. Mean age,

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[4] **OrB1081. Clinical criteria only as compared to clinical-immunological criteria for initiating ART following the 2003 WHO guidelines in a Cambodian patient cohort.** ***S. Chel, W. Schrooten. Sihanouk Hospital Center of HOPE, Phnom Penh, Cambodia.***

and the percentage of those with stage C disease before start of HAART, remained constant. The percentage of IDUs dropped from 20 to less than 10 percent.

The odds of reaching an undetectable viral load have improved: Compared to an odds ratio of 1 in those starting HAART in 1995/1996, the OR was 2.6 in those starting HAART in 1998, 3.8 in 2000, and 4.0 in 2002-2003. However, Kaplan-Meier plots of AIDS free survival show that those starting in more recent years did do better than those starting earlier. As a matter of fact, 1998-9 does best. There is preliminary evidence of worsening of prognosis for the year after 2000.

Summary: 80 risk strata have been used which have high discriminatory power. While viral response improved over time, however this does not appear to translate into improved prognosis – why?

Possible explanations:

1) Non-related deaths being classified as AIDS?
2) Composition of the study populations is changing, more people from the South
3) Is there a drop off in use of prophylaxis? If true, this should favor some opportunistic infections rather than others

Further analysis is necessary.

Less side effects?

Hirschel-[5] Swiss HIV Cohort Study researchers cataloged side effects, by specifically asking about them in all patients having a cohort visit during one month. The first such study was done in 1999; it was repeated in 2003. Over that span protease inhibitor use dwindled from 76% to 42% of the study group, while nonnucleoside use rose from 11% to 26%. The Swiss team recorded drops in prescriptions of d4T (50% to 22%), nelfinavir (45% to 24%), and indinavir (22% to 7%), but wider use of lopinavir (1% to 9%), efavirenz (12% to 25%), abacavir (10% to 36%), and AZT (48% to 65%).

Clinical side effects that clinicians attributed to antiretrovirals fell significantly from 67% of the cohort in 1999 to 53% in 2003 ($P < 0.001$), while the overall rate of abnormal lab readings held steady at about 40%. Prevalence of fat accumulation or loss rose significantly, while rates of diarrhea, nausea, and high cholesterol fell significantly ($P < 0.05$ for all).

The rising prevalence of fat changes probably reflects accumulating antiretroviral experience in the Swiss cohort, the researchers conclude. Although overall side effect rates have dropped, they note that more than half of their patients still suffer from antiretroviral toxicities.

Source: O. Keiser, M. Rickenbach, A. Telenti, et al. Did the burden of adverse events due to antiretroviral treatment change over the last four years? The Swiss

[5] Inspired by a summary written by Marc Mascolini, and published on the Conference Website

HIV Cohort Study. XV International AIDS Conference. July 11-16, 2004. Bangkok. Abstract WePeB5949.

It also works in Uganda and Brazil

OrC1158. The introduction of ART in an active community based cohort in Uganda and its impact on HIV related mortality. ***P. Munderi, H. Grosskurth et al.Medical Reasearch Council/ Uganda Virus Research Institute, Entebbe, Uganda***

(Koulla) Historical comparison on AIDS and death before and after ART. The Entebbe cohort was set up in 1995, initially to evaluate pneumococcal vaccine. 2766 enrolled, majority with CD4+ 200 or less, 6000 person years of observation.

In February 2003, under the MRC research program, the DART trial was initiated, enrolling ART-naïve adults with CD4+ counts <200, but in fact >50% below 100. Patients in DART were compared with the period from May 1995 - Jan 1998 in the Entebbe cohort.

The decrease in mortality following initiation of ART was approximately 10 fold. However, after 1998, the Entebbe cohort also saw reduced mortality due probably to Bactrim and INH prophylaxis.

Conclusion: Even in very advanced patients with CD4+ <50 ART is highly beneficial.

OrC1160. An ecological study of HAART in Brazil: The impact of universal access on AIDS incidence and mortality (1984-2000). ***M.E.M. Enriquez,, F.I. Bastos et al. Stanford University, Stanford, United State.***

1996 saw free access to HAART in a developing world country with a changing epidemic: more females, more heterosexual transmission, pauperization. Objectives: analyze nationwide trends in AIDS incidence and mortality; impact of HAART according to gender differences and geographic differences. 120'000 deaths with more in men. Mortality rates decreased for both sexes after 1996, but declines were more pronounced declines in men than women. Regional rates for decline are less in the North than in the South. Access to drugs may be a problem i.e. 200+ drug dispensing units in the south with only 12 in the North. Inequalities between genders and regions have to be addressed.

6.2. Reverse Transcriptase Inhibitors

6.2.1. Nucleoside analogues NRTIs

Reverset

Eron: Robert Murphy presented additional data on **dd4FC**, a cytidine nucleoside analogue reverse transcriptase inhibitor[6]. 10 days of monotherapy of **Reverset™** in treatment-naïve individuals or as an added single agent in patients who were treatment experienced and had a measurable viral load on HAART.

- In treatment naïve patients receiving 50, 100 or 200 mg daily HIV RNA levels fell by 1.7 to 1.8 log10 c/mL and 37.5, 50 and 87.5% of subjects had HIV RNA < 400 c/mL at 10 days, respectively.
- Ten treatment experienced patients were enrolled with 8 receiving 200 mg dd4FC daily and 2 received placebo. Half of the treated patients had > 3 TAMs, 5/8 were on TDF and 5/8 were on 3TC containing regimens. Mean viral load decline was approx 0.8 log10 c/mL, 4 of 8 had HIV RNA fall below 400 c/mL and all patients had some decline in HIV RNA. Notably after discontinuation of the dd4FC HIV RNA remained 0.4 log10 c/mL below baseline though all data collection was not complete in all the patients.

Ten days of therapy with dd4FC was well tolerated in both treatment naïve and treatment experienced patients. The data suggest that dd4FC may be a simple once daily nucleoside analogue which is very potent in treatment naïve individuals and may have some activity in treatment experienced individuals with nucleoside analogue resistance.

Tenofovir and stavudine (d4T) compared

(Gallant 4538) Hirschel- HAART appeared in 1996, but progress continues. Newer drugs are easier to take, with lesser side effects, but continued excellent efficacy. To judge the latter, one measures the percentage of patients whose viral load becomes undetectable.

In the so-called Gilead 903 study all 600 patients were treated with efavirenz and 3TC. In addition, half received tenofovir, and half received d4T. Mean plasma HIV RNA at baseline was 81,300 copies/mL, and approximately 40 % of participants on each arm had more than 100.000 copies at study entry. Mean CD4 T cell count at baseline was 276 and 283 in the TNF and d4T arm respectively. The study was doubly masked, and lasted 144 weeks (nearly three years).

Efficacy was excellent in both groups: Approximately 80 percent of patients had a viral load below 50 after 24 and 48 weeks, and still 70 percent after 144 weeks. Regarding toxicity however, tenofovir scored better. For instance, lipodystrophy was observed in 3 percent of those on tenofovir compared to 19 percent of those on d4T, peripheral neuropathy in 3 and 10 percent respectively, cholesterol rose less, and triglycerides not at all. Fears of renal toxicity proved unfounded, but patients with pre-existing renal failure did not qualify for the 903 study. There remains some doubt about possible bone loss observed in both groups, reason to continue to follow the patients for at least another 2 years.

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[6] **MoOrB1056. Potent anti-HIV-1 activity of Reverset™ following 10 days of monotherapy in treatment-naïve individuals.** ***R.L. Murphy[1], M.J. Otto et al. Northwestern University, Chicago, IL, United States***

In conclusion, tenofovir/3TC/efavirenz is an efficacious and surprisingly non toxic drug combination that can be given once daily.

Zala: Gender issues regarding efficacy and safety were highlighted in a sub analysis of the Gilead 903 study that compared TDF + 3TC + EFV versus d4T + 3TC + EFV (De Ruiter[7]). In general, results and toxicities did not differ between males and females. Of note, a loss in hip and spine BMD was significantly greater in females, although this was not translated in a higher rate of bone fractures.

6.3. Protease Inhibitors

6.3.1. Ritonavir-boosted indinavir

Zala: Pending further therapeutic options in resource limited settings, NRTI sparing regimens were presented as an alternative for patients failing a nucleoside-based regimen. The HIV-NAT 009 explored the efficacy of switching patients from a failing double nucleoside regimen to a combination of ritonavir boosted indinavir (800/100 BID) in combination with efavirenz (600 OD) (Boyd[8]). At 96 weeks of follow up, 42 (69 %) patients were able to achieve and sustain < 50 copies/mL in an ITT analysis. Dislipemia and nephrotoxicity were common adverse events. Improvement in markers of nucleoside toxicity including hemoglobin and liver enzymes were observed following switching. In view of the low average weight in Thailand (51 kg in this study), the indinavir dose was probably excessive; the authors now use 400 to 600 mg b.i.d.

6.3.2. Lopinavir/r and Fosamprenavir/r

Eron- Since 2000, Lopinavir/r (Kaletra ®) has been the drug of choice in cases of failure of a first protease-inhibitor containing regimen. A possible alternative was Amprenavir which was hampered by its pill burden (at least 14 pills daily when combined with ritonavir). Fos-amprenavir is a pro-drug of amprenavir, with better absorption. AUCs and half-life are prolonged by ritonavir, so that once daily administration appears possible.

OrB1055. GW433908 (908)/ritonavir (r): 48 week results in PI-experienced subjects: A retrospective analysis of virological response based on baseline genotype and phenotype. ***R C Elston, E DeJesus et al. GlaxoSmithKline, Stevenage, United Kingdom.***

Eron- One hundred and forty nine subjects were randomised to fos-amprenavir/r 1400 mg/200 mg QD, 149 to fos-amprenavir/r 700 mg/100 mg BID, and 130 to LVP/r 400 mg/100mg BID. Both drugs were given with nucleoside analogues optimised with genotype resistance testing, in subjects who had documented treatment failure on either one or two previous PI-containing regimens. Subjects

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[7] **OrB1083. Long-term safety and efficacy of tenofovir DF (TDF) versus stavudine (d4T) in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral-naïve women: 144-week results.** ***A. De Ruiter, A.K. Cheng et al. St. Thomas' Hospital, London, United Kingdom.***

[8] **MoOrB1084. Indinavir/ritonavir 800/100mg bid and efavirenz 600mg qd in patients with combination nucleoside failure: 96 week outcomes of HIV-NAT 009** ***M. A. Boyd, P. Phanuphak et al. [1]HIV-NAT, Bangkok, Thailand.***

could not receive NNRTI. The baseline characteristics of age, race, sex, CD4 and HIV RNA were comparable across groups. Subjects randomised to LPV/r had less protease inhibitor and nucleoside RT inhibitor treatment experience. At entry, i.e. at the time of baseline resistance testing, subjects did not have to be on a PI-containing regimen, though two-thirds were. Baseline PI resistance was modest with approximately 7-11% of subjects having 3 or more primary PI mutations. The proportion of subjects with 3 or more thymidine analogue mutations at baseline was higher in the fos-amprenavir/r BID arm (38%) compared with either the once daily fos-amprenavir/r arm (28%) or lopinavir/r arm (24%). Tenofovir was used commonly in all three arms (approximately 60% of subjects).

The primary analysis was the HIV RNA area under the curve minus baseline over 48 weeks. For fos-amprenavir/r daily, fos-amprenavir/r twice daily and lopinavir/r the AUC-BL were -1.49, -1.53 and -1.76 log10 c/mL, respectively. The differences did not reach statistical significance. However, the lower bound of the confidence interval for Fos-amprenavir's effect on VL was outside the limits pre-defined for equivalent efficacy so that the trial could not establish that 908/r is equivalent to lopinavir/r. We are left with some uncertainty regarding the relative efficacy of these two boosted PI therapies in moderately PI-experienced patients, especially given the lesser treatment exposure of subjects in the lopinavir/r arms (which would tend to skew the results in favor of lopinavir/r)

- Extended follow up of randomised clinical trials of fosamprenavir, presented in prior meetings were also displayed in poster form. The SOLO Trial had shown comparable efficacy and safety of 908/r 1400mg/200mg QD and nelfinavir BID, both with a background of ABV/3TC over 48 weeks in ART-naïve subjects. 210 patients rolled over from the SOLO trial continued a 908/r QD regimen in the APV30005 by 48 additional weeks. After a total of 96 weeks on fosamprenavir, 113 patients were available for analysis. 96 % and 86 % of subjects had vRNA, 400 copies and < 50 copies/ml respectively. Median change in CD4 T cell count from baseline was + 205 cells at week 48 to + 263 cells at week 96.

> **OrB1057. IMANI-1 TC3WP Single drug HAART- proof of concept study. Pilot study of the safety and efficacy of Kaletra (LPV/r) as single drug HAART in HIV + ARV-naive patients-interim analysis of subjects completing final 48 week data.** ***J C Gathe, Jr., J Nemecek et al. 1Therapeutic Concepts, PA, Houston, United States***

Effective treatment for HIV equals multiple drugs (or does it ?)

Hirschel- Eight years ago, the era of highly active anti-retroviral therapy started when several drugs, each with only short-time efficacy, were combined. The combination blocked development of resistance, and since then, all effective treatment combinations have used at least three drugs.

Many were surprised therefore, when Joe Gathe reported on patients treated with only Kaletra (ritonavir-boosted lopinavir) last November at ICAAC. Follow-up at that time was still short (24 weeks), and there was doubt as to whether the promising results would hold up.

Well, they do. The 30 patients were quite sick when they started treatment, with a high mean viral load of 262,000 c/mL, and a low mean CD4 cell count of 169.5 cells/mm3. After 48 weeks on Kaletra only, two-thirds (20/30) had HIV RNA < 400 c/mL. Most of the 10 subjects who were no longer on LPV/r monotherapy changed therapy for non-virologic reasons. On average, CD4 cell counts increased substantially (317 cell/mm3). Selection of resistant genotypes did not occur. These provocative initial, non comparative data suggest that the strategy is now being tested in two randomised clinical trials, one of which uses LPV/r for maintenance treatment following induction with combined therapy. Potential advantages include sparing of multiple ART classes, limiting toxicity and decreasing cost. The pill burden (3 pills twice daily), however, is not less than what's achievable with some of the more popular combination regimens.

Resistance development during long-time lopinavir treatment is discussed in Chapter 6.7.1.3.

6.3.3. Saquinavir/r

If you have a good drug, test it in Thailand!

Hirschel-Zala: The effect of boosted BID saquinavir has been evaluated in the MaxCmin 1 and 2 trials. At this conference, results from two studies on once daily ritonavir boosted SQV (1600/100) were presented.

The STACCATO study was designed to explore a strategy of CD4 guided treatment interruptions in patients receiving ARV in Europe, Canada, South America and Thailand. The first 167 treatment naïve HIV infected Thai patients enrolled in the Staccato study completed 24 weeks of induction therapy with SQV-hgc/r 1600/100 mg OD plus 2 NRTIs. Efficacy and CD4 cell counts were evaluated at 24 weeks (Ananworanich[9]).

In intention-to-treat analysis, 91 percent of patients had a viral load of < 50 copies per ml. This is, to my knowledge, a new record, and may be due both to the intrinsic activity of the drug combination used, and to the excellent compliance of Thai patients. Median change from baseline in CD4 cell count over 24 weeks was 109 cells/mm3. Main side effects of therapy included diarrhea (19 %), nausea and vomiting (12 %) and peripheral neuropathy (13 %), probably related to the nucleoside backbone, since changed to tenofovir/3TC.

Compared to IDV/r, SQV/r is equally efficacious but less toxic

Zala - The SPRINT trial (JSG Montaner[10]) was a randomized, open label, multicenter trial designed to compare once-daily SQV/r with twice-daily IDV/r plus

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[9] **B4469. A Prospective Cohort Study of Efficacy and Safety of 2 NRTIs plus once-daily Ritonavir boosted-Saquinavir Hard Gel Capsule (SQV-HGC/r) at 24 weeks.** ***J. Ananworanich, B. Hirschel. et al. The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Geneva University Hospital, Geneva, Switzerland***

[10] **B4488 Simplified protease inhibitor trial (SPRINT): Antiviral effect of once daily saquinavir SGC plus ritonavir (SQV/r) vs twice daily indinavir plus ritonavir (IDV/r)** ***J.S.G. Montaner. J. Singer et al. Canadian HIV Trials Network, Vancouver, British Columbia, Canada.***

2 NRTI. The primary outcome of the study was the proportion of patients who had pVL <50 copies/mL and who were still on their originally assigned PI at 24 weeks. A total of 147 patients (80 % male) were enrolled. Baseline characteristics of participants were comparable between treatment arms including proportion of PI naïve patients (90 %) and median pVL (5.0 log10/ml). Median change in plasma HIV RNA from baseline was 3 log10 in each treatment arm. Proportion of patients with < 50 copies/ml and still on the assigned PI was 51 % (SQV/r) and 42 % (IDV/r) {p=ns}. However, proportion of patients discontinuing therapy due to an AE was 10 % and 26 % respectively {p=0.02}. In summary, SQV 1600 mg/RTV 100 mg once daily and IDV 800 mg/RTV 100 mg twice daily with 2 RTIs were equally effective in achieving pVL <50 copies/mL at 24 weeks. However, the IDV/RTV arm had a higher rate of discontinuations due to adverse events.

These and other studies confirm the concept that once daily ritonavir-boosted PIs are effective and safe to use with PK support to ensure adequate plasma drug levels. A new formulation of saquinavir is awaited to reduce pill burden and to improve the convenience of OD saquinavir/r based regimens.

6.4. Other substances

6.4.1.Entry Inhibitors

6.4.1.1. Enfurvitide (T-20 – Fuzeon ®)

Eron- Long term (96 week) data were presented on enfuvirtide (T-20) plus background therapy optimised by genotypic and phenotypic resistance testing as part of the TORO I and TORO II studies [11] Over 50% of subjects originally randomised to enfuvirtide were still on therapy at 96 weeks. Twenty-six percent of all subjects originally randomised to enfuvirtide plus OB had HIV RNA < 400 c/mL at 96 weeks and 17% had HIV RNA < 50/mL at this time. Thirty-nine percent and 31% of all subjects randomised to enfuvirtide plus OB had at least a 50 cell and 100 cell increase in CD4 count, respectively, at this time point. Diarrhoea and fatigue which were common during the first year of therapy were much less common in the second year. The incidence of pneumonia which was approximately 0.5 to 1% per 8 week period did not increase from the first year to the second.

Cheaper and orally bioaivailable enfurvitides?

Hirschel: Enfuvirtide (Fuzeon) has the disadvantages of high costs of production, and that it has to be injected. Jiang et al.[12] used high-throughput screening to identify small molecules which bind to gp-41 and inhibit the conformational change necessary for membrane fusion, just as Fuzeon does. These compounds will

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[11] **OrB1058 TORO: 96 week virological and immunological response and safety evaluation of enfuvirtide with an optimised background regimen** ***K Arastéh, M Salgo et al. EPIMED c/o Vivantes Auguste-Viktoria-Klinikum, II, Berlin, Germany.***

[12] **OrA1232 Identification of small molecule HIV-1 fusion inhibitors that block the gp41core formation.** ***S Jiang, A K Debnath et al. New York Blood Center, New York, NY, United States***

hopefully lead to the development of fusion inhibitors which are orally bio-available and cheaper to make than Fuzeon.

6.4.1.2. Co-receptor inhibitors

Hirschel: A novel CCR5 antagonist, 873140, exhibits potent in vitro anti-HIV activity[13]. This is the product developed by GSK, with an IC50 of only 0.3 nM in vitro, prolonged receptor occupancy (weeks…) and good oral bio-availability. Additive or synergistic activity when combined with current RTIs and PIs.

The epitopes of gp-41 which interact with CCR-5, and CXCR-4 have been defined over the past few years. It is now possible to construct peptides with similar 3-dimensional structure as these epitopes, with the hope that they will inhibit entry. One of the candidate peptides, called POL2438, runs out to be a highly specific blocker of CXCR4; in vitro activity was observed at a concentration of 10 nM [14].

Sei et al.[15] screened a library of substances at the National Cancer Institute with an assay system designed to detect blockers of the gp120-CD4 interaction. They came up with NSC 13778, an antimony-containing compound of molecular weight 319, which shows antiviral activity at approximately 1 microM, and competes with gp120 for CD4 binding.

A humanized monoclonal antibody directed against CD4 was tested in reconstituted immunodeficient (SCID-hu) mice [16]. Viral loads became undetectable for 14 days after a single injection. Presumably the antibody blocks the interaction of gp120 and CD4.

6.4.1.3. Maturation Inhibitors

Maturation inhibitors disrupt conversion of the gag (capsid) precursor protein (CA-SP1 or p25), to the mature form p24. A small molecule, PA-457, which inhibits this step was first presented at the CROI 2003. It is not an anti-protease, but directly targets the gag precursor. Further details are now available:

- Inhibitory concentrations are low (10nM), and the drug has anti-HIV activity after oral administration in scid-hu mice. Synergy or additivity with established anti-HIV drugs [17] PA-457 appears to undergo glucuronidation mediated primarily by 1A3. It does not inhibit the cytochrome P450 system.

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[13] **OrA1231 A novel CCR5 antagonist, 873140, exhibits potent in vitro anti-HIV activity.** *J Demarest, L Boone et al. GlaxoSmithKline, Research Triangle Park, NC, United States; [2] ONO Pharmaceutical, Osaka, Japan*

[14] **OrD1207 HIV/TB perception among dense populations in Bangkok, Thailand** *O Rhucharoenpornpanic, T Rodraksa et al. AIDS Control Division, Department of Health, BMA, Bangkok, Thailand*

[15] **OrA1308 A new class of small-molecule HIV entry inhibitors that target the gp120-binding domain of CD4.** *Q Yang, S Sei et al. Laboratory of Antiviral Drug Mechanisms, SAIC/NCI-Frederick, Frederick, MD 21702, United States*

[16] **OrA1230** *In vivo* **control of HIV-1 replication with PRO 140, a humanized monoclonal antibody to CCR5.** *M Franti, P Poignard et al. Progenics Pharmaceuticals, Inc., Tarrytown NY, United States*

[17] **PeA5643 The first-in-class maturation inhibitor, PA-457, is a potent inhibitor of HIV replication both** *in vitro* **and** *in vivo. G P Allaway, C A Stoddart et al. Panacos Pharmaceuticals, Gaithersburg, MD, United States*

These data suggest that PA-457 will not have significant drug-drug interactions. PA-457 exhibits good oral bio-availability and a long half-life in rats and marmosets with moderate oral bio-availability in mice and dogs [18]

- Continuous culture in the presence of PA-457 results in the emergence of resistant mutants. These mutants map to the p-25 gene, which supports the proposed mechanism of action.

6.5. Scheduled Treatment Interruptions (STIs)

Hirschel- Consider your average successfully treated HIV-infected patient. He (or she) is in his forties; his CD4 cell count, although previously low, is now above 500. His risk of AIDS-related complications is close to zero, and his life expectancy probably normal, i.e. some forty years. Forty years of continuous anti-retroviral therapy? In view of the inconvenience, expense, and side effects of HAART, many patients eye such prolonged treatment with little enthusiasm, and would like to stop.

Blunt the rebound

A symposium on STIs started with an overview by Franco Lori examining the rationale for STIs. These certainly reduce pill burden (yes), and probably costs and toxicity. Regarding toxicity, a beneficial effect on lipids is evident in studies by Dybul et al., and Lori's own data. Apart from that, the cost and toxicity benefit has yet to be clearly shown in the long-term studies. The same is true for quality of life advantages. Regarding the disadvantages of STIs, such as a fall in CD4 counts, development of resistance, and increase in contagiousness, they are all linked to the viral rebound during STIs. Diminish the rebound, and you'll improve the risk-benefit profile of STIs – the question is how to blunt the rebound. Many interventions, from hydroxyurea to GM-CSF to therapeutic vaccination, have been tried, and Lori is quite optimistic about this approach – an optimism which I (BH) do not share.

Stopping therapy could invite trouble. The virus will surely rebound and might become resistant, and CD4 cells will decline again. Is it better to bear with continuous therapy, or to undergo scheduled treatment interruptions (STIs)? The short answer is that nobody knows, but that many try to find out.

Endgame for wowo

One approach which looked promising three years ago involved treating for one week, then stopping for a week, then treating again for a week, and so on (*week on – week off* or wowo). It was hoped that the treatment interruption would be too short for viral rebound to occur; no viral rebound means no CD4 count decline and no increase in contagiousness. However Jintanat Ananworanich (TuSy191, and AIDS 2003, 17:F33–F37) showed that with a protease inhibitor-based combination in Thailand, there was an unacceptably high rate of viral breakthrough. Using

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[18] **PeA5644 In vitro and in vivo disposition of PA-457, a novel inhibitor of HIV-1 maturation.** ***D E Martin, G P Allaway et al. Panacos Pharmaceuticals, Gaithersburg, United States***

efavirenz, Mark Dybul (Symposium, no reference) now reports that failures have also occurred in Uganda. The one week on, one week off approach is likely to be abandoned.

STI and resistance

Many patients and physicians worry about the development of resistance during STIs. It is easy to stop, but when you need the treatment again, will it still work? Ananworanich[19] reported on patients who had their treatment (2NRTIs+SQV-HGC1600 mg/RTV100 mg QD) interrupted as long the CD4 count exceeded 350. After 96 weeks of such CD4-guided therapy, they were again treated continuously. Results were reassuring: After 24 weeks of continuous therapy, 23/24 had a viral load below 50 copies per ml. Subjects who followed at CD4 guided therapy interruption took 46% less antiretroviral medication than those on continuous therapy. This small study suggests that CD4 guided therapy may be an effective way to reduce cost of therapy though there did not seem to be a reduction in toxicity or an improvement in quality of life in this study. Ironically, in developing countries where the cost of a CD4 count or viral load may approach the cost of one month's therapy with generic medications the savings of a CD4 guided therapy may be modest.

Here come the French: Window and Trivacan

CD4-guided therapy implies measuring the CD4 count; such measures are not available everywhere. Hence the proposal to interrupt therapy for fixed periods. The French trial named "Window"[20] ANRS 106– Window: A prospective, randomized, multicenter trial of intermittent therapy in HIV-infected patients with successful viral suppression under HAART] enrolled 400 patients who were randomized to either continuous therapy, or to a schedule of 8 weeks on, 8 weeks off therapy for 96 weeks. Final results will only be available at the end of 2005, but so far, things are going well, with only a moderate decrease in CD4 cells. 52% of subjects have completed the study and 7 (approximately 3%) had met the immunological primary endpoint (decline of CD4 counts to < 300 per μL). At the start of "Window", 30 percent of patients had viruses with one or another drug

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[19] **OrB1283 A randomised trial of continuous, CD4-guided and one week on – one week off HAART in 74 patients with chronic HIV infection: week 108 results.** ***J. Ananworanich, K. Ruxrungtham et al. The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT).***

[20] **OrB1285 ANRS 106– Window: A prospective, randomised, multicenter trial of intermittent therapy in HIV-infected patients with successful viral suppression under HAART.** ***B Marchou, P Aboulker et al. . ANRS 106 study group, Hosp Purpan, Toulouse, France.***

resistance mutation, with no increase during the trial. About 80 percent of patients had a viral load below 400 copies at the end of each 8-week treatment period. Patients with mutations reacted just as well to treatment, as patients with wild-type virus.

Dr. Danel and her colleagues presented the study design for a large treatment interruption study that is ongoing in Abidjan[21]. Progress report on a structured treatment interruption (STI) trial: Trivacan ANRS 1269 trial, Abidjan, Côte d'Ivoire). The study with a planned enrollment of 840 is now fully enrolled with most of the patients receiving an EFV-based therapy. After > 6 months of follow-up, patients with CD4 > 350/mm3 and undetectable viral load are randomized into three arms: (i) continuous HAART, (ii) fixed STI cycles of 2-month treatment interruption followed by 4-month re-treatment and (iii) unfixed STI cycles with CD4 cell count-guided re-treatment and treatment re-interruption. More than 70% of patients who have passed the 6 month time point are eligible for randomization based on HIV RNA and CD4 cell count and most of the patients eligible for randomization have been randomized.

In another interim report of an ongoing study, Dr. Marchou of the ANRS presented data from a study comparing continuous HAART to 6 cycles of alternating 8 weeks off and then 8 weeks on therapy for a 96-week period (**.** The primary endpoint is **a** confirmed CD4-cell count decrease to < 300/mm3 (primary end-point). Secondary endpoints include plasma viral load (pVL), resistance, safety, clinical lipodystrophy, quality of life, and cost-effectiveness. Patients with a nadir CD4 < 100 cell/mm^3 and those on NVP or abacavir were excluded. 197 subjects per arm have been randomized. Surprisingly the study team revealed that Viruses from a subset of patients on the intermittent therapy arm were examined for resistance development and no increase in the prevalence of resistance was noted over 40 weeks.

In summary, the safety data regarding resistance and the effect of re-treatment look encouraging. However, advantages and disadvantages of STIs can only be gauged by comparison with a continuously treated control group. Results from such comparative trials will have to await 2005, 2006, or even later: the largest study, called SMART, will enroll 6000 patients and is expected to continue to the end of the decade.

Important STI trials currently in progress:

Name	Sponsor	July 2004: N recruited/total	Endpoints	Timeline	Comments
SMART	NIH	2000/6000	AIDS or death	2009	Only clinical endpoint trial. Compares CD4

[21] **OrB1284 Progress report on a structured treatment interruption (STI) trial : Trivacan ANRS 1269 trial, Abidjan, Côte d'Ivoire** ***C Danel, R Salamon et al. Program PACCI, Abidjan, Cote d'Ivoire.***

					guided (stop > 350, start < 250) with continuous therapy
WOWO[22]	NIH	20/20 in USA, 70/70 in Uganda	VL rebound twice > 50	2005	Results from Uganda show more failures than expected, on efavirenz/d4T/3TC: (9/33 so far). M. Dybul now champions 5 days on, 2 d off.
STACCATO	Swiss – Thai	Recruitment complete, 547 pts	VL, CD4 drugs used, resistance	End 2005	WOWO arm abandoned, because of viral load failure in 19/36 pts
WINDOW	ANRS	400/400 pts	CD4 < 300	End 2005	Trial in France, 8 wks on, 8 wks off drugs
TRIVACAN	ANRS	400/600 pts	CD4 < 300	2006	Ivory coast, 3 arms, with continuous treatment, CD4-guided, and 8 wks on / 8wks off
PART	ISS – Italy	400/400 pts	VL failure, CD4, res.	2005	STIs of fixed, increasing length. Early data show considerable resistance, especially in pts on NNRTIs

6.6. Keeping Part of a Failing Regimen

Treatment that works even while it doesn't work

Eron- Many clinicians follow patients on HAART who have had a good CD4 cell response but do not completely suppress viral replication or who have rebound of HIV RNA in plasma on therapy. These patients have a risk of toxicity from therapy and a real risk of further resistance evolution if their therapy continues. Stopping therapy is likely to be safe over the short or medium terms and should minimize

[22] RCuser 02 : WOWO : one week on, followed by one week off therapy

resistance evolution and toxicity. However off therapy the CD4 cell counts will fall gradually in most patients and therapy will need to be restarted at some point in all likelihood.

In a simple but extremely clever study Castagna and her colleagues took advantage of this clinical dilemma and randomized a group of patients with high CD4 cell counts, detectable viral loads and the M184V 3TC resistance mutation who wanted to stop therapy to 1) stopping all antiretrovirals or 2) stopping all therapy except 3TC. The primary endpoint was a fall in CD4 cell count to < 350 cell/mm^3. Unlike almost all other antiretroviral 3TC has only been shown to select for a single mutation (M184V) and continued 3TC would likely have little "mutational" risk for the patients. In addition, there have been ongoing questions about the potential benefit of an M184V mutation in terms of viral fitness or the possibility that 3TC might have continued antiretroviral activity even in the face of the 184V mutation. This study was ideally design to address these questions directly. Fifty patients were randomized. Patients maintained on 3TC had a smaller decrease in mean CD4 cell count and substantially smaller increase in HIV RNA (approximately 0.5 log10 copies/mL vs. 1.2 log10 copy per mL increase in the full interruptions arm). All 20 patients on the 3TC who had been sequenced maintained the 184V mutation and none had further resistance evolution. While replicative capacity increased in many of the patients from whom data were available on the full interruption arm; no patient studied on the 3TC only arm had an increase in replicative capacity. Caveat: At randomization, these "failing" patients had a median CD4 count of 700. From our own experience in trying to set up a similar trial in Switzerland, we know that we just don't have any of those patients…

6.7. Resistance to Anti-Retroviral Drugs

6.7.1. Mechanisms

6.7.1.1. Generalities

Low-level rebound: What to do?

Pett: Lafeuillade[23] presented a study of genotypic testing in clinic patients with viral rebound at low levels. This issue raises many challenges including what to do with these patients in terms of treatment and how to overcome amplification difficulties when virus load is low. Among 1200 patients, **22** patients with VL 50-1000 cp/mL were identified. Prior Rx: 3 with NRTIs (n=10), 4 with NNRTI and 8 with PI-based regimens. Median VL was 240 cp/mL at time of first genotype. At the time of the next genotype. the VL was approximately the same, but CD4+ T-cell counts were increased. 7/22 had unchanged mutations whereas 15 had new mutations. **Conclusion: resistance is developing during low level viremia, while CD4+ T-cell counts are still stable. The long term risk of not switching is the**

[23] **OrB1293 Resistance selection in patients with stable low levels of HIV-1 viremia.** ***A Lafeuillade,C Poggi et al. General Hospital, Toulon, France***

accumulation of further mutations with loss of viral suppression, a narrower spectrum of ART to switch too and ultimately a decline in CD4+ T-cells.

Replication capacity

Pett: Haubrich[24] presented data on virus replication capacity (RC), a measure of the ability of a virus to replicate in a certain environment. The assumption is that if the virus is less replication fit it will have lower virulence. Replication capacity varies widely in patients who are ART-naïve. After exposure to drugs the replication capacity shifts to the left, i.e. it declines on treatment. What are the clinical correlates of this? Does this translate into reduced CD4+ T-cell decline in those with less fit virus despite virologic failure?

84 patients were included, median VL 4.2 $\log_{10}$ copies/mL, median PIs used were 2, 49 mths of ART. At baseline there was a reduced susceptibility to nelfinavir and IDV. The median RC was 67. In the univariate analysis the factors associated with reduced RC were low baseline VL and high CD4 count. Certain mutations affected fitness: RC was 41 for those with the M184V vs 110 (p=0.001) for those without 184. Also, the more thymidine analogue mutations (TAMs) the less the RC. There was no strong association of PI mutations with RC except for the 82 mutation however. RC of mutant virus did not predict the response to the next HAART regimen.

6.7.1.2. RT inhibitors

Plan for success, but prepare for failure

Pett - Soriano[25]: Managing Drug Resistance in Clinical Practice.

Success of ARV = potency (inhibitory activity and genetic barrier – to sustain potency for some time) x convenience (pill burden/toxicity profile)

Two mechanisms of resistance to NRTIs:

1) Reduced binding. Such resistance is usually specific for one drug, and associated with reduced fitness, examples M184V, K65R.

2) Easier removal of the drug i.e. excision by pyrophosphorolysis. Such resistance is broad spectrum and does not diminish fitness. Example: TAMs are broad spectrum and don't affect viral fitness.

During prolonged therapy with only partly effective combinations of NRTIs (Trizivir…) increasing numbers of NAMS accumulate; when in addition the M184 mutation occurs, sensitivity to the whole NRTI class is lost. In this setting, switching as soon as failure is detected is advisable.

There is some evidence that FTC selects slower for M184 than 3TC. M184V causes hypersusceptibility to AZT, TDF, d4T, and reduced viral fitness. Strains

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[24] **OrB1294 Determinants of replication capacity (RC) in HIV-1 isolates from ART-experienced adults failing a PI based regimen.** ***R H Haubrich, R Schooley et al. University of California, San Diego, San Diego, CA, United States.***

[25] **Bs195 Managing drug resistance.** *Vincent Soriano, Spain.*

with K65R are hypersensitive to AZT, show variable loss of sensitivity to ABC, 3TC, DDI, and lose sensitivity to D4T.

In the 903 study tenofovir TDF selected for K65R, but this mutation was also found in the d4T arm. Increases in K65R (10-15%) are being seen in clinic populations, accompanying the increased use of TDF. There may be an antagonism between K65R and TAMS.

In conclusion : Plan for success, but prepare for failure

NNRTI resistance after single-dose NVP for prevention of MCT

OrB1289 Profile of NNRI associated mutations in women exposed to a single dose of nevirapine during delivery in Thailand. N Ngo-Giang-Huong, *M J Lallemant et al. Harvard School of Public Health/IRD054/Chiang Mai University, Chiang Mai, Thailand*

Pett: High rates of NVP resistance mutations (21 to 50%) have been seen in women given single dose NVP in the intra-partum period on a background of AZT. Ngo-Giong-Huong reported on the mutations seen in HIV-infected women in Thailand where the dominant circulating subtype of HIV is AE. 1445 women in this cohort had been exposed to NVP and of these, 324 women commenced an NNRTI-based regimen subsequently. All had had a genotype performed at a median of 12 days post-partum (7-17 days) and 134 (41%) harbored NNRTI resistance mutations. 96 had a single NNRTI mutation: 54/96 (57%) had K103N with the G190A in 21% as the second most common. Moreover, 8% had the Y181C mutation (this differs from data reported from other subtypes). In those with multiple mutations (2+) all had the K103N. The frequency of mutations did not appear to vary in relationship to the sampling time. Moreover, higher HIV VL was associated with a higher frequency of single and multiple mutations (p=0.01) with the highest rates seen in those with baseline VL >5 log10 cp/mL. **Conclusion: single dose NVP given to women in the intra-partum period is associated with high levels of NNRTI mutations and the risk for their development is greater in women with higher baseline VL; NNRTI mutations not previously described in this setting have been described in this Thai study and factors underlying this are unclear. The influence of underlying AZT mutations including TAMS on the emergence NNRTI mutations have not yet been analysed.**

6.7.1.3. Protease inhibitors

And the winner is…. Kaletra!

OrB1291 Extensive resistance testing during 5 years of lopinavir/ritonavir treatment in antiretroviral-naive HIV infected patients: Results from study m97-720. C Hicks, *M King et al. Duke University Medical Center, Durham, United States.*

Pett: **5-year data on resistance on Kaletra.** Treatment started for 2 weeks with various doses of Kaletra monotherapy, then d4T + 3TC backbone was added. By week 48 the most appropriate dose of Kaletra was determined and all were switched to this. 100 patients enrolled, 68 on study at week 252. 13 discontinued due to AEs, 9 due to loss of follow-up, 10 due to adherence/other issues. In ITT analysis (loss = failure) 67% <400 cp/mL and 64% <50 cp/mL after five years of

follow-up. In as-treated analysis, 99 and 94% had VL <400 and <50 cp/mL respectively. Overall, 84 had no loss of virologic response at all. Of the others, 11 had blips and 73 had none. 16 met the criteria for loss of viral control (VL >500 cp/mL), of which 8 remained on study and 8 discontinued. In all, 27 patients were eligible for resistance testing. Primary and secondary protease mutations/polymorphisms were identified and examined as was RT resistance. 17/27 had a successful genotype, 10 were not amplifiable, and median viral load at failure was 575 (range 513-828). LPV/r resistance detected was nil, d4T TAMS nil; 3 had M184V with evidence of phenotypic resistance. The presence of M184V was not associated with a higher viral load rebound. 6 patients had a substitution at a new protease site at rebound. On phenotypic susceptibility testing to Kaletra, the rebounding virus had a mean of = 0.7 x WT susceptibility to Kaletra.

Conclusion: Kaletra-based combinations are durable and well tolerated. Despite new substitutions at secondary PI mutations/polymorphisms, phenotypic resistance testing showed no resistance. Virus was re-suppressed to below LLQ after rebound using the same combination - viral rebound probably related to adherence.

6.7.1.4. Enfurvitide

OrB1292 Genotypic resistance assay for entire gp-41 sequence with identification of gp-41 polymorphisms in enfuvirtide-naïve patients and new gp-41 mutations in patients failing enfuvirtide
M R Loutfy, S L Walmsley et al. 1McGill University, Montreal, Quebec, Canada.

Pett: In patients receiving T-20 as part of a failing regimen, it appears that the HR-1 and HR-2 regions, particularly at positions 36-45 (the GIV and QQNNL region) are a hot spot for the development of T-20 resistance.

Two populations were studied: 404 (64 with non B clade virus) T20 naïve and 41 pre and post T20 failures.

Results: 127/328 of the codons in gp41 were highly conserved, 74 partially conserved, 127 variable in the B consensus virus. More natural polymorphisms were seen in non-clade B viruses. Amino acid insertions occurred at 4 locations with variable prevalence across clades. In 76 patients treated with T20, 41 had samples at baseline and on study for analysis. There was a high frequency of mutations in the GIV areas. Six new mutations including 33, 73, 75, 126, 138, 278 were described. It was apparent that mutations are cumulative with the first mutation developing after approximately 2 months, and increase over time. The correlation of these mutations with clinical outcome needs to be assessed, as does fitness and phenotypic resistance.

6.7.2. Subtypes and Resistance

Bs192 . Mechanisms of ARV resistance: HIV subtype-specific challenges. ***Marcelo Soares. Brazil.***

Pett- The prevalence of L210W is higher in subtype B compared to subtype F, and K70R is more frequent in subtype F. Certain subtypes of C appear to be hypersusceptible to PIs (e.g. Kaletra) and this appears to depend on a single

mutation. Moreover, in subtype C, some mutations such as D30N (resistance to nelfinavir) are extremely rare.

The group went onto explore whether D30N affects viral fitness. D30N can only appear with other mutations i.e. N83T with subtype C. All the D30N mutants decrease replicative capacity (RC) but this appears to be considerably more pronounced with subtype C than B. In conclusion, subtype C appears to skew the L90N pathway of resistance possibly due to structural hinderance, even though the structural basis for these phenotypic observations are not well understood.

Summary: different mutation patterns in different subtypes eg C may affect susceptibility to drugs, the development of resistance and hypersusceptibility to ARVs. The question is therefore, can the interpretation of mutations defined largely using subtype B virus be used for non B subtypes? So far, no new mutations conferring resistance have been identified. Different mutations and the way they are interpreted may influence the choice of ARVs in the developing countries world where non B subtypes predominate.

6.7.3. Transmission of Resistance

Don't panic!

Bs194 Epidemiology of transmission of drug-resistant virus. ***Jonathan Kaplan. United States.***

Hirschel- Kaplan explored the epidemiology of transmission of drug resistant virus in 3 populations: ARV naïve and recently infected; chronically infected ART-naïve and ART treated. In the first of these populations, the presence of resistance is presumably from recent infection from partner(s) with ART-treated HIV. One of the major problems with the study of transmitted resistance in this setting is the difficult to identify recently infected persons – although use of a detuned assay can overcome this. Prevalence 5-8% with report of a higher prevalence in Belgium (29%). Variations could be due to methodology including: genotype vs phenotype; selection of mutations/assay; location/risk population.

8.3% prevalence using genotype but with lower phenotypic resistance. Resistance in recently infected individuals is stable or in decline since 2000, after a rise observed between 1996 and 1999. Almost nothing is known from recent infections in LDCs. The question will become more important with the increased availability of ART in LDCs.

6.8. Side Effects

Pls harden your arteries

ThOrB1355. Determination of subclinical atherosclerosis in patients on long-term nevirapine, efavirenz, and protease inhibitor-based antiretroviral therapy by ultrasound measurement of carotid artery intima-media thickness and multislice cardiac CT measurement of coronary artery calcium. ***G Pierone, B Platt et al. AIDS Research and Treatment Center of the Treasure Coast, Ft. Pierce, United States.***

Pett: Pierone presented data on the changes in surrogate markers of cardiovascular risk namely carotid artery intima-media thickness (CIMT), coronary artery calcification and brachial artery reactivity over one year in patients on a PI-based or NNRTI-based regimen. Mean duration of HAART exposure was 3 years, 40 patients were on NVP, 40 on EFV and 40 on a PI-based regimen.

Results: The groups were well matched except those taking PI were more likely to be male (90% vs 66-73%), had significantly lower CD4+ T-cells at baseline (195 vs 433-456) and higher viral load i.e. 4706 vs 75-125 cp/mL. In addition, the PI group had slightly lower baseline LDL cholesterol but the groups were otherwise well matched for age, smoking, diabetes and Framingham risk score (note that on average this score was considerably higher than an aged-matched HIV-negative population). All patients had abnormal brachial artery reactivity, however, there was no difference in carotid artery intima, media or plaque thickness between the PI and NNRTI groups. There was a ten-fold increased risk of patients on PI for calcium deposition >100 in coronary plaques; other risks for this included duration of HIV infection, age and HT. Importantly, there was a dramatic increase in intima media thickness over one year – which equated to a substantial increase in Framingham risk. **Summary: PI-based therapy resulted in a greater increase in coronary artery calcium deposition, without any difference in intima thickness at one year. There was a striking increase in CIMT in both groups despite aggressive control of lipids. These data need to be confirmed in longer and larger studies.**

Does ritonavir boosting nix the favorable metabolic profile of ATV?

ThOrB1356 Maintenance of favorable *in vitro* metabolic profile of atazanavir when combined with low dose ritonavir. ***M A Noor, O P Flin et al. Bristol-Myers Squibb Company, Princeton, NJ, United States***

Pett: Noor explored the effect of atazanavir and ritonavir on insulin resistance of adipocyes *in vitro*. Background: insulin resistance and new onset DM are a direct effect of PI and seen in healthy volunteers given PI. The mechanism appears to be via direct inhibition of GLUT4 transporters in the cytoplasm of adipocyte and myocyte cells. All PIs decrease glucose uptake, with ritonavir and lopinavir showing the greatest inhibition and nelfinavir and SQV a lesser effect. ATZ shows little effect on the inhibition of glucose uptake. The objective of the study was to explore the effects of adding low dose ritonavir to atazanavir on insulin stimulated glucose uptake in adipocytes. Results: Insulin-stimulated glucose disposal was decreased by 24% with RTV but not affected by ATZ. Note that in those developing clinically overt type 2 DM, this index is reduced by approx 40%. Using human adipocytes, low concentrations of RTV, with or without the addition of atazanavir had no effect on insulin stimulated glucose uptake.

Conclusion: In this cell system, there does not appear to be any inhibition of glucose uptake by atazanavir with or without low dose ritonavir; further study is required in vivo.

Gynecomastia

ThOrB1357 Gynecomastia associated with hypogonadism in HIV infected patients. ***A Biglia, J.L. Blanco, J M Gatell et al. Hospital Clinic, Barcelona, Spain.***

Pett: Blanco described some data on gynaecomastia in HIV-infected men. Gynecomastia prevalence rates of 2.8-5% have been described in HIV+ve males, the prevalence in the general population being <1%. Pathogenesis unclear. Risk factors considered included: lipodystrophy, ARVs, co-existing drugs, recreational drugs, alcohol and hepatitis C coinfection. Hypogonadism is very common, approximately 15%-20% prevalence in HIV +ve males.

Objective: This was a case control study from the cohort of >2000 male patients. 40 patients with true gynecomastia (1.8 percent) and 44 randomly chosen controls were chosen. Patients were subject to breast sonography, clinical examination and laboratory tests including measurement of free testosterone, FSH and LH. There was no difference in the baseline characteristics, including time on HAART. Positive associations included hepatitis C infection (p=0.03) and lipoatrophy (p=0.02). Gynecomastia was not specifically associated with any one drug. Low free testosterone (p=0.006) due to either primary or secondary hypogonadism was strongly associated. **Conclusion: the prevalence of gynecomastia was similar to the general population. Lipoatrophy, hepatitis C co-infection and hypogonadism as defined by low free testosterone were associated.**

Osteonecrosis

ThOrB1358 Impact of treatment with HAART on osteonecrosis (OST) incidence in HIV infected patients ***M Mary-Krause, D Costagliola et al. Inserm EMI 0214, Paris, France***

Pett: **Mary-Krause** explored HAART and osteonecrosis using a 56'000 patient database with 228'000 yrs of follow-up and identified 122 cases. 74 cases were validated. Majority of patients were gay male, aged in their 40's. They had lower CD4 count nadir i.e. 79 vs 180 cells/μL, had been exposed to HAART for longer and had higher rates of past AIDS-defining infections i.e. 52% vs 28%. In the regression model, the risk for osteonecrosis increased with duration of HAART exposure, RR 2.5 for <12 mths increasing to a RR of 6.3 for 60 mths or more of HAART. **Conclusion: longer exposure to HAART is associated with increased risk of osteonecrosis, but the exact underlying pathogenesis of this bone disease with HAART is unclear. Further work is required to determine which drugs or ART classes are more associated and what strategies can be undertaken to minimize risk of bone disease in this setting.**

Increase in risk of pre-eclampsia and fetal death

ThOrB1359 Increased risk of pre-pclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. ***A Suy, J M Gatell et al. Hospital Clínic, Barcelona, Spain.***

Pett: A Spanish group reported on increase rates of pre-eclampsia (Pre-E) and foetal death in HAART treated women. Previously pre-eclampsia had been very rare in the setting of HIV and even rarer than in HIV-negative women. Now it appears that rates have increased above those seen in non pregnant women. Cohort: 472 women, 122 on HAART and pregnant with a control group of HIV +ve and –ve women. These women were prospectively studied from one centre. Pre-E definition: BP >140/90 + proteinuria after 22nd week of pregnancy and/or fetal death after 22nd week.

Results: 3% Pre-E and 0.5% fetal death. All pregnant women 2001-3 showed stable rates. In the multivariate analysis: smoking and multiparity were protective. In the HIV-infected women compared to the HIV- women, there was a 5 fold increased risk for pre-E and fetal death. CD4+ were normal, VL undetectable and patients were all on HAART (largely NVP based). Other risk factors were the time from HIV diagnosis to pregnancy and the duration of HAART pre-pregnancy 6.6% Pre-E vs 2.8% (p=0.04). There was no particular association with any specific ARV or drug group. Markers of endothelial dysfunction markers and insulin resistance were all significantly raised (but numbers are very small with 9 in each group). It's unclear why this is occurring. **Conclusion: increasing incidence of Pre-E and fetal death are being seen in the HAART era. Duration of HIV-infection and total exposure of HAART were significant risk factors. However, despite this, there were no maternal deaths and most importantly since the use of HAART in pregnancy no vertical transmission has been seen in this group.**

D4T/ddI produce lipodystrophy, 3TC/ABC do not

Pett: Shlay[26] compared prospective data on body composition changes and lipids in ARV-naïve patients receiving abacavir+ 3TC (N = 93 of which 50 in metabolic substudy) vs d4T + DDI (89, of which 46 in metabolic study). Mean follow-up was 33 mths with 7% missed visits. Baseline: Mean CD4+ 234-268, most of white ethnicity, 70% in each group on PI.

In the 1st 4 mths after HAART commencement there was an increase in BMI for both arms, followed by a statistically significant decline in the DDI/d4T group in BMI, total body fat, hip circumference, waist circumference and mid arm circumference after 4 mths. HDL-cholesterol declined for ddI+d4T, while it increased for ABC+3TC, but neither were significantly different from baseline.

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[26]: **ThOrB1360 Body composition and metabolic changes in antiretroviral-naive HIV-infected patients randomised to didanosine and stavudine (ddI+d4T) vs. abacavir and lamivudine (ABC+3TC).** ***J C Shlay, S Raghavan et al. Denver Community Programs for Clinical Research on AIDS (CPCRA), University of Colorado Health Sciences Center, Denver, CO, United States.***

However, the two rates did differ significantly from each other. In addition, there were increases in insulin resistance and insulin levels in the DDI/d4T only arm despite both arms using PI backbones.

Newfill

Eron: Serra presented anecdotal results from over 500 patients he has treated with PMMA injections for facial lipoatrophy[27] Polymethylmethacrylate (PMMA) for facial atrophy treatment: 5 years follow-up]. Many of the "before" and "after" photographs he showed demonstrated noticeable improvements however it was unclear how the photographs were selected. This therapy, which was relatively inexpensive ($500 for a course of treatment), may have limited availability outside of Brazil.

6.9. Pharmacokinetics

Turboboost: Atazanavir, ritonavir, and saquinavir

WeOrB1235 The ATSAQ-1 cohort study: Pharmacokinetic interactions of atazanav*ir (AZV) and saquinavir (SQV) in a ritonavir (RTV) boosted protease inhibitor therapy regimen. N H von Hentig, S Staszewski et al. University Hospital Pharmazentrum, Frankfurt/M., Germany.*

Zala- Dr von Hentig and his colleagues studied the pharmacokinetics of atazanavir combined with both RTV and saquinavir without nucleoside analogues and compared them to atazanavir/r and saquinavir/r with nucleoside analogues in 40 HIV-1 infected adult patients, taking SQV 1000mg BID and AZV 300/RTV 100mg QD. The ATSAQ-1 cohort study: Pharmacokinetic interactions of atazanavir (AZV) and saquinavir (SQV) in a ritonavir (RTV) boosted protease inhibitor therapy regimen). The results were compared to PK data from 100 patients treated with SQV 1000mg/RTV 100mg BID + 2 or 3 reverse transcriptase inhibitors (RTI) and 50 patients treated with AZV 300/RTV 100mg BID +2 or 3 RTI. However, I do not believe this was a randomised study. No antiretroviral activity data were shown. When given as a combination of ATV/SQV/r, median atazanavir AUC levels were raised by about 30-35% and median SQV AUC levels were also significantly increased (approximately 50%). Median ATV Cmin levels were also increased significantly (424 to 584 ng/mL). However the median C_{min} concentrations for saquinavir did not increase.

In conclusion, ATV boosts SQV, but to a lesser degree than does ritonavir.
ATV+RTV boosts SQV more than RTV alone: Here comes the turboboost!

Tipranavir lowers plasma levels of just about everything

WeOrB1236 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 *S Walmsley, K Curry et al., University of Toronto, Toronto, Canada.*

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[27]: **MoOrB1060 Polymethylmethacrylate (PMMA) for facial atrophy treatment: 5 years follow-up**
L K M Oyafuso[1], M S Serra[2], B M Troppe[31] Hospital de Infectologia Emilio Ribas, São Paulo, Brazil; [2] CT-AIDS CREMERJ, Rio de Janeiro, Brazil; [3] Hospital Universitário Clementino Fraga Filho - UFRJ, Rio de Janeiro, Brazil

Zala- Tipranavir is likely to be the next new antiretroviral approved in developed countries for the treatment of HIV infection. Sharon Walmsley and her colleagues presented pharmacokinetic data obtained from a study of TPV/ritonavir when combined with one of three other ritonavir boosted protease inhibitor regimens. 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). TPV/r has very good activity in vitro against protease inhibitor resistant HIV-1 and is likely to be used in patients who have substantial treatment experience and resistance and in whom many clinicians consider using 2 protease inhibitors boosted by ritonavir. Patients with ≥3 protease mutations at codons 33, 82, 84, and 90 were randomised to:

1) TPV/r (500mg/200mg) control,

2) TPV/SQV/r (500mg/1000mg/200mg),

3) TPV/APV/r (500mg/600mg/200mg) or

4) TPV/LPV/r (500mg/400mg/100mg), all BID.

All patients received a pre-selected investigator-defined optimised background regimen. For the first 2 weeks, all patients received an RTV-boosted single PI regimen. After 2 weeks of treatment, TPV was added to the dual-boosted PI arms. This study design allowed a direct randomised comparison of each of the boosted PI (plus optimised background therapy) with the same plus TPV.

TPV lowers amprenavir and lopinavir trough levels by approx 50% and saquinavir trough levels by approximately 85%. Baseline resistance testing showed very PI resistant virus with mean fold changes in IC50 ranging from a low of 41 fold to amprenavir to 361-fold to RTV. The baseline fold resistance to TPV was 4.7 fold. Over two weeks TPV/r plus optimised background resulted in a mean decrease in plasma HIV RNA of 1.15 $\log_{10}$ copies per mL compared to 0.38, 0.21 and 0.29 log10 copies/mL for LPV/r, APV/r and SQV/r, respectively. The combinations were all very well tolerated. **These results suggest that TPV/r will be very useful in our highly PI experienced patients though the durability of response is likely to be also dictated by the strength of the background regimen.**

No PK interactions between tenofovir, abacavir, and 3TC

WeOrB1237 In vitro anti-HIV-1 combination studies of tenofovir with abacavir and lamivudine in primary cells *F Myrick[1], M D Miller[2], K Borroto-Esoda [1]Gilead Sciences, Durham, NC, United States; [2]Gilead Sciences, Foster City, CA, United States*

Eron- Combinations of tenofovir/abacavir/3TC, as well as tenofovir/ddI/3TC have produced unacceptable rates of virological failure. It is still not clear why, although rapid selection of resistance mutations, particularly K65R, certainly plays a role. Michael Miller, from Gilead Sciences, presented in vitro data on the antiviral activity of these combinations. In vitro anti-HIV-1 combination studies of tenofovir with abacavir and lamivudine in primary cells). These experiments were conducted in activated PBMCs from healthy donors that were infected with wild-type HIV-1 (HXB2) in the presence of each 2-drug combination and with fixed

concentrations of 3TC overlaid on the 2 drug combinations. The combinations of TDF/3TC and abacavir/3TC were also tested. After 4 days, the antiviral effect of each drug combination was determined by measuring HIV-1 p24 antigen production. 3-5 replicates of each drug combination were averaged. The data were analyzed with the MacSynergy II program and by isobologram analysis.

Overall the various two and three drug combinations showed additive effects that were consistent and convincing across multiple assays and both analysis techniques. The 2-drug combinations of TFV-3TC and ABC-3TC gave a suggestion of synergy in some of the analyses. There was no antiviral antagonism observed for any of the 2- or 3-drug combinations in these primary cells.

Dr. Miller also summarized in vitro drug metabolism results presented elsewhere showing that intracellular concentrations of the active metabolites of TDF and abacavir were not affected when cells were exposed to both compounds simultaneously.

Taken in summary these data suggest that the poor activity of the triple nucleoside combinations, TDF/abacavir/3TC and TDF/ddI/3TC are unlikely due to antiviral antagonism between these agents and that intracellular drug metabolism is not the explanation for the poor results with the TDF/abacavir/3TC triple nucleoside combination.

NVP PK in HCV/HIV

WeOrB1238 Pharmacokinetics of nevirapine in HIV-HCV-coinfected patients. ***L Hénipret, R Garraffo et al. Infectiology Unit, CHU, Nice, France.***

Eron- In HCV/HIV co-infected patients who had mild HCV disease, near normal LFT, and were on prolonged NVP therapy (approximately 3 years), Dr. Heripret and her colleagues showed that NVP levels were no different than NVP concentrations in similar patients who were only HIV infected. Pharmacokinetics of nevirapine in HIV-HCV-co infected patients). However this study is subject to substantial bias given that all the patients had been on NVP for a prolonged period. This subset of patients, who had good clinical responses to NVP and limited toxicity, would be unlikely to include patients who had low levels and suboptimal response or high levels with early toxicity.

Fluconazole increases nevirapine exposure

WeOrB1239 The effect of fluconazole on nevirapine pharmacokinetics ***J Geel, J Pitt, R Wood et al. Cape Town, South Africa***

Eron- In a study that was designed and conducted several years ago, Dr. Pitt and her colleagues studied the effect of nevirapine on fluconazole pharmacokinetics in HIV-infected volunteers whose HIV RNA was suppressed on combination therapy with abacavir/lamivudine/zidovudine. The effect of fluconazole on nevirapine pharmacokinetics). 24 patients on a stable regimen of three nucleoside analogue antiretrovirals were first exposed to fluconazole (200 mg daily) for 11 days and then had nevirapine added at 200 mg daily for 14 days then 200 mg twice daily for an additional 14 days. PK studies were performed on day 11 and day 39 (the last

day of NVP dosing). The nevirapine effect on fluconazole pharmacokinetic parameters was minimal. However, compared to historical controls NVP AUC, C_{max} and C_{min} were increased by approx 50% due to lower clearance of nevirapine in the study subjects. Very serious toxicity was noted following the administration of NVP with 25% (CI 7-43%) of patients developing serious hepatotoxicity including two cases of clinical hepatitis (8.3%) and four cases of transient grade 4 transaminase elevation (16.7%). This rate of toxicity, while high, is not surprising given that the subjects were predominantly black women with relatively high CD4 counts in whom higher rates of hepatotoxicity have previously been described. The investigators stated that the toxicity did not correlate with drug level.

Conclusion:

The current dosing guidelines do not recommend changing the dose of either fluconazole or NVP when they are co-administered. At the present time there is not enough data to recommend changing NVP dose, but this PK study clearly suggests the need for very close monitoring of both the liver function tests and clinical status when NVP and fluconazole are co-administered to populations who have a predisposition for increased NVP hepatotoxicity.

A significant limitation of the study is that the estimated effect of fluconazole on NVP PK is based entirely on historical control. The controls were taken from previous NVP studies that were carried out in part in South Africa so it is probable that the baseline demographic in these controls were similar to this study population. Several audience members suggested that providing the demographics of the control population or even matching controls to the study population would be helpful in interpreting these potentially very important data.

The Thai government has developed their own fixed dose combination of nevirapine, lamivudine and stavudine. Dr. Srinarong presented data on the drug properties of this tablet known as GPO-VIR S30.[28] ([WeOrA1240] Fixed-dose combination tablets of nevirapine, lamivudine, and stavudine). No data on the activity of this compound were presented nor were the pharmacokinetics presented. There was uniform content of the 3 agents within the tablets, there was excellent dissolution properties and excellent stability over time at condition which included a temperature of 40^0 C (104^o F) and 75% relative humidity. The cost of this therapy with this tablet in Thailand is $30.00 (US) per month. **Generic fixed drug combinations, depending on their source are equivalent to the individual drug components and are cost effective.**

6.10. Eradication, therapeutic vaccination, new targets

IL-2, IL-7, OKT3, and other flushers of the reservoir

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[28] **WeOrA1240 Fixed-dose combination tablets of nevirapine, lamivudine, and stavudine.** ***P Srinarong, K Kraisintu et al. Research and Development Institute, Government Pharmaceutical Organization, Bangkok, Thailand.***

TuSy171 HIV eradication. ***Roger Pomerantz, United States***

Eron - Roger Pomerantz discussed HIV-1 eradication. I am not sure why we don't use the word 'cure'. Perhaps it is too frightening to think of eradication so bluntly. Dr Pomerantz expertly outlined the formidable barriers to eradication which include: 1) ongoing low level replication from productively infected T-cells and long-lived cell populations such as macrophages, 2) latently infected memory T-cells (perhaps the longest lived reservoir, 3) T cells with HIV in a pre-integration state, 4) defective viral transcripts within cells that may be available for recombination, 5) virus trapped on dendritic cells or in endosomes of monocytes and macrophages and 6) sanctuary micro or macro environments such as the testes, retina or CNS. Other very uncommonly infected cells that play no role in HIV pathogenesis could nonetheless provide the embers of HIV-1 that rekindle active replication when therapy is stopped.

One strategy presented by Dr. Pomerantz for eradication includes maximum suppression of active HIV-1 replication and then stimulation of the latent HIV-1 in quiescent memory T-cells to activate and release virus. His group used HAART that included ddI and hydroxyurea in 3 patients, suppressing virus to one copy per mL then added OKT-3 to broadly stimulate CD4 cells. Despite HIV-1 levels below measurable using multiple markers, all 3 men had rebound of plasma HIV-1 RNA when therapy was discontinued though the time to rebound was between 6 week and 6 months which Dr. Pomerantz saw as an encouraging sign. The source of rebound virus was blood in two of the men but was unidentified in another.

Another potential stimulator of latent HIV-1 is IL-7 and Dr. Pomerantz outlined ex vivo data supporting that IL-7 may be a more potent stimulator of latent virus than IL-2 or IL-2/PHA, though these molecules may actually stimulate different subsets of latently infected T-cells. Though not mentioned by Dr. Pomerantz other strategies to drive HIV-1 from latency by specifically disrupting suppression of transcription initiation at LTR site are being examined.

Therapeutic immunization

TuSy172 Immune-based therapy. ***Brigitte Autran. France***

Pett- Brigitte Autran discussed therapeutic immunization as a strategy where HIV antigens are delivered to patients whose viremia is suppressed by therapy with the hopes of augmenting HIV-1 specific immune responses allowing control of HIV1-replication off therapy. Barriers to this approach include limited immunogenicity of current HIV vaccines and inadequate understanding of immune correlates of control of HIV-1 replication, though strategic treatment interruptions studies (STI) in acutely infected individuals suggest that at the very least, HIV-1 specific cellular immune responses can be augmented. To date therapeutic immunization studies have been disappointing. Dr. Autran pointed out that the ANRS 094 study results suggested that level of HIV-1 RNA in plasma of therapy correlated with stimulation of cellular immune response induced by HIV-1 canary pox vaccination. However she also noted that the same canary pox vaccine studied with or without Remune in the QUEST study resulted in no better control of viral replication off therapy than

placebo. Other, perhaps more immunogenic, vaccines or vaccine combinations are being tested.

SiRNAs

TuSy173 Molecular-based therapy. ***Mario Stevenson, United States.***

Eron- Dr Mario Stevenson discussed small interfering RNAs as a molecular strategy to inhibit HIV replication. These small molecules which occur in vivo as a host mechanism for clearing ssRNA (predominantly mRNA) can also be created in vitro or transfected and expressed in cells ex vivo. These siRNA block mRNA by binding to an as yet unidentified enzyme (SLICER) and to mRNA with a specific sequence leading to cutting of the mRNA molecule. siRNA are a very useful tool for molecular virologist as they can target any part of the HIV-1 genome, are highly sequence specific and cells appear to tolerate high quantities of small RNA molecules. Multiple regions of the HIV genome could be targeted. However, introducing siRNA into cells of HIV-1 infected individuals is difficult: Dr Stevenson pointed out that these molecules in their current form would likely have to be given by infusion and may require constant levels to be active. In addition HIV-1 infected cells could not be specifically targeted and these molecules might not penetrate sanctuary sites. An alternate approach would be to transform bone marrow (lymphocyte) precursor cells ex vivo so that they express siRNA and then re-infuse these cells (gene therapy). The track record for gene therapy leaves something to be desired at this point however. Dr. Stevenson remained optimistic about the eventual clinical utility of this approach, an optimism not shared by this author.

New targets

TuSy174 Identifying new targets for novel HIV therapies. ***Amalio Telenti.. Switzerland***

Eron- Finally Dr. Telenti discussed the identification of new targets for inhibition of HIV replication. He pointed out there are 5 HIV-1 accessory proteins (tat, rev, nef, vif and vpr) that could be targeted to inhibit HIV replication. These targets are more difficult to inhibit with small molecules as their function involves protein-protein interactions or protein-nucleic acid interaction, though Dr. Telenti reminded the audience that enfuvirtide or T-20 targets a non enzymatic protein-protein interaction. He also pointed out the there are 37 known host proteins involved in HIV-1 replication and there are likely many more that have not yet been discovered. Drug developers have been somewhat “shy”, to use his term, to pursue some of these targets however molecules that bind to CCR-5 or CXCR-4 and inhibit HIV-1 binding are good examples of feasible host targets. Endogenous inhibitors of retroviral replication such as TRIM5-alpha (REF-1) and APOBEC 3G may also give us clues how we can develop new inhibitors of HIV-replication.

7. Opportunistic Infections

7.1. Hepatitis

7.1.1. Hepatitis C

WeOrB1325 Is hepatitis C infection an independent risk for death among persons with HIV infection on highly active antiretroviral therapy? ***P S Sullivan, M I Wolfe et al. Centers for Disease Control and Prevention, Atlanta, United States***

Pett: Background: ***HIV accelerates the course of HCV but the effect of HCV on HIV course is less*** clear with conflicting data from different cohorts. The ASD project reviews medical records of 16,667 HIV infected adults prospectively in 10 different centres in the US between1996-2003. The outcome of the analysis was all cause death with variables such as CD4+ T-cell count, VL, AIDS-OI and demographics controlled for. In addition, other confounding variables eg alcoholic liver disease, hepatitis B, IVDU etc were added in. Results: 24% had a hx of IVDU, 52% of these were HCV +ve. **Survival without HCV was higher (p =0.03), 5 yr survival was 90% without HCV and 84% with HCV/HIV infection. HR for death was 1.3 with HCV (data on causes of death not analysed yet).**

In another model including alcoholic liver disease, HCV did not appear to be a risk for death (HR 0.9). KM plots for survival were similar whether HCV/HIV or HIV mono-infected. However, what appears to drive decline in survival are the other confounding variables including alcoholism etc. **Limitations: incomplete information including non adherence to medication such as HAART not controlled for. Based on this data HCV does not appear to increase mortality in the setting of HIV. Recommendation: decrease alcohol consumption and adhere to HBV vaccination.**

These data are in apparent conflict with what we found in Switzerland, considering only patients on HAART. The excess death rate (in excess of what would be expected in an age-matched HIV-negative population) in successfully treated patients on HAART, was 21.7 per 1000 patient-years in HIV/HCV co-infected patients, but only 4.2 in HIV mono-infected patients. However, it is not clear whether this is due to hepatitis C infection *per se* or to alcoholism, “lifestyle” etc. (see Lancet 2003;362:877).

WeOrB1327 Impact of chronic viral hepatitis co-infection on response to antiretroviral therapy and HIV disease progression in the HIV-NAT cohort, Thailand, 1996-2001 ***C J Duncombe, G J Dore et al. HIV-NAT, The Netherlands, Australia, Thailand Research Collaboration, Bangkok, Thailand.***

Pett: Duncombe explored the ***impact of HCV on response to HAART and progression of disease in co-infected patients in Thailand***. The cohort used were those enrolled into 8 randomised clinical trials between December 1996-March 2001 at HIV-NAT (N=692). HCV was defined as HCV antibody +ve at baseline. Of those with HCV/HIV only coinfection (n=50 (7%)) 72% were male, baseline CD4+ 260, VL 4.4, hetererosexual HIV transmission; only 10% of the co-infected reported IVDU as their route of HIV transmission. Over 48 weeks, the HCV/HIV coinfected group experienced the same drop in HIV VL - approx 1.5 log10. In weeks 4-8, there was a smaller CD4+ increase in HCV/HIV, but ultimately this was not statistically significant at 48 weeks. 3.3%, 6%, 8% progression to AIDS in HIV, HIV/HBV, HCV/HIV patients respectively. **Importantly, there was 3 fold increased hepatotoxicity in those with HCV coinfection. This was a highly selected clinical trial participant population**

and by definition required fairly normal ALT/AST, and therefore these data could not be directly extrapolated to all HCV/HIV coinfected patients.

WeOrB1326 Impact of highly active antiretroviral therapy interruption strategies in plasma hepatitis C virus kinetics in human immunodeficiency and hepatitis C virus co-infected patients *C Tural, B Clotet et al. HIV Clinical Unit, University Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain.*

Pett: Tural looked at the impact of ART STI on the kinetics of HCV in co-infected patients. This was a Spanish study (TIBET) where ART-naïve patients commenced HAART for 48 weeks; when CD4+ >500 cells/μL, VL <50 cp/mL, ART was stopped. The criteria for reintroducing therapy: CD4+ <350, VL >100'000 copies/mL. 76/100 interrupted HAART. Of these, 15 patients with HCV/HIV coinfection were analysed in the first "off period".

Results: male, IVDU, HAART 49 mths, VL <50, CD4+ nadir 354, 7/15 had HCV genotype 1, median HCV VL = 5.81 log10 cp/mL, GB virus C in 7. Median time off therapy was 24 weeks. Interestingly, 5/15 (33%) showed a marked reduction in HCV viral load of >1.5 log at week 8 (p=0.028), these patients also had the highest increase in HIV viral load over the same time frame. Early decrease in HCV viral load was followed by a late increase in HCV VL at week 24-48. One of the factors affecting HCV kinetics was the presence of GB virus C at baseline which inversely influenced HCV kinetics. **In conclusion: While HCV VL is not related to underlying liver disease it is a predictor of response to HCV therapy with IFN/RBV. If this data is reproducible then HCV treatment could be introduced at a time when the HCV VL is declining in the first few months after HAART STI.** However, the danger of HAART cessation is a drop in CD4+ which negatively influences response to HCV treatment. Moreover, the late increase in HCV VL after week 24 are of concern. It is unclear what the nature of the interaction between GB virus C and HCV is, or for that matter the effect of GBV-C on HIV.

WeOrB1328 The role of GBV-C viraemia and HCV viraemia in the response to antiretroviral therapy in a cohort of HIV-infected subjects *G Antonucci, M R Capobianchi, G Ippolito et al. INMI L. Spallanzani V. Portuense , Rome, Italy.*

Pett: Capobianchi explored the ***effects of GBV-C and HCV co-infection in HIV***. Background: several prospective studies point to a beneficial affect of co-infection with GBV-C HIV co-infection, and have suggested the interaction affects the cytokine milieu in the body. ICONA cohort is an Italy-wide cohort of HIV infected adults since 1997 with 6000 patients now enrolled. 296 HCV/HIV +ve and 104 HCV –ve/HIV+ve were selected (total 400 patients). Median follow-up 178 weeks. 30% GBV-C +ve (n=117), GBV-C infection being commoner in IVDU. If GBV-C is present at baseline: statistically significantly higher CD4, lower VL and less likely to have had prior ADI. Initial response to HAART i.e. viral suppression and increase in CD4+ T-cells was not different based on GBV-C after starting HAART. However, the relative hazard of having a virological relapse was halved when the patient had GBV-C (0.03). **Summary: the effects of coinfection with GBV-C virus in HIV and HIV/HCV coinfected patients is not well understood. The presence of GBV-C virus may protect CD4+ T-cells pre-HAART and reduce**

the incidence of virologic failure on HAART by unknown mechanisms. However, other variables such as adherence to HAART should be considered before attributing causality to this co-infection.

7.1.2. Hepatitis B

WeOrA1329 Long term treatment with adefovir dipivoxil 10 mg (ADV) in patients with lamivudine-resistant (LAM-R) HBV and HIV co-infection results in significant and sustained clinical improvement.
Y. Benhamou, T. Poynard et al. GH Pitie-Salpetriere, Paris, France.

Pett: Benhamou reported on the ***long term effects of low dose adefovir*** (10mg) in 3TC- resistant HBV/HIV co-infected patients. 24% 3TC resistance is seen after 1 year and 90% after 4 years. This pilot study was established to evaluate the safety and efficacy of ADV in lamivudine resistant HBV/ with HIV co-infection. 10 mg were added to existing HAART including 3TC 150mg bid. There were 4 years of follow-up. Results: 35 patients enrolled with median age 39 yrs. Mean log10 HBV VL was 9.76, 94% were Hepatitis EAg +ve, mean ALT was 81 and 5 had cirrhosis at study entry. The HBV DNA declined rapidly over the first 12 weeks, then continuously declined i.e. -4.7, -5.9, -6.2 log decline at year 1, 3 and 4 respectively. Some patients experienced a short lived flare in ALT in 1st 12 weeks which then progressively decreased. At week 192, 58% had HBV VL <1000 cp/mL and 70% had normal ALT. Of those having baseline, year 1 (n=15) and 2 (n=12) liver biopsies, there were improvements in the fibrosis scores in 1/3 and ½ respectively. There were no changes in CD4+ or HIV VL. 3 lost eAg and 3 discontinued 3TC with no loss of HBV VL decline. No resistance to adefovir was observed, and sequencing revealed no resistance mutations. Safety: No nephrotoxicity seen. However, no data on bone density changes presented. **Despite decreased HBV VL and improved fibrosis scores, 2 of the 34 developed hepatocellular cancer and one died due to disease progression.**

Conclusion: the durability of suppression of HBV in 3TC resistance isolates is encouraging. The use of TDF in the setting of HBV/HIV co-infection will be of even greater importance.

7.2. Tuberculosis

PI 06 on TB and HIV by Papa Salif SOW of Senegal

Koulla- Over one-third of the world population is infected by *Mycobacterium tuberculosis* and HIV infection contributes largely to the TB epidemic. At least 11 million adults with HIV/AIDS are co-infected with *Mycobacterium tuberculosis* and of these 71% are in sub Saharan Africa and 22 % in South-East Asia. Tuberculosis represents the most common cause of morbidity and mortality in people living with HIV/AIDS.

The HIV epidemic drives the TB epidemic because HIV infected people are more susceptible to develop clinical TB when exposed to Mycobacterium tuberculosis, and are therefore more contagious. However, the probability of survival of patients treated for TB was much lower in HIV positive patients compared to HIV negative

patients. Therefore, the average HIV/TB patient remains infectious for a shorter period than the HIV-negative TB patient.

The speaker emphasized the need to decrease the burden of TB in People living with HIV/AIDS (PLWHA) by establishing intensified TB case-finding in HIV voluntary counseling and testing centres, in women enrolled in mother to child transmission prevention (MTCT) programs and in HIV home care programs with concrete examples from Haiti, Soweto and Cambodia where such interventions have worked. There is a need to ensure tuberculosis infection control in health care and in congregate settings. On the other hand there is also a need to decrease the burden of HIV in tuberculosis patients through HIV testing and counseling in TB patients, use of co-trimoxazole as preventive therapy, offering care and support and ensuring treatment with antiretrovirals.

Introducing isoniazid preventive therapy for 6 to 9 months after exclusion of active tuberculosis in HIV infected patients with latent TB greatly reduces the incidence and death from TB.

He indicated the challenges of integrating TB and AIDS care which are mainly drug interactions, side effects, occurrence of immune reconstitution events, stigma and non disclosure of HIV status as well as the overwhelming of already overstretched TB programs.

In conclusion it was recommended to put in place coordination body for TB/HIV actions at all levels, to carry out joint TB/HIV program, to use DOT strategy for both TB and HAART, to conduct monitoring and evaluation for both diseases and to allocate more financial resources for both diseases.

When treating HIV and TB, keep it simple

Hirschel- In developing countries, tuberculosis (TB) is the commonest serious infection in the HIV-infected. TB is treated with four drugs; after two months, two of the drugs are stopped whereas the other two are continued for another four months. But HIV/TB co-infected patients also need three anti-HIV drugs. Can all of these be given together? Will the mix be toxic? Will HIV-treatment interfere with TB treatment and vice versa?

A presentation of Manosuthi from Thailand[29], used standard TB treatment (Rifampin, Isoniazid, Ethambutol, and pyrazinamide for two months, followed by rifampin and isoniazid for 4 months) together with efavirenz, 3TC, and d4T. 84 ART-naïve patients treated for Tb for >1 mth (mean 2 mths) were enrolled, mean

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[29] **MoOrB1013 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.** ***W Manosuth, A Thakkinstian et al. Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.***

age 35 yrs, 83% male, mean weight 50 kg, CD4+ T-cells 32 x 10^6/L. 12 hr trough EFV levels at 2 and 4 weeks were equivalent between the two arms, 7.5% had EFV levels <1mg/L; 52-55% with EFV levels 1-4 mg/L and 15 and 18 patients in the 600 and EFV 800 mg arms respectively had EFV levels > 4mg/L. 1 patient with EFV >4 mg/L discontinued HAART because of CNS toxicity (headache). Time to full HIV virologic suppression was equivalent between the 2 arms. In the average patient, TB treatment was started first, and HIV treatment added after approximately two months, and this was well tolerated.

Based on liver enzyme induction caused by rifampin, there was concern that efavirenz would lose its efficacy, and would therefore have to be increased in dose. Manosuthi found that in their patients that didn't seem to be necessary.

In conclusion, when you need to treat both TB and HIV:

(1) start with TB

(2) after two months, add efavirenz, 3TC, and d4T

(3) don't change usual dosages

Further work will probably be necessary to reassure sceptics who worry about the difference in body weight between small and skinny Thais, and big and not-so-skinny Americans, for example. In LDCs however, patients with TB have often lost an enourmous amount of weight before presentation. For instance, in the folowing report from South Africa, average body weight was only 55 kg.

Once-daily HAART combined with DOTs for TB

MoOrB1014 Initiating and providing antiretroviral therapy for TB/HIV coinfected patients in a rural tuberculosis directly observed therapy program in South Africa: The Sizonqoba study. ***N R Gandhi G Friedland et al. Yale University School of Medicine, New Haven, Connecticut, United States.***

Pett- Gandhi *et al* presented preliminary data from a project in rural South Africa exploring the introduction of once daily ART (DDI, 3TC, EFV) in ART-naïve HIV-TB co-infected patients currently receiving quadruple therapy for TB through a DOT community program utilizing DOT supporters and DOT observers within the patient's family. Patients enrolled were on TB treatment at least one month, and had disclosed their HIV-TB status to at least one family member. By July 2004, 23 patients were enrolled, 10 male, 13 female, mean CD4+ 88 cells/uL, HIV plasma RNA 93,000 cp/mL mean weight 55 Kg. 3 month data available for 11 participants, mean increase in CD4+ T-cells from baseline of 198 cells/uL, all had HIV plasma VL below the level of quantifications, mean weight gain of 6.5 Kg and 100% adherence with both TB and ART DOT. Further results are awaited.

Session Sy 14: Managing patients with HIV/AIDS and TB: a clinical and programmatic challenge, Tuesday July 13, 2004.

The programmatic challenge was presented by Paul Nunn whose presentation was on the global TB/HIV Policy: Two Diseases-One patient recently published by WHO. He briefly summarized the different chapters of this book comprising 1. Principles; 2. Rationale; 3. The Policy and 4. Conclusions.

We deal with 2 diseases in one patient. No separate 3rd program is required and patients should receive both services for HIV and TB in the same place. The rationale for joint TB/HIV activities is based on the fact that HIV drives TB incidence and mortality in high prevalence areas, that DOTS alone is not sufficient to control TB in such areas and therefore joint TB/HIV interventions are needed to control HIV-associated TB. TB is not only part of the problem but also part of the solution. TB/HIV policy aims to have joint interventions in order to control HIV-associated TB, to expand DOTS and to treat those who need ARV treatment.

These objectives will be met through implementation of systematic HIV counseling and testing, use of HIV prevention methods, use of cotrimoxazole preventive therapy, HIV/AIDS care and support and ARV therapy to TB Patients. To decrease the burden of TB in PLWHA, identify TB case finding, offer isoniazid prevention and by implement TB infection control in care and congregate settings.

7.3. Other infections and tumors

MoOrB1017 Clinical profile and outcome of cryptococcal meningitis in Ethiopian AIDS patients treated under local conditions *Z M Melaku, G M Mitikie Faculty of Medicine, Addis Ababa University, Addis Ababa, Ethiopia*

Eron-: Melaku *et al* presented a retrospective study of ***cryptococcal meningitis (1997-2003) in Ethiopia.*** This is the commonest fungal OI in Ethiopia and elsewhere in the developing world. Of the 102 patients identified, the clinical presentation differed from those described in developed countries in that the patients had been symptomatic for longer i.e. 28 days (2-210 days). Headache (99%), fever (97%), vomiting (93%), altered mentation (46%), seizures (33%) and cranial nerve palsies in 24% were observed at presentation. Overall mortality was very high at 80%. Only 18 patients received fluconazole and outcomes appeared slightly better with respect to clinical improvement and mortality than with conventional amphotericin B (n=46) although numbers were small. CSF pressure monitoring was not undertaken. 38 patients received no treatment and were assumed to have died ultimately. Data was not presented on dose of medication, duration of treatment or how patients were allocated to treatment or non-treatment. The author concluded that in the roll-out of ART to developing country there were still major problems with access to appropriate treatment of OIs. In order to reduce the morbidity and mortality of cryptococcal disease, access to fluconazole for prevention and treatment is needed.

8. Pediatrics and mother-to-child transmission

8.1. Diagnosis of HIV infection, and treatment in children

McNally - In bridging session BS02 entitled “Paediatric AIDS: Diagnosis and Changes of Management” the four speakers gave a comprehensive review of the care of HIV infected children. They highlighted several urgent points that need to be addressed if children are not to fall behind adults in accessing care including anti-retrovirals in resource constrained settings.

ART needs to be adapted to children

Dr Di Gibb from the MRC Clinical Trials Unit in the United Kingdom presented an overview of the use of anti-retrovirals in children. Children differ from adults in that nearly all transmission is vertical and infants have immature immune systems, higher viral loads, variable CD4 counts requiring that CD4% is used and an active thymus ensuring a good immunological response to HAART. In countries such as the United Kingdom where paediatric HAART is available there has been a five fold decrease in death and progression to AIDS in children. The side-effect profiles of the drugs are quite good but the tolerability is variable depending on the drug.

There are several factors limiting the wide use of anti-retrovirals in children in resource constrained settings. Some of the drugs are prescribed according to weight and some by surface area with no consistency even with the same class of drugs. This needs to be rectified. Due to the unavailability of pharmokinetic data, efavirenz is not licensed for use in children under 3 years of age. However, the differentiation between TB and LIP in children is extremely difficult and children often receive courses of anti-tuberculous therapy. As efavirenz is the recommended NNRTI in children on TB therapy urgent PK studies need to be performed in children under 3 years old. Concerns that PK of ARVs may be different in the malnourished is particularly important in children. In addition, the need for ART to be timed in relation to food can be particularly difficult in infants who are fed often. However, Dr Gibb's main point was to highlight the need for fixed dose combinations of antiretrovirals for children. Adult tablets can not be used in younger children even if divided up due to the different ratios of drugs required (ie higher doses of NVP for under 15kg). Children are being left behind in access to antiretrovirals and there is therefore an urgent need for drug companies to produce combined therapy for children. One generic company (CIPLA) has started to produce infant and paediatric formulations of the drug Triamune and there is an urgent need for fast track pharmacokinetic studies and regulatory approval to ensure that children have the same rights to care as adults.

A Network of AIDS Clinics For Children

Dr Heidi Schwarzwald spoke on the particularly important role of multi-disciplinary care in HIV infected children. In the 1990s Baylor became involved in the care and treatment of HIV infected children in Romania where 90% of all HIV infected persons are children.

In April 2000 they opened a state of the art clinic in collaboration with the Romanian government and private funders. The clinic includes clinicians, nurses, a dentist and a social worker. There are currently 452 children on HAART and the daily inpatient census has dropped from 30 to 4. Based on the success of the Romanian clinic Baylor International has now also opened a multi-disciplinary clinic in Princess Marina Hospital, Botswana (June 2003) and a clinic is in the process of being built in Mexico. The different sites hope to focus on care and treatment of HIV infected children with a multi-disciplinary and family centred

approach, reverse the brain drain of staff and hope that by improving care they can increase the impetus for HIV testing and destigmatize the disease.

Home-based Care in Uganda

Dr Kibrige, a Ugandan paediatrician emphasised the need for ambulatory paediatric care whenever possible. Child Advocacy International has been working in Uganda to try and maintain care of HIV infected children in their homes. Once a child is diagnosed as HIV infected a clinic worker goes with the child and carer to their home where they are established on medication with a simplified drug regimen and factors such as food provision and transport to hospital are addressed. The program even has a mobile dispensary to reduce the need for hospital visits. The program has been caring for children for 3 years. There has been a reduction in mortality over the previous three years despite lack of access to antiretrovirals. This has been due to a nutrition education and support, health education, child and mother support clubs, an income generation project and improved quality access to care. There has also been an education program for care givers, the community and health care professionals.

Problems in resource-constrained settings

The last speaker, Dr Phillippa Musoke also from Uganda gave an excellent review of evidence based optimal care for HIV infected children in resource constrained settings. It is critical to diagnose HIV as early in infancy as possible as the mortality is high with 30% of untreated HIV infected infants dying in the first year, and only 5-10% living beyond age 5. However, the need for PCR-based diagnosis is a problem in resource poor setting and there is an urgent need for further developments in infant testing. She highlighted the difficulties in the clinical diagnosis of HIV in Africa as the rates of HIV are high in children admitted with common paediatric diseases such as severe pneumonia and malnutrition. Infant feeding remains one of the most difficult areas in the management of HIV exposed children. Exclusive breastfeeding with early weaning is beneficial in reducing mother to children transmission of the virus but can lead to malnutrition. There is therefore a need for high energy protein supplementation when weaning. However with the roll-out of ART in many African countries there are more questions to be answered such as can HAART be used safely in breastfeeding mothers to reduce HIV transmission to their children, and what is the clinical relevance of the high levels of NVP resistance seen in the infants on the HIVNET012 study.

Dr Musoke shared the concerns of Dr Gibb that the difficulties in confirming the diagnosis of HIV in infancy, the rapid disease progression in African children and the lack of availability of combination drugs for children meant that they were not receiving equal standards of care to adults and that this needs to be addressed as a matter of urgency. Her final slide summed this up “Provide HAART for children and their mothers. Everybody has been a child, they need access to care now”.

Session B05, on Pediatric Diagnosis and Treatment:

Sicker mothers, sicker children

Dr Elizabeth Obimbo presented the results of a prospective study of 79 Kenyan infants and their mothers[30] which aimed to determine whether there was a relationship between maternal and infant viral loads and infant disease progression. All infants were ART naïve. 49% of the infants had died by two years old. There was a significant positive association between the mothers and infants' viral loads. The infants' median peak HIV1 viral load was 5.6 million, declined 4 fold to a set point of 1.3 million copies/mL and was 1 log higher than maternal viral load. Infant HIV1 viral load was highly associated with time of HIV1 acquisition (median peak HIV1 VL of 7.8 million copies/mL in infants infected before 1 month old and a median peak HIV1 VL of 3.7 million copies/mL in infants infected after 1 month old.). Maternal viral load was a strong predictor of infant death with 20% mortality in infants of mothers with viral loads of <10'000 million copies/mL rising to 65% in the infants with maternal VL of greater than 100'000 million copies/mL. Infant viral load was also a strong predictor of mortality with 22% mortality in infants with viral loads less than 1 million copies/mL rising to 63% mortality in infants with viral loads greater than 10 million copies/mL. Finally, maternal death was associated with a 3 fold increase in infant death. As Africa scales up its ART in children the speaker concluded that both maternal and infant viral loads could be used as a guide for commencing treatment.

ART in children in UK: Could do better

Dr Doerholt then reported on CHIPS follow-up data of HIV infected infants in UK and Ireland[31]. A previous study had shown a reduction in mortality of HIV infected children since 1997 but had not seen a similar decline in mortality in infants under one year. There was a 62% reduction in infant mortality since 1997 but no change in the time to progression to AIDS. Only 54% of infants had undetectable viral load 12 months after initiating therapy but there was a rapid increase in CD4% with a good immunological response. Most HIV infected infants in the UK continue to be born to mothers whose status was not known during their pregnancies. The high rates of disease progression in infants suggests closer follow-up in those not started on ART early.

New guidelines for starting ART: TLC >3500 at ages <18 months, TLC < 2500 in older children

Current guidelines regarding indications for ART in children rely on the percentage of CD4 cells: <25% at ages below 18 months, <15% above 18 months. However,

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[30] TuOrB1187 **Maternal and infant viral load impact disease progression in HIV-1 infected African infants.** *E M Obimbo, G John-Stewart et al. University of Nairobi, Nairobi, Kenya.*

[31] TuOrB1188 **Poor virological response to HAART among infants in the collaborative HIV paediatric study (CHIPS) in the UK and Ireland.** *K Doerholt, M Gibb et al. MRC Clinical Trials Unit, London, United Kingdom.*

many of the CD4 machines used in HIV endemic areas are not able to perform the CD4% required for paediatric care. Dr Gibb presented data from on the use of total lymphocyte counts as predictors of disease progression in HIV infected children[32]. The World Health Organisation Guidelines published last year suggest commencing treatment when the TLC is below 2500 in infants less than 18 months and below 1500 in older children. Results from a meta-analysis of data from 8 cohort studies and 5 trials were presented, including 3917 children, and 981 AIDS-or-death events, and 559 deaths. All the children were either treatment naïve or had only received AZT monotherapy.

The study found that the risk of death, using the proposed TLC cutoffs, was not equivalent to the risk of death using the CD4 percentage. In infant <18 months, risk of death when TLC=2500 was higher than when CD4=20%, and in older children risk of death when TLC=1500 was higher than when CD4=15%. In other words, the TLC cut-offs are too low, and when used as an indication for ART, there is a risk that children will have AIDS or die before ART can be started.

However, when the TLC cut-offs were increased to TLCs of 3400 < 18 months and 2300 >18 months prediction of death was as good as CD4%. Total lymphocyte counts performed well as a marker for starting therapy in this European cohort when higher threshold levels were used and there is an urgent need for more longitudinal studies to examine the use of TLCs in resource constrained settings.

A pediatric AIDS severity score (PASS)

Dr McIntosh reported on a Pediatric AIDS Severity Score (PASS) developed from an analysis of predictors of mortality[33]. The most comprehensive model for predicting mortality, termed the "Full" Pediatric AIDS Severity Score (FULL PASS), included CD4% less than 15 (HR=4.9), CDC category C (HR=2.8), a low (<70) or invalid neuropsychological score (HR=2.4), a general health rating of less then 5 (HR=2.6) and an elevated symptoms score (HR=3.3). These determinants were highly predictive of mortality (C statistic = 0.850). For resource limited settings, a Simple PASS model was developed using the same cohort, which included CD4% less than 15 (HR=5.5), CDC category C (HR=3.2) and weight less then the 10th percentile (HR=1.7). These determinants were also highly predictive of mortality (C statistic = 0.831) using a separate validation data set.

Botswana: 672 treated children, with VL BLQ in 84%

TuOrB1191 Response to antiretroviral therapy among treatment naive children in Botswana *H B Jibril, E Kostova et al. Botswana-Baylor Children's Clinical Center of Excellence/Princess Marina Hospital, Gaborone, Botswana.*

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[32] **TuOrB1189 Predictive value of total lymphocyte count (TLC) for disease progression in untreated HIV-infected children in Europe and USA.** *D M Gibb W Shearer et al. Medical Research Council Clinical Trials Unit, London, United Kingdom.*

[33] **TuOrB1190 The pediatric AIDS severity score (PASS): A multidimensional AIDS severity adjustment for pediatric HIV infection.** *G R Seage, W M Dankner et al. Harvard School of Public Health, Boston, MA, United States.*

Botswana has a national HIV1 seroprevalance of 37.4% and children are one of the four priority groups for free antiretroviral therapy. Data was presented on 672 children who commenced ART between April 2002 and October 2003. 84% of the children had complete virological suppression by 3 months and this was maintained at a year. Good immunological responses were also present by three months and maintained. 7 children (3.3%) required a switch of therapy and this was always due to virological failure as opposed to drug toxicity.

Thailand: Somber legacy of nucleotide-only treatment

TuOrB1192 Incidence of reverse transcriptase genotypic mutations in children treated with dual nucleoside reverse transcriptase inhibitors: HIV-NAT 013 study. ***R Lolekha, J Ananworanich et al. Queen Sirikit National Institute of Child Health, Bangkok, Thailand.***

The final lecture of the day examined the incidence of reverse transcriptase genotypic mutations in Thai children treated with dual NRTIs for greater than 6 months. This was a cross sectional study on 95 paediatric patients with a mean age of 6.6 years and a median CD4% of 16%. There was at least one NRTI genotype mutation in 96.8% of these infants and at least 40% of children had 4 nucleoside analogue mutations (NAMs). The presence of resistance mutations did not differ among regimens used and worryingly there was an M184V mutation in 7 children who had had DDI but not 3TC suggesting cross over of resistance to NRTIs. Neither the disease status of the child nor the duration of antiretrovirals had an effect. These results suggest that the Thai national salvage regimen of d4T/3TC/NVP will not work. Alternative regimens, were they available, would currently cost 10 times as much…

Symposium 16 on Caring for Children infected by HIV

AIDS orphans: There are no good solutions

There are currently 12 million children worldwide orphaned by AIDS. This symposium highlighted one of the themes coming out of the conference that care and resources world-wide are focussed on adults. The world is lagging behind in its response to children. Even if there were no more HIV infections, the number of orphans will continue to increase for at least a further ten years.

In 2001 UNGASS developed a framework for the care of vulnerable children and orphans (OVCs). Rwanda has a “family for each child policy” which it developed after the genocide. Today there are 613,000 orphans but only 3745 live in institutions. Odette Nyiramilimo, a Rwandan senator concluded that they had learnt several lessons from their program including that each country should design its own policy and action plan according to its needs and that women should be more involved in decision making.

Prof Veronin cares for HIV infected and affected children in St Petersburg. The number of HIV positive children in Russia is growing rapidly, official statistics state that there are 7000 children infected but it is probably nearer to 13 000. As it is very difficult to find families for HIV infected orphans the hospital has its own centre where they live. Prof. Veronin emphasised that children are all individuals

but that to the outside world they are still only seen as HIV positive. All the children however have the same needs, to love, be loved by a family and to be healthy.

The next speaker was a young Thai woman Ms Songkeaw whose uncle and aunt had both been diagnosed with HIV in 1995. The villagers ostracised her cousin as she grew up. Her uncle eventually died and with time the village has learnt to support the family. However Ms Songkeaw and her cousin have used their experiences to help support other young people affected by HIV.

Malawi is one of the countries most affected by the HIV pandemic with 14.4% of 15-59 year olds infected leaving an estimated 800,000 orphans. World Vision gave an update on their program which uses volunteers and village support groups to care for OVCs.

Dr Anne Peterson from USAID gave an overview of the current situation. In HIV endemic areas this includes children who have lost one or both parents, those caring for sick parents, the extended families who are carrying much of the child care burden and the community as a whole.

In order to start decreasing the number of orphans there is an urgent need to reduce the number of new infections and to scale up access to care quickly in order to extend the time parents are around to care for their children.

8.2. Prevention of mother-to-child transmission

Price to pay for simple prevention of MTCT by nevirapine

TuBs196 Implication of drug resistance on scaling up ART and PMTCT. ***Marc Lallemant. Thailand.***

Hirschel and Pett- Lallemant for the PHPT group: PHPT-2. See also N Engl J Med. 2004 Jul 15; 351:217-28, and 229-240

In the PHTP-2 study of the prevention of mother-to-child transmission, all mothers received zidovudine starting with week 28, and all children received zidovudine for one week. In addition, in arm 1, mothers and children received 1 dose of nevirapine at the time of birth. In arm 2, only the mothers received nevirapine, and in the control arm 3, both mother and child received placebo.

The intervention reduced mother-to-child transmission from 6.8 to less than 3 percent. The difference between the two nvp arms was not statistically significant. However, the single dose of nevirapine selected resistance mutations in 32 percent of the mothers. After birth, these mothers often needed treatment, with 50 percent on NVP/3TC/d4T within 2 years post partum. Does the intrapartum nevirapine diminish the effectiveness of treatment with NVP/3TC/d4T?

Unfortunately the answer seems to be yes, because 24 weeks after starting treatment, only 38 percent of those exposed to nevirapine and having resistance mutations, and 52 percent of those exposed but without resistance mutations, had a viral load below 50, compared to 68% of those who had never taken nevirapine.

This of course poses a dilemma. In Thailand, NVP/3TC/d4T costs 352 US dollars per person per year; alternative therapy, if available, would cost 3500 US dollars per person per year. Can the development of nevirapine resistance after prophylaxis of mother-to-child transmission be prevented?

In a late breaker presentation from Johannesburg, McIntyre[34] tested the addition of Combivir (zidovudine plus 3TC) to nevirapine, for 4, or 7 days

This intervention appeared to be successful, because when tested 2 or 6 weeks post-partum, only 9.8 (4/43) percent of women on Combivir plus nevirapine had resistance mutations, compared to (9/18) 50 percent who only received nevirapine. Caveats: (1) no zidovudine during pregnancy, (2) the 50 percent in the nevirapine only group is the highest so far reported and the denominator is only 18 women.

9. Developing Country Issues

9.1. Simpler and cheaper diagnostics

There were six oral presentations in Session B04 titled “Diagnostic and Monitoring tools” These presentations primarily focussed on the diagnosis of HIV and CD4 monitoring in resource constrained settings.

Oroquick salivary rapid tests were highly sensitive and specific when evaluated in 240 South African children between 12 and 18 months old[35]. The test was painless and required minimal skills compared to blood letting. The study is continuing and will enrol children 6 month old for further evaluations. There is also a need for further field testing as these were performed under research conditions.

An evaluation of five rapid blood tests in Tanzania found that all were equally sensitive and specific with 99.3% concordance between the tests and 98% concordance with ELISA. There were only 18 invalid tests out of 2587 samples taken.

Dr Sandy Walker from Melbourne, Australia reported on the External Quality Assurance Scheme for the Asian and Pacific Region HIV Testing run by the National serology reference laboratory for 90 laboratories in 28 countries. 30% of the laboratories reported errors when the program first started in 1992 (mostly false positives), but there were no errors in the most recent panel which she concluded was due to the EQAS monitoring and education of laboratory staff.

MSF have been evaluating the PARTEC cyflow counter for CD4 T-cell results in rural Malawi as the availability of CD4 counts is a necessity for government ART

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[34]: **LbOrB09 Addition of short course combivir (CBV) to single dose viramune (sdNVP) for prevention of mother to child transmission (MTCT) of HIV-1 can significantly decrease the subsequent development of maternal nnrti-resistant virus** ***J McIntyre, D Mayers et al. Perinatal HIV Research Unit, Univ of Witwatersrand, Johannesburg, South Africa.***

[35] **TuOrB1146 Oraquick saliva testing for HIV infection - a painless alternative to routine blood testing in paediatric patients** ***A Naeem-Sheik,,G Gray, et al. E Vardas Institution, Johannesburg, South Africa***

rollouts but is often difficult and expensive. The PARTEC cyflow counter is small and portable, easy to use, has a high capacity, runs on a car battery and is relatively cheap. 300 samples were analyzed on the machine with paired samples tested at a nearby reference laboratory. Precision was good, there were high rates of concordance with the reference lab and the technicians found it easy to use.

Concerning the use of total lymphocyte counts in HIV infected children see chapter 8.1.

9.2. Scaling up

Drug Prices in Developing Countries: Patents, generics, TRIPS, and Doha

Andrieux – What determines prices for ARV in developing countries? (S. Lucchini et al. MoOrD1033). The analysis was based on 1030 transactions in 14 developing countries including Brazil from 1998 to 2002. ARV prices declined at a constant rate from 1998 to 2000, with an accelerated decrease in 2001, and a more limited decrease in 2002. Price difference between branded and generic drugs decreased. Higher volumes generally were purchased at lower prices.

- Factors associated with higher prices: PIs, patent protection, higher HIV prevalence, recommendations of PIs for first-line treatment, existence of intermediaries (wholesalers).
- With lower prices: Participation in the WHO's accelerated access initiative, public programs for ARV delivery, and above all, the introduction of generic competition.

Conclusion: To keep prices low, ensure competitive decentralized negotiations with multiple suppliers including generic manufacturers.

Andrieux – Improving World Trade Organisation (WTO) rules for pharmaceutical patents in LDCs (M. Wang[36])

High prices for ARVs are justified (by the pharmaceutical industry) by the costs for Research and Development, and the need for new drugs in order to stay ahead of developing resistance. In exchange for the social utility represented by investment in R & D, the producer is granted a legal monopoly called a patent, lasting 20 years. Internationally, patent rights are enforced by the so-called TRIPS (trade-related aspects of intellectual property rights) agreement.

However, as a general rule, treatments are "too expensive" if they cost more than one half of gross domestic product per person / year of life saved. By that standard, even the average cost of 60 $/month for FDC (including monitoring and care) is still too high.

Doha declaration 2002: "We recognize the gravity of public health problems afflicting many countries, especially from HIV, TB, malaria and other epidemics.

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[36] MoOrE1071 **Improving WTO rules on HIV pharmaceutical patent for developing countries** *M Wang University of the Sciences, Philadelphia, United States*

We agree that the TRIPS agreement does not and should not prevent members from taking measures to protect public health." From this, countries derive the right to determine what constitutes a "public emergency", where the usual restraints on trade specified by TRIPS would no longer apply, and where access to ARVs would be increased by:

- compulsory licencing: A country ensures production of a patented substance by a local manufacturer
- parallel imports: A country imports drugs from another country where the drug is not patent-protected

Canada has introduced legislation to implement the WTO decision. The bill would allow Canadian generic manufactures to obtain compulsory licences to supply lower-cost pharmaceutical products to countries where those products are not patented or patent barriers to importation have been resolved (e.g., via compulsory licence), see Elliott R. et al. [37]. It remains to be seen whether this initiative will have a beneficial effect.

Exceptions from the regular TRIPS rules, in the WTO framework, face several problems:

- ponderous and time-consuming case-by-case review for compulsory licensing
- absence of local production capacity, doubts about the legality of parallel imports
- limited range of off-patent generics

The author proposes a new framework to give the developing countries more sovereign power to relax patent restrictions on HIV medicine. It would propose preferential pricing for HIV medicine, among others, as a possible solution. Third, the new framework would require international stakeholders to engage in a public-private partnership that involves supernational agencies, national governments, NGOs, and community activists to address the human rights issues in pharmaceutical access in their own national context

Koulla - Four speakers presented their experiences on scaling up of ART in resource constrained settings (Tuesday Symposium Sy12).

Brazil, Thailand, Uganda

The Brazilian experience was presented by Ricardo Marins[38]. Brazil has an HIV incidence rate of 12.8/100'000. The estimated number of People living with HIV/AIDS (PLWHA) is 600'000 in 2000 with 310'310 AIDS cases, and 150'000 deaths by 2003.

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[37] **MoPeE4033 TRIPS from Doha to Cancún...to Ottawa: WTO patent rules and Canadian civil society advocacy for global treatment access** *R Elliott[1], # Members of Global Treatment Access Group[2] Canadian HIV/AIDS Legal Network & Global Treatment Access Group, Toronto, Canada; [2]MSF, CLC, CCIC, ICAD, Oxfam, NSI, SAGA, MIHI, CAP-AIDS, WVC, CARE, R&D, Toronto, Montreal, Ottawa, Canada*

[38] **TuSy179 Brazil free national AIDS treatment program.** *Ricardo Marins .TBC. Brazil*

The Brazilian government responded as early as 1983 with strong participation of the civil society, multi-sectorial mobilization, and a balanced approach between prevention and treatment. Universal access and free of charge ARV treatment began in the mid 90's. Major aspects of the ARV program included development of treatment guidelines, development and installation of National ARV logistic control system for CD4 count, viral load determination and 12 laboratories organized in a network for genotyping. Capacity building was a crucial component.

The Brazilian success in offering universal access was due to the local production of ARVs as well as to the capacity to monitor response to treatment through standard laboratory exams. The involvement of patients and NGO's in all actions and control was also important. Mortality due to AIDS, and the incidence of opportunistic infections have declined by approximately 75 percent.

The experience of Thailand (Viroj Tangchaorensathien[39]) was similar to that of Brazil including high-level political involvement translated into action by offering ART with standard lab follow up tests and local ARV production which has facilitated the inclusion of many patients.

The Ugandan experience was presented by Cissy Kityo[40]. Uganda has about 1.1 million persons infected with HIV of whom about 150'000 need ART. However only 20'000 have access to ARV and the majority pay out of their pocket. Standard lab tests such as CD4 count and Viral load are not widely available.

Médecins sans Frontières

The 4th speaker was a representative of Médecins sans Frontières[41]. Alexandra Calmy who presented the rich experience of this International NGO which has been working in many resource constrained countries both in Africa and out of Africa. From pilot project to assess the feasibility of treatment with ARV in developing countries, they have moved to a public health intervention with over 12'058 patients put on ART since 2001. They developed simplified treatment protocols and monitoring tools for non medical personnel.

Over 70% of their patients are on free generic fixed dose combination of stavudine + lamivudine + nevirapine with good clinical response and little side effects. One year survival was 84%, with most deaths occurring in the first weeks after starting treatment. In those patients who had monitoring, the rise in CD4 counts during the first year was 134 cells, and 80% had VL <400 after 24 weeks (see The Lancet

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[39]: **TuSy181 Thailand Ministry of Health program for scaling up of ART.** ***Viroj Tangcharoensathien. Thailand***

[40]: **TuSy180. Ugandan cost recovery model for country wide provision of ART.** ***Cissy Kityo. Uganda***

[41] **TuSy183 MSF programs for implementation of free ART in resource poor settings.** ***Rachel Cohen. Belgium***

2004; 364:29). Calmy's presentation got considerable attention in the American Press, with a page 1 article in the Herald Tribune and the New York Times by Larry Altman.

All speakers agreed to continue the use of proven good quality generics of fixed dose combination as first line ARV therapy. They all put emphasis on the benefit gained by involving the community as well as patients to foster patients' adherence to treatment, the need to continue negotiation for ARV price reduction with Producers of these drugs.

There were conflicting opinions as to whether to offer free ART to patients or to have a cost recovery even at very little cost.

9.3. Adherence in developing countries

Lack of adherence is a major cause of failure of antiretroviral therapy. Understanding adherence in resource limited settings is critical before antiretroviral therapy hopefully became widely available. Early adherence to HAART in patients enrolled at the HIV treatment program in Rio de Janeiro was studied (Hofer[42]). In this survey, adherence was measured by self reporting and missed appointments in patients who had completed at least 6 months of ART. Among a total of 220 patients interviewed, 104 were considered adherent to therapy. Main variables associated with lack of adherence were: family interferences with the treatment, years known to be HIV positive, concerns of patients about drug interactions, financial problems and dosing interval.

In a second study from Senegal, adherence to ART through a 4 year period was evaluated in a cohort of 167 patients enrolled at the Senegalese National Program (Laniece[43]). Pharmacy records were used to estimate missed doses within the 30 days prior to drug dispensing. Probability of being highly adherent was 0.78 (CI: 0.74-0.81). Factors associated with low adherence (<95%) were symptomatic disease, treatment duration, monthly cost of HAART and a PI based regimen.

In another study, adherence to ARV was evaluated in a group of 70 HIV infected individuals able to afford the cost of a generic co-formulation of d4T, 3TC and nevirapine, in the city of Kampala (Oyugi[44]). Monthly estimations of adherence were performed by self report, visual analogue scales and pill counts. At 12 weeks of therapy, adherence scores were above 90 % for all measurements.

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[42] **WeOrB1319 Factors associated with antiretroviral adherence in public clinics in Rio de Janeiro, Brazil.** ***C B Hofer, L H Harrison et al. HUCFF Universidade Federal do Rio de Janeiro -Brazil.***

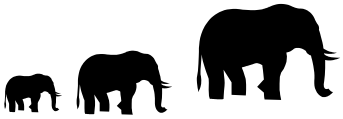
[43] **WeOrB1320. Determinants of long-term adherence to antiretroviral drugs among adults followed over four years in Dakar, Senegal.** ***I Laniece, I Ndoye et al. French Cooperation/Multisectorial Aids Control Program, Dakar, Senegal.***

[44] **WeOrB1323 Treatment outcomes and adherence to generic Triomune® and Maxivir® therapy in Kampala, Uganda** ***J H Oyugi, D R Bangsberg, University of California San Francisco and Academic Alliance for AIDS Care and Prevention in Africa, San Francisco, United States.***

All of the above papers stress that adherence to HAART is possible for people receiving therapy in a resource limited setting. Socioeconomic factors clearly emerge as a barrier for adherence in undeveloped areas of the world.

10. Varia

Investigators from the University of Alabama compared oxandralone in addition to aerobic and resistive exercise vs. aerobic and resistive exercise alone in a placebo-controlled trial of patients with 2 or more signs or symptoms of metabolic dysfunction on highly active antiretroviral therapy[45]. Double blind placebo controlled study of exercise and oxandrolone on lean mass, fat distribution, blood lipids, bone density and training markers in HIV infected men and women on HAART. Baseline characteristics were substantially (though perhaps not significantly) different between treatment groups in this small study in which only 16 subjects in each arm completed the course of therapy and exercise. As an example the mean weight at baseline appeared to be approximately 8 kg higher in the oxandrolone treated group. Fat free mass increased to a significantly greater degree in subjects treated with oxandrolone. However LDL cholesterol and total cholesterol increased on oxandrolone and HDL decreased, raising serious concerns about this strategy.



[45]: **MoOrB1059 Double blind placebo controlled study of exercise and oxandrolone on lean mass, fat distribution, blood lipids, bone density and training markers in HIV infected men and women on HAART.** ***B A Smith, M S Saag et al. University of Maryland, Baltimore, Baltimore, Maryland, United States.***