Despite any significant breakthroughs, the 5th International AIDS Society conference in Cape Town, South Africa, July 19-22, 2009 provided a critical opportunity for contemplation and discussion for the future of antiretroviral drugs for treatment, prevention and hopefully a cure. This was the second international AIDS meeting in South Africa, highlighting the interminable need in developing countries, especially South Africa where one out of five adults is HIV-positive. Activists at the meeting demanded access to better clinical infrastructure and second line antiretroviral drugs that are not accessible in many parts of the developing world. The meeting brought attention to HIV/AIDS globally and a continued commitment for funding despite the global economic recession.

While scale-up in parts of the developing world has been effective, there is a long way to getting anywhere near the developing country standard. The 3 X 5 goal set by the World Health Organization that was never met was a critical setback to the progress that has been made in research for life-saving antiretroviral drugs. At the opening session, IAS President Julio Montaner expressed outrage at the retrenchment in AIDS global funding from international leaders at the recent G8 meeting, especially in light of scale-up successes, the growing push for earlier and better treatments, the hope for new biomedical prevention strategies, and the deadly threat of tuberculosis.

Most of the oral sessions at the meeting focused on reviewing the current state-of-the-art treatment, biological prevention strategies, patient management and epidemiological data in order to bring continuing education to clinicians and practitioners where the epidemic is raging. Given the timing and location of this conference, translating science into operational practice was also a major focus.

**When to Start Treatment?**

Consideration of when to start HIV therapy is less of an issue for millions who just simply need access to treatment. Yet there was considerable discussion and presentations at IAS to change policy as to when people should start HIV treatment. Researchers and policy makers urge beginning antiretroviral therapy at 350 and even 500 CD4 cell counts, but the current DHHS guidelines still...
lag behind the IAS and European Guidelines, despite the lack of randomized prospective studies. The question of just when to start is unknown even though cohort studies are providing some evidence.

Jose Gatell from Barcelona laid out the reasons for starting earlier in resource-rich settings. He explained the obvious — that HIV therapy has increased survival rates significantly — but said if treatment was started at >500 CD4 cells it would still take five years to match the survival rate in the general population. There is also evidence for starting earlier in retrospective cohort studies published in the Lancet last year and elsewhere, although there is some controversy due to the nature of the cohort designs.

The START study, a large prospective, randomized study to prove that starting therapy >500 CD4s has benefit is still 5 years away and recruitment is expected to be a challenge. It is understood that earlier treatment has shown benefits in reducing AIDS morbidity and mortality keeping HIV levels low and decreasing inflammation. However, there was also more news about increasing non-AIDS related conditions in people who are living longer, such as cancers, bone issues and heart disease. (see below)

In the long-term, Gatell made the case for cost effectiveness in starting earlier as well as use of HIV therapy for prevention. All in all it appears the horse is out of the barn with assessment that starting treatment is a positive thing and would benefit the community and the individual.

**PrEP and Treatment for Prevention**

Universal testing and treatment would also prevent the spread of HIV according to Reuben Granich from WHO. He provided a mathematical model that showed in ten years there would be a 95% reduction in HIV cases if there were universal testing and immediate HIV therapy combined with other prevention interventions. By 2050 HIV prevalence would be less than 1%. Granich stated that the initial costs of treatment for prevention would be high, but over time there would be actual cost savings. However he added that human rights, community engagement, feasibility, impact and costs would have important roles in any treatment as prevention strategy.

Treatment as prevention was shown effective in a large African cohort study of sero-discordant couples. The study showed a 79–90% reduced transmission in the HIV-negative partner in the couples in which the positive partner was on HIV therapy after a year and a half follow-up. Transmission was significantly higher in the couples where the positive partner was not on HIV therapy.

Lynn Paxton from the CDC made the case for pre-exposure prophylaxis (PrEP) in HIV by describing its use in other disease states such as TB. In HIV PrEP has proven effective in small studies of macaque monkeys. Now, there are nine human trials planned or underway across the globe in different populations that will begin providing data as early as early 2010.

One red flag presented at IAS may be the use of tenofovir (Viread), which is in all the current PrEP trials. Since tenofovir can reduce bone mineral density (BMD), one small sub-study from Botswana showed lower bone density in 57% of study participants at baseline, raising concern over pre-existing low BMD and using regimens with tenofovir. Biomedical prevention strategies such as PrEP make sense; effectiveness results are expected in early 2010. Acceptance and roll-out of such a strategy is much less understood and an area of intense discussion.

There were several other studies, and sessions on PrEP challenges, priorities, future funding and feasibility were a major focus of muted excitement at the conference.
**Antiretroviral Facelifts**

New ways to improve current HIV drugs were presented in several studies in Cape Town. Isentress (raltegravir) and unboosted Reyataz (atazanavir) were shown to be effective in a small study where NRTIs were not used. Out of 27 treatment-experienced participants in the open label study, 25 were able to control HIV and only one developed resistance to Isentress after 24 weeks. This is obviously a small uncontrolled study, however, it offers insight into a new approach for people with treatment experience.

Another new integrase inhibitor from GSK showed to have powerful suppression of 2.5 logs with only 50mg dose in an early ten-day monotherapy study. Encouragingly, it also appears to not be cross-resistant to Isentress or elvitegravir thus far. Clearly, integrase inhibitors offered the most excitement in the thin antiretroviral pipeline presentations at IAS.

A “weekend off” strategy of intermittent HIV therapy was presented by Cal Cohen from Boston. The FOTO (five days on two days off) study looked at this strategy in 60 people who were undetectable, and on a stable regimen of Sustiva (efavirenz), Viread and Emtriva (emtricitabine) for a total of 48 weeks at baseline. The study showed similar virologic and CD4 responses at three time points. The implications for a short treatment interruption such as FOTO are cost savings, improved adherence and reduced toxicity. This strategy may work well because Sustiva has a long half-life, and stopping for a “weekend” does not affect viral load outcome, adherence or toxicity according to this study.

Similar efficacy was seen in a Kaletra (lopinavir/ritonavir) once vs. twice daily regimens containing optimized background NRTIs in treatment experienced patients. The 48-week study showed that using Kaletra once a day, currently approved in those who have not started treatment, is non-inferior (meaning no better) to twice a day dosing, which is the dose used in treatment-experienced individuals. 600 people were selected for the trial. Adherence improved in the once daily dosing while side effects were not significantly different whether participants took Kaletra once or twice daily.

The use of Prezista (darunavir) boosted with ritonavir monotherapy was shown to be non-inferior to Prezista/ritonavir + NRTIs in a 48-week open label study. The participants had to be stable and darunavir/ritonavir naïve and no history of virilologic failure. As expected CD4 counts remained stable in both groups. Side effects were similar in both groups. Despite the fact that this study was uncontrolled, it shows promise when used in regimens without NRTIs. There was another Prezista/ritonavir monotherapy study in Europe that showed almost similar responses, confirming this strategy in an open label design.

MERIT, a large randomized, controlled trial with Selzentry (maraviroc) + Combivir (zidovudine + lamivudine) demonstrated similar efficacy to Sustiva + Combivir. At IAS a 96-week re-analysis was presented using the newer enhanced tropism assay. Those participants who were randomized to receive Selzentry had better CD4 counts and lower lipids at the end of the study. Selzentry is approved for treatment-experienced individuals with CCR5 tropic virus. This re-analysis with the newer sensitive tropism assay should give more distinct results in this drug’s data set for FDA approval in first line therapy.

While the news is good for a newer enhanced tropism test for CCR5 tropic virus, the test is expensive and takes a long time to get the results. The more exciting news is a new genotypic test was compared to the tropism test and proved to be just as accurate in determining who is eligible.
for taking Selzentry. This news bodes well for Pfizer in conjunction with the MERIT re-analysis in their pending FDA hearing for first line therapy.

Treatment Complications

Studies have shown various results regarding the use of Ziagen (abacavir) in the breadth of cardiovascular issues. At IAS, a larger retrospective cohort study of over 19,000 people at the Veterans Administration showed marginal increases in acute myocardial infarction (AMI) and cerebrovascular accidents (CVA). These heart-related conditions were not statistically significant with Ziagen, yet chronic kidney disease was seen at baseline in more in people who used Ziagen.

Another prospective sub-study showed no difference with inflammation biomarkers, endothelial dysfunction, insulin resistance, and hypercoagulability between Ziagen- and Viread-based HIV regimens. These markers are important lab values for understanding heart disease and inflammation which are current hot topics in HIV.

While studies are showing differences in effectiveness and dosing schedules, it is also good news to see a major researcher, Pedro Cahn from Argentina, giving the death knell to Zerit (d4T) by demanding that doctors say “good-bye” to prescribing it, noting that it is a standard treatment in the developing world yet one of the most toxic.

Aging and HIV

In developed countries life expectancy is increasing in part due to the success of HIV therapy. As people with HIV grow older they are dying of natural causes of death. But when you combine aging, HIV therapy and HIV disease with ongoing immune activation, the situation becomes very complex.

The effects of HIV are strongly related to the effects of aging. Common cellular processes are affected by HIV and the aging process. The combination is appearing to affect morbidity and mortality. Immune activation is an area of intense research in aging and long-term HIV disease. In Cape Town, there was a new understanding of HIV and the immune system’s role in activation in the lymph nodes and the gut where crucial immune function and molecular signaling occurs. Immune responses and thymic activity are also known to be blunted in older people. Also, it was mentioned that people who are older do not respond as well to HIV therapy, but are more likely to adhere to the medications.

Cardiovascular disease is more common in HIV-positive individuals than HIV-negative. Risk factors such as family history and smoking are the main reasons for cardiovascular issues. Yet in HIV there is little evidence that HIV drugs, specifically protease inhibitors, contribute much if at all. Much is still to be learned about the complexities of cardiovascular disease in HIV, the role of HIV drugs, and ongoing inflammation as this population ages.

It’s not news that non-AIDS cancers are increasing in older, long-term cohorts of people living with HIV. Anal and head and neck cancer are on the rise in the UK and the US. Brian Gazzard, from the UK, spoke of several possible mechanisms for the rise in cancer as people with HIV age. Risk factors include lower CD4 cells and age.

HIV Associated Cognitive Disorder (HAND) is seen in 39–53% of people with HIV. Neurological conditions in the aging HIV population are increasing, specifically dementia. However, memory loss appears to be more common than loss of brain function. A better understanding of
brain cellular and enzymatic interactions with antiretroviral drugs was presented at IAS. There is also some evidence that HIV may encourage Alzheimer’s disease, affecting brain function. The complexities of neurological conditions in older HIV populations clearly need more research.

**Prospects for a Cure**

Much was discussed in Cape Town about prospects for eradication of latent T cells and viral persistence. Anthony Fauci from NIAID discussed the considerations in ongoing research for a cure. Eradication of HIV in some HIV-positive people would result in a “sterilizing cure” while a “functional cure” in others would mean no eradication, yet the immune system would be able to control HIV without therapy. He said the strategy would require aggressive drug regimens and would likely depend on the timing of starting therapy.

However, Wafaa El-Sadr from New York spoke of the need for re-conceptualizing the pathogenesis of HIV where clinical latency is a misperception. Once infected with HIV there is constant immune system activity. She discussed the need for more treatments to control HIV-associated inflammation that appears to be one of the culprits behind immune system activation evident in the SMART study of treatment interruptions.

David Margolis from North Carolina spoke of his work with valproic acid, an HDAC inhibitor which has seen mixed results as one way to activate latent T cells. He mentioned there are more potent HDAC inhibitors used in cancer therapy. What is needed is other animal models, better basic understanding of virology, better ways to measure molecular functions, and more strategies to attack persistent pro-virus. A big question remains as to how to purge HIV without harming the immune systems of patients.

Basic science research was presented on molecular mechanisms, pathways and possible treatment possibilities for eradication and “unlocking” or activating latent T cells. Treatment for activation would have to begin within 6–9 months of initiation and may include particular drug therapy targets, IL-7, monoclonal antibodies and treatment vaccines. Though this science is in very early stages, it is clearly getting more attention as it is given plenary and oral presentations at a major HIV conference. Stay tuned.
Much focus of the IAS conference was HIV therapy for treatment, prevention and a cure. The state of HIV research is exciting today as there appears to be more possibilities for enhancing current treatments, using HIV drugs for prevention and research in viral persistence. Unfortunately, as we have witnessed before, the politics and funding do not always meet the needs of the state of research and care. As was said many times at the meeting, “AIDS is not in a recession.”

Coverage of one major conference by one person is not possible. Please visit the IAS website for further information on abstracts and presentations or these other sources of information: AIDS-meds, The Body and NATAP. [Lucho, these three are links, and I’ll add them back in.]