Moi University CAB Hosts the Walter Reed Project CAB

By Amina Shali, CAB Vice Chair
Moi University Clinical Trials Center

Moi University CAB members hosted our partners and fellow CAB members from Walter Reed Project Kericho on the 10th March this year.

This is the second year of what both CABs term “educational for both parties, distance notwithstanding.” Kericho is 300 kilometers from Eldoret, and the bad roads have people jiggling all the way, but given the interesting topics expected at these meetings, makes it worthwhile.

On the agenda was CAB Outreach, A5263 protocol, a discussion on CAB challenges and possible solutions and general issues pertaining to CAB. CAB Challenges and Possible Solutions was an interactive and most interesting topic, and some of the emerging issues were (1) financial constraints to facilitate outreach, (2) ACTG Conference Call in-attendance, (3) training for CABs, (4) outreach, (5) linking with the community, (6) information, (7) time, as a resource, (8) protocol understanding, (9) difficulty in understanding presenters during conference calls, and (10) accessing the internet.

Possible Solutions

Among the plans in the restructuring were that every protocol written would be required to add CAB expenses to the budget in the future, thus alleviating financial constraints to a point and helping in outreach work. This meeting came on the heels of the Kericho community fiasco, where folk thought that blood was being sold for a fee at the Walter Reed project site, and our brainstorming was a way of preventing future misunderstandings.

(Moi Univ., Continued on page 2)
A Phase IV, Prospective, Randomized, Open-Label Evaluation Of The Efficacy Of Once-Daily Protease Inhibitor And Once-Daily Non-Nucleoside Reverse Transcriptase Inhibitor-Containing Therapy Combinations For Initial Treatment Of HIV-1 Infected Individuals From Resource-Limited Settings (Pearls) Trial

The main purpose of this study was to compare the safety and effectiveness of antiretroviral combinations for treatment of HIV infection. The study completed analysis of the primary endpoint data and the findings are presented here.

A total of 562 men and 483 women from 9 countries in 4 continents were randomized between May 2005 and August 2007 to initial antiretroviral therapy with efavirenz with either emtricitabine-tenofovir or lamivudine-zidovudine. Median baseline characteristics were: 34 years of age, CD4+ count 167/uL, plasma HIV-1 RNA 5.0 log_{10} c/mL. Participant follow-up was 184 weeks.

The primary efficacy endpoint was time from randomization to regimen failure defined as the first occurrence of confirmed plasma HIV-1 RNA $\geq 1000$ copies/mL at $\geq 16$ weeks, HIV-1 disease progression at $\geq 12$ weeks, or death. The primary safety endpoint was time to first dose modification or Grade 3 or 4 adverse event.

The results of the study showed that the antiretroviral drug efavirenz given in combination with either emtricitabine-tenofovir or lamivudine-zidovudine was effective for treatment of HIV-1 infection. However, people who took the combination of efavirenz given with emtricitabine-tenofovir had fewer abnormal laboratory test results during the study. More people in the lamivudine-zidovudine group changed their antiretroviral therapy due to a side effect than people who took efavirenz with emtricitabine-tenofovir, particularly HIV-infected women.

Most members are at work or are just leaving for home when conference calls come through, was given as the main reason most CAB members do not attend calls.

Onsite training, like the protocols A5225, presented by Dr. Lazarus Momanyi, the Walter Reed Project principal investigator, and A5263, presented by Dr. Simon Wachira, the Moi University ACTG site pharmacist, would suffice for now as none of the sites currently has money for CAB training.

- Other site/unit staff could train members on topics like TB, malaria, hepatitis and Kaposi’s sarcoma, as most are trained in these fields and are willing to help out the CABs.

Educating the community through Outreach was preferred to be done as a CAB unit when possible. Reaching out individually was also found to be acceptable, though with the kind of skeptical community we belong to, strength in numbers of CAB members at a meeting would yield better results.

Setting target groups for outreach visits was found to be the best option.

- Among some of the ways of acquiring information were conference calls, internet, CAB Newsletters, and information from CSS members.

- Any CAB member finding useful information for the CABs was requested to forward the same to members, just as the CSS disseminates information to all members at CAB meetings and through E-mail.

Good planning for CABs at the beginning of the year was found to be important. Organizing priorities through a year Work Plan, so as to keep track of all activities, and keeping files would be useful for CAB members joining later.

Reading out a study protocol, portion by portion by members themselves at a CAB meeting, would speed up members’ understanding of the protocols. In the beginning it would be useful for the members themselves to try to understand it first, then have a Principal Investigator or a site staff member go through it with them to gauge their understanding, particular attention being paid to Inclusion/Exclusion Criteria.
It was realized that none of the sites could provide internet service to all its CAB members all at once, but if planning is done, some members could be granted use during lunch time breaks and on Fridays when site staff were not too busy.

Unlike the Moi University CAB, the members of the CAB from the Walter Reed Project have not had formal CAB training, and it was important to let our visitors discuss what they thought a CAB was. Here are some of their answers:

- CABs should strive to educate the community on the importance of research.
- CABs should listen to the concerns of the community and present the same to the researchers.
- CABs should inform the community on importance of understanding eligibility criteria and informed consent.
- CABs should keep the confidentiality of participants’ information.
- Recruiting a past trial participant into a CAB is encouraged as that person would be able to meet the concerns of a community.

**Protocol A5263**

Dr. Simon Wachira presented on protocol A5263 – *A Randomized Comparison of 3 Regimens of Chemotherapy With Compatible Antiretroviral Therapy for Treatment of Advanced AIDS in Resource Limited Settings* - in a simplified version for the benefit of CAB members, since both sites are participating in this protocol.

Some of the answers to concerns put to the Dr. Wachia were that in our community “Patients go to the hospital late, thus their disease would almost always be at the late stage,” thus limiting the number of participants completing the trial.

Moi University will visit Walter Reed project site in June this year for a reciprocal meeting. There were refreshments and we were joined by the Moi University Clinical Research Center Site leader, Dr. Abraham Siika, during this sumptuous lunch.
The interviews discussed in the previous CAB newsletter, and many others, can be seen at www.ifarablog.org. I also stumbled across quite a few posters and attended many sessions. Here is some more exciting news.

**Innovative Therapeutic Approaches and Drug Resistance**

In a surveillance of transmitted and acquired HIV drug resistance using WHO surveys in resource-limited settings, S Bertagnolio et al. (paper #52) did not see much transmitted drug resistance (30 resistance surveys in 16 countries from 2002 – 2010). One giant reason was the fact that of those still on treatment at one year, 90% were undetectable, and following the logic that a suppressed person is not going to get reinfected easily, about half of those whose treatment did fail failed with mutations to the drugs they were on, suggesting poor adherence versus reinfecion. Of course, those who did fail for whatever reason could then be reinfected, and the results may depend somewhat on when you do the resistance test relative to the real time of failure.

Using routine viral load monitoring to reduce the rate of accumulated genotypic resistance to ART in Uganda (S Reynolds et al. paper #53), showed that regular (annual) viral load monitoring reduces the rate of accumulated genotypic resistance to NRTIs and NNRTIs; therefore, access to viral load testing and simple, low-cost assays remain important goals in resource-limited settings. Although to me, “regular” versus “timely” needs to be clearly defined. If the regimen fails the day after your viral load test, you won’t find out till the following assay (year?), which I am not sure will do anyone much good, as resistance mutations build up.

Therapeutic darunavir (a protease inhibitor) and etravirine (a non-nuke) concentrations in cerebrospinal fluid was measured by B Best et al. (paper #643). Both of Tibotec’s new drugs seem to be present in the cerebrospinal fluid in quantities that should contribute to control of HIV replication in the nervous system.

“Coadministered HAART and CYP450 enzyme-inducing antiepileptics: implications for HIV/epilepsy treatment in resource-limited settings.” by J Okulicz et al. (paper #646), showed that people taking phenytoin, carbamazepine, or phenobarbital with ART were more likely to reach virologic failure than those using nonenzyme-inducing drugs like lamotrigine, levetiracetam, pregabalin, or gabapentin, for seizures or neuropathy. They conclude that concurrent use of enzyme-inducing anti-epileptics with HAART should be avoided when possible.

In a substudy of A5208, it was seen that women on nevirapine in seven African countries had lower clearance of the drug than what had already been reported (from 1.6 – 2.0 L/hr). This led to lots of Grade 3 rash, Grade 3 liver elevations, and even discontinuations for Grade 2 toxicities (14%). Baseline CD4 above 250 was associated with all of the above (rash, liver elevations, and discontinuations). The authors conclude that these findings deserve more investigation. For the moment, women with more than 200 CD4+ cells should probably not start nevirapine, and possibly a different dosing could be considered for future study (B Dong et al. paper #647).

Another ACTG study reported was the A5175 substudy of sex- and geographic-based differences in atazanavir (ATV) pharmacokinetics in people treated with didanosine-EC, emtricitabine (FTC), and ATV by A Andrade et al. (paper #648). To recap, men in this study were more likely to fail. Here it was seen that ATV clearance was 79% slower in women than in men. Clearance was 60% faster in South Africa and Peru and 38% faster in Brazil, Thailand, Zimbabwe, and Malawi than in people from the US, Haiti, and India. Overall, men had a faster clearance, a lower amount of drug in their blood (AUC), and about half the concentration of ZDV – all significant differences.

Another PK study, this one in Thailand (J Ananworanich et al., paper #649), showed that raltegravir once daily (QD) at a dose of 400 mg is sufficient. Assuming that dosing can be guided by the AUC (total drug in the blood over the dosing schedule), 400 mg QD reached levels equaling 400 mg BID, as well as in maximum concentration. The thing is, minimum concentration, another important...
I just wanted to say thank you in my own way:
Anticipation filled the air, excitement and wonder abound.

The chair is empty, waiting, calling out in a hope
The room, which seemed so still moments ago,

Now is filled with beaming faces, brought together
With one mission, one hope one desire

The start, the laughter, the sadness and the resolve
I sit in amazement, wonderment and humility

I see in the eyes of those around me,
Commitment, passion and conviction,

All the gifts that I will take
Strength, compassion and love

Stealing the gifts you offer, hording, holding,
Like a child with his favorite toy

I have brought back to my city to share, as you have shared,
The unspoken understanding of community

By Graig Cote

That was then this is now
I look back but move forward
I love who I am and all
that I am. A woman all
woman superwoman because
of you I learned me. I am
every woman I learn to love
me me so that I could be
the Woman this is why I
feel I deserve the
chance to represent the
CAB

By Rita McDaniel
parameter, although possibly not so with raltegravir, was quite a bit lower on the QD regimen. This is versus what is seen in "western" populations.

One more PK study in Africa looked at rifabutin and lopinavir/r in people with TB on HAART (S Naiker et al., paper #650). Looking at three times a week versus QD, they saw that a QD regimen of 150 mg of rifabutin reached recommended maximum concentration levels.

Vaccines

Argos Therapeutics presented its final analysis of a phase 2 study of an autologous dendritic cell immunotherapy (AGS-004) (J-P Routy et al., paper #385) which showed a delay in viral rebound and time to peak viral load during a structured treatment interruption (STI) and a reduced viral load compared with pre-ART levels, which was associated with induction of memory CD8+ T cells. The induction of effector memory T cells (CD28+CD45RA–CD8+) prior to an STI correlated with the level of viral control during the STI. Control of viral replication trended toward an inverse correlation with HIV-specific CD4+ T cell activation. Fifty percent of the participants continued their STI beyond 12 weeks and received booster doses of AGS-004.

Levels of cellular immune activation and MDSC (myeloid-derived suppressor cells) are elevated after administration of an HIV-1 dendritic cell (DC) therapeutic vaccine (autologous DC loaded with HIV-1 peptides). B Macatangay from University of Pittsburgh (paper #386) showed that dendritic cell vaccines can cause a transient cellular immune activation that should be looked at in more detail.

An HIV-1 tat epitope vaccine significantly reduces viral load in ART-naïve asymptomatic HIV-infected patients (G Goldstein et al., paper #388) was a setpoint study that hypothesized that antibodies induced by HIV-1 tat epitope vaccination would reduce productive HIV infection, and a vaccine called TUTI-16 was administered to 22 naïve HIV-positive people. There was a highly statistically significant reduction in HIV viral load from baseline during the study in the TUTI-immunized groups compared with placebo, suggesting that very small increments of antibody suffice to lower the viral load. The company, Thymon, LLC, is a non-commercial research organization out of New Jersey.

Glaxo looked at the safety, reactogenicity, and immunogenicity of an adjuvanted protein HIV vaccine in HIV-1-infected participants in Germany (T Harrer et al, paper #389). Comparisons of viral load change from baseline showed a significant difference between the ART-naïve groups (vaccine versus placebo) in favor of the vaccine group. Comparisons of HIV-1-specific CD4+ T cell responses detected significantly higher frequencies in favor of the vaccine groups in both the naïve and experienced groups. The vaccine was more immunogenic (it produced more HIV-1-specific CD4+ T cells) in ART-experienced people than in ART-naïve people. CD8+ T cell responses have not been reported.

Chronic Inflammation

Tim Shacker (U Minnesota) gave an overview of chronic inflammation in HIV as a cofactor in progression. Even with fully suppressive modern HAART, there is a 10-year ageing difference between HIV positive and HIV negative populations. At any given time, CD4 cells are depleted by some 50%. And these populations do not come back. The cytokine storm is eventually lowered, but not normalized. Increased cIMT, IL-6, D-dimer, and C-reactive proteins are all linked to early mortality. In treated populations, dementia can still be present as well as neuronal degeneration and a progressive clinical deterioration via cardiovascular disease, metabolism, osteoporosis (IL-6 stimulating osteoblasts), an accelerated ageing, senescence, kidney disease, cancers, and endocrine diseases. Microbial translocation is due to a disrupted gut epithelium.

Looking at the reduction of chronic inflammation in selected patients with raltegravir (RAL) intensification, K Lichtenstein et al. (paper #276) showed that the addition of RAL to people receiving virologically suppressive regimens, but with poor CD4 count responses, results in improvements in the CD4/CD8 ratio; reductions in activated CD4 cell percent, pro-inflammatory cytokines, and effector memory cells; while RANTES, a protective chemokine, increased in people, particularly those with low CD4/CD8 ratios at baseline. Clinical relevance of these findings will require further study and clinical correlation.

In what may be considered an important paper (L Roberts et al. paper #991) —genital tract inflammation in women participating in the CAPRISA TFV microbicide trial who became infected with HIV: a
mechanism for breakthrough infection—the authors reported that women who became infected with HIV did not have increased cytokine levels during early infection relative to preinfection. However, women who became HIV infected had significantly higher concentrations of inflammatory IL-1β, IL-6, IL-7, TNF-α, MIP-1α, MIP-1β, and GM-CSF before infection relative to women who remained uninfected. The authors suggest that these high levels of genital tract inflammation may facilitate breakthrough infections and that enhancing the efficacy of TFV gel may require augmentation with an anti-inflammatory agent.

Interleukin-7 (IL-7) is the latest immune-based therapy to undergo investigation. In paper #376 by I Sereti et al, recombinant IL-7 expands CD4 T cells in peripheral blood and gut mucosa of chronically HIV-infected immunological non-responders. It is hoped that IL-7 will expand T cell pool in both peripheral blood and mucosal sites, which in turn may improve immune restoration in chronic HIV infection. In this small study, they were able to say that CYT107 (IL-7) administration can significantly expand CD4 and CD8 T cells with lower expression of PD-1 (programmed death-1 cells) while increasing the expression of gut homing molecules that may result in the restoration of the CD4 population of the gut mucosa.

In a comparison of the effects of ART initiation during primary versus chronic HIV-1 infection on biomarkers of central nervous system disease (D Muthulingam et al., paper #412), CSF HIV-1 RNA decay, trajectory or set point white blood cells in the cerebrospinal fluid, albumin ratio, or NPZ-4 (all biomarkers) did not differ between the groups (primary or chronic infection). This strange result may have been due to the fact that no primary person failed his/her regimen, while some in the chronic arm did, possibly due to build up of resistance mutations due to irregular adherence, etc.

An interesting paper on why macaque models are very helpful—the RON receptor tyrosine kinase, a negative regulator of inflammation, is decreased during SIV-associated CNS disease (D Cary et al., paper #432). The use of a well-characterized SIV infection model in macaques shows that during acute SIV infection in the brain, active inflammation may be initially controlled by RON. However, after prolonged infection, RON expression decreases, genes that quell inflammation are repressed, and inflammatory mediators are induced to directly promote CNS disease.

Putting the essence of your whole study in the title is brilliant, and in their paper, G Thorborn et al. (paper #263) explain that the elevated regulatory T-cell-mediated suppressive potential, but not Treg:IL-17 ratio distinguishes chronic asymptomatic treatment-naive HIV+ subjects from patients who progress to disease, and this elevated Treg response is lost as people progress to disease.

In primary HIV infection, fatigue and CSF inflammation were looked at by M Grill et al. (paper #413). They saw that at least some component of fatigue (including mood states and depression scores) in recently infected people may be related to HIV and inflammation within the CNS compartment.

In another substudy of ACTG 5248, N Funderburg et al. (paper #318) looked at treatment-naive people receiving raltegravir and their CD4 turnover post-viral control. They saw that this turnover (Ki-67+, CD38, HLA-DR) was delayed more than in uninfected controls and never reached the same levels, and this correlates with markers of microbial translocation (sCD14, IL-6 and TNF1).

In an Italian study (E Merlini et al, paper #309) looking at atherosclerosis (ATS) and microbial translocation, the authors saw that HAART-treated HIV+ patients with ATS-related vascular damage present an activated/senescent, apoptotic, and pro-inflammatory immune profile, all correlating with high microbial translocation markers. By showing a correlation between sCD14 and carotid IMT, they found that innate immunity to translocating bacterial products may contribute to increased CV risk in treated HIV infected patients.

C Shive et al (paper #320) showed that immunologic failure despite suppressive HAART is related to increased inflammation and is evidence of microbial translocation. IL-6 (an inflammation factor), D-dimer (a measure of coagulation), and sCD14 and LPS (microbial translocation factors) were measured in people who were not controlling their virus despite being undetectable for more than 2 years (in 63 people), 21 people with good control, and 20 HIV-uninfected people. sCD14 and IL-6 were higher in non-controlled people, and D-dimer, although not...
different between people on treatment, was significantly higher than in uninfected people, suggesting a persistent prothrombotic tendency in treated HIV infection irrespective of immunologic restoration.

Flagellin is a toll-like receptor considered a marker for microbial translocation. In a Swedish study (S Abdurahman et al, paper #313), the authors saw ELISA-estimated plasma levels of anti-flagellin IgG antibodies higher in treated controlled people than in HIV negative controls. After 2 years of ART, levels of anti-flagellin antibodies were not reduced, with higher levels in people with persistent viremia. They posit that flagellin should be considered an important antigen involved in immune activation and the pathogenesis of chronic HIV-1 infection.

In a large study in rhesus macaques, T Glavan et al. (paper #314) studied gene expression profiles in the gut mucosa and saw that significant increases in the expression of anti-inflammatory cytokines IL-10 and TGFβ were associated with dampened expression of pattern recognition receptors (PRR), particularly in the intestinal mucosa. An effective CD4+ T cell restoration was associated with decreased expression of IL-10 and a PRR and cytokine expression profile that mirrored the acute stage profile.

For much more on microbial translocation, please go to http://www.retroconference.org/2011/Sessions/028.htm

Search: For more on innate immunity, please go to http://www.retroconference.org/AbstractSearch/ and type in innate immunity

For more on transmission and transmission factors, do the same.


For more detailed information on all this, please go to the CROI website at http://www.retroconference.org/AbstractSearch
Studies on AGS 004, an autologous cell therapy in phase IIB by Argos Therapeutics, located in North Carolina (http://www.argostherapeutics.com/), and Vacc4x, a phase II therapeutic vaccine by Bionor Pharma located in Norway (http://www.bionorpharma.com/) were recently featured in an article by AIDS treatment activist Jeannie Gibbs in the March 2011 issue of A & U (http://aumag.org/wordpress/?p=1319). Vacc-4x is four modified peptides derived from the protein encasing the genetic material of HIV that are intradermally injected in combination with an adjuvant (granulocyte-macrophage colony stimulating factor-GM-CSF). This therapeutic vaccine targets dendritic cells and stimulates the proliferation of both CD4+ (helper) and CD8+ (killer) cells. The CD8+ cells acquire the ability to recognize infected cells expressing the characteristics represented in the modified peptides. Vacc-4x aims to stimulate cell-mediated immunity.

Following further analyses of an international, randomized, double-blind, placebo-controlled, multicenter phase IIb study of Vacc-4x, the company reported an unexpected statistically significant viral load reduction. The study was designed to test HIV patients’ ability to stay off ART after having been immunized with the therapeutic vaccine. Although the study did not meet primary endpoints, the findings from the additional analysis showed that treatment difference with regard to viral load was statistically significant both within the study period and when compared with viral load prior to ever starting ART. In participants who received immunization, viral load never returned to its pre-ART level, which normally happens when being taken off these drugs.

Argos Therapeutics’ AGS-004 utilizes small plasma samples from infected patients to amplify large quantities of messenger RNA that encode selected viral antigens. This technique has the added advantage of amplifying the multitude of patient-specific viral variants evolving in the infected patient, allowing for the creation of a therapy perfectly suited to the individual. The viral sequences presented to the immune system to recognize and attack the virus are compatible with the virus with which that person is infected. The simultaneous presence of autologous viral sequences and dendritic cells may result in a novel immune response, personalized to each patient, which will successfully control residual virus or viral rebound following the cessation of ART. Data from a phase I trial of AGS-004, presented at the XVII International AIDS Conference in 2008, demonstrated that the primary endpoint of induction of T cells response to patient-specific HIV antigens were met.

While Bionor Immuno has made a presentation on Vacc-4x to the Translational Research and Drug Development (TRADD) committee and Argos Therapeutics has received facilitation via NIH grants for the development of AGS-004, both promising therapies continue to develop outside of the ACTG.

DermaVir, a nanoparticle-based therapeutic vaccine being developed by Genetic Immunity (http://www.geneticimmunity.com/GI100.html) located in Budapest, is an experimental HIV/AIDS vaccine that combines three key elements of rational therapeutic vaccine design: a single plasmid DNA (pDNA) immunogen expressing 15 HIV antigens, a synthetic pDNA nano-medicine formulation and a dendritic cell-targeting topical vaccine administration. DermaVir’s mechanism of action is natural transport by epidermal Langerhans cells to the lymph nodes to express the pDNA-encoded antigens and induction of precursor/memory T cells with high proliferation capacity, which has been consistently demonstrated in mice, rabbit, primate, and human studies. The safety, immunogenicity, and preliminary efficacy of DermaVir have been demonstrated in HIV-infected persons in phase I and phase II trials, including ACTG A5176 and six other studies[7,8]. A phase II study on DermaVir in HIV-infected children is nearing initiation in IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials Group).

VRX496, being developed by Virxsys (http://www.virxsys.com/), uses an autologous process that removes CD4+ T lymphocytes from patients and genetically modifies them with VRX496, expands them to provide multiples of modified cells, and re-infuses these cells into the patient. The Investigational New Drug (IND) application for VRX496, which was approved by the FDA, was the first for any biologic therapeutic product using an HIV-based lentiviral vector. The phase I and phase II clinical trials have demonstrated safety for trial participants.

Adaptimmune (http://www.adaptimmune.com/) is collaborating with the University of Pennsylvania School of Medicine on the development of Adoptive T

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cell therapy, a process involving taking blood cells from an HIV-infected person, manipulating them to improve their therapeutic potential when outside the body (ex-vivo), and returning them to the person. Based on a highly unusual T cell clone specific for an immunodominant HIV-1 gag detectable in 75% of HIV-infected patients, (TCR) binding clones were isolated from a patient exhibiting long-term nonprogression. Enrollment is ongoing in an open label, phase I multiple arm study started in November 2009 to evaluate safety, tolerability, and antiviral effects of escalating doses of a single administration of autologous T cells modified using lentiviral vectors expressing an increased affinity version of this gag-specific TCR.

Another therapeutic vaccine study was just announced. ACTG 5281 is a phase I, placebo-controlled, dose-escalation clinical trial being conducted in the US to assess the safety and immunogenicity of a fixed dose of Profectus Bioscience’s multi-antigen HIV plasmid DNA (MAG-pDNA) vaccine administered with various doses of GENEVAX(TM) interleukin-12 (IL-12) pDNA adjuvant and delivered using the electroporation (EP) based TriGrid(TM) delivery system.

There are many other studies that can be covered in future articles. The IAS Pathogenesis conference in Rome this summer will undoubtedly be providing a number of new presentations on IBTs in commercial and academic development in the US and Europe, which activists and clinicians will be looking at with renewed interest, following the announcement of the first sterilizing cure of an HIV patient.

While the pipeline for ART is still advancing, the future of IBTs for HIV infection is facing unique challenges. There is still significant bias against structured therapeutic interruptions, which are essential to evaluate the clinical effects of IBTs in research settings. Regulatory considerations for IBTs for HIV are still lacking specific guidance at the FDA, further discouraging life science companies from entering this challenging arena. Additionally, the greatest barrier to the development of HIV immunotherapy is the lack of an effective biomarker. While committee formations and reorganization plans by the Office of AIDS Research may help refocus clinical investigation priorities, the current financial circumstance of the life science industry continues to deteriorate for small biotechnology companies with innovative HIV programs, despite the Qualifying Therapeutic Discovery Project Tax Credit Extension Act of 2011[7]. Ensuring these companies are able to support studies of new treatments is an essential component for the successful development of IBTs for HIV infection.

Immune system hyperactivation is now acknowledged as a primary driver of HIV disease progression and a growing list of associated pathologies, which are being reported despite successful treatment with ART. A new class of ARV medications known as antiviral-hyperactivation limiting therapeutics (AV-HALTs) has been proposed that would both reduce viral load and the excessive immune activation. ViroStatics, a small Italian/US biotechnology company, recently established the human proof of concept for their first-in-class NRTI-based AV-HALT, VS411. Data presented at CROI 2011 demonstrated that VS411 was able to safely and significantly reduce viral load and four markers of excessive immune activation and proliferation in just 21 days.

There are other therapies to address HIV-associated immune activation and inflammation in maturing stages of clinical development, including TBR-652. TBR-652 is a CCR5/CCR2 antagonist in phase IIb by Tobira Therapeutics.

The ACTG has recently begun to focus more on inflammation and immune hyperactivation with A5258, a randomized, double-blind, placebo-controlled study to evaluate the use of chloroquine in chronically infected HIV patients who are not receiving ART. Unlike VS411 and TBR-652, chloroquine has no significant impact on viral load. Last July saw the National Association of People with AIDS sponsor a satellite symposium during the XVIII International AIDS Conference in Vienna that was featured in an article in Nature[8]. In the article, Steve Bailous, Vice President of Community Affairs at NAPWA was quoted, “We need to have hopes, and some of the therapeutic vaccines look really promising, If we can’t raise our hopes there, then where?”

David Miller is a member of the Cornell ACTG CAB and a Board member of the AIDS Institute. He works with Health
**Duke University DART CAB Participates in Local AIDS Walk + Ride**

*By David Palm*

It was a bright and sunny Saturday in downtown Raleigh on May 21st as the 2011 AIDS Walk + Ride got underway at slightly after 3 pm. Several of our CAB members, staff, and family showed up to enjoy the day with us: Jacquie, Julia, Rachel, Trish, Royce and David J., Kevin and David P., Hormel, Rolando, Michael, Gordon, Keith, Midge and her husband, and Debbie. For those who were there last year, this year was even better: We had our table in the shade (thanks Rachel and Julia), banners and materials (thanks Trish, Julia, and Rachel), some cool breezes, and lots of bottled water. Many participants visited our table, viewed our displays, and took with them pamphlets and information.

Between contributions and donations by our team members, donors, and friends, the Duke DART CAB Team raised $1,310 for the Alliance of AIDS Services - Carolinas (AAS-C) and other area beneficiaries such as the DART CARE Fund and the Duke Pediatric AIDS Clinic. A job well done to everyone!

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People in the South Bronx as the Treatment/Policy Education/Advocacy Coordinator; David is the former Co-Chair of the NYC HIV Planning Council Advisory Group, a veteran of ACT UP NY and a member of the Bronx HIV CARE Network and the Campaign to End AIDS. David was an organizer for the NAPWA Treatment Horizons Satellite Symposium at the XVIII International AIDS Conference. David is a member of various AIDS activist organizations and generally asks too many questions.

Mariel Selbovitz, MPH, received her BA from Cornell University and her Master in Public Health John Hopkins School of Public Health. She is a member of the Cornell ACTG CAB and is the HIV/AIDS Treatment Policy Education Advocacy Program Coordinator at Health People. Mariel was a leading organizer for the NAPWA Treatment Horizons Satellite Symposium at the XVIII International AIDS Conference. Mariel has international experience in harm reduction; she has worked at a drug consumption room in the Netherlands and needle exchange programs in New York, Boston, and Washington DC. She can usually be found trying to figure out how to put herself on a coffee drip.

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Many of us from the Washington University Clinical Research site sat with anticipation in the audience at the June 2011 AIDS Clinical Trial Group meeting as the Young Investigator award winner was announced. Then came the announcement: Dr. E. Turner Overton had won the John Carey Young Investigator Award this year - our very own Dr. Overton!!!

It was a bitter sweet award for the community at the Washington University Community Advisory Board (CAB). Dr. Overton is part of us – he supports the CAB with patience, explanations, humor and just plain old good science. Not to mention that many of the CAB members are his patients.

Dr. Overton joined the Infectious Diseases Division in 2004. He received his MD from the University of Tennessee in Memphis, Tennessee. He was an Internal Medicine resident at the University of Alabama in Birmingham, Alabama. He did his fellowship in Infectious Diseases at Washington University School of Medicine and Barnes-Jewish Hospital. The major focus of Dr. Overton's current research is in vaccine responses in HIV infected individuals. Another focus of his research relates to co-infection with HIV and the hepatitis viruses, and more recently HIV and aging.

As I mentioned earlier, this is a bitter sweet award for our Washington University site, for Dr. Overton is leaving us and joining to the University of Alabama where he will help to build an HIV/HCV co-infection clinic there.

At our final CAB meeting, Turner thanked the CAB for their amazing engagement, the knowledge of the complex nature of research protocols and the level of feedback we have provided to him. Turner said, “Throughout my time at Washington University, the CAB has been a tremendous resource as I developed ideas for studies. I come away from the CAB meetings re-invigorated about the projects and ideas thanks to their enthusiasm and interest.”
Introduction

I managed to travel to Uganda during the December holiday and visited Makerere University, Mbarara University, and Bugema University. During my interaction and learning I discovered that Uganda has done a lot as far as eradicating HIV/AIDS is concerned. For me I would like all countries in Africa south of Sahara to emulate Uganda if AIDS is to be reduced or eradicated. Fighting HIV/AIDS has posed enormous challenges worldwide and it has been difficult to contain it. However, Uganda has shown that an early and multisectoral strategy can reduce the prevalence and infection of HIV/AIDS. After its discovery in 1982, the epidemic grew to a cumulative 2 million HIV-infected persons by the end of 2000. However, Uganda established the AIDS Control Programme in 1987, which helped to reduce the epidemic through public health education, improved transfusion services, care and support of infected persons, and a surveillance system to monitor the epidemic.

After a decade of tireless fighting against HIV/AIDS, Uganda recorded a downward/declining trend of HIV/AIDS in 1996 (being the first country in Africa to manage HIV/AIDS). Further decline of the disease is still recorded to date, e.g., in Kyamulibwa in the Masaka district. Data show that to achieve these results, all countries in sub-Saharan Africa must accept and have political will to kick out HIV/AIDS.

Uganda with approximately 22 million people in 2001 was the first developing country to encounter HIV/AIDS. The disease developed silently taking advantage of poor health care, lack of access to safe water and sanitation, and insecurity. The early years of HIV/AIDS was characterized by mystery and rumors followed by discovery as a disease and later being declared an epidemic. HIV/AIDS and its consequences have by now had a direct impact on at least one in every household in the country.

History Of HIV/AIDS in Uganda

The first case of ‘slim disease’ HIV/AIDS was reported by a health worker in Rakai District in South West Uganda. The disease was characterized by fever, STDs, and TB, and mostly affected traders who traveled extensively across Uganda. At first people believed that the disease was witchcraft. The epidemic spread rapidly because of ignorance and unfavourable cultural practices. The spread of HIV/AIDS doubled after every 6 months, attracting concern from relevant authorities which then moved in.

National Response

Enabling policies

Having felt the pinch of the epidemic, the high-profile political effort was created to facilitate the need to openness about HIV/AIDS. The responsibility was decentralized to the sectoral, district and at the community level through legislative administration and directives. In 1992 Uganda AIDS Commission was formed to coordinate multisectoral national response. Also partnership between political, religious, educational institutions, NGOs, and communities was promoted. The plan’s fund to assist and curb the pandemic was disbursed directly to the district level and local level as per the needs.

Institutional capacity building

The institutions have been set up or strengthened at the national level to provide services, conduct research, and act as training centres for staff. Such institutions include Uganda Virus Research Institute for laboratory monitoring of HIV infection and antiretroviral drugs, National Blood Transfusion Services, and the Joint Clinical Research Centre. Also the Ministry of Health is used to implement the HIV/AIDS control effort. Private organizations have not been left behind in the fight against HIV/AIDS, i.e., centres such as Uganda Network of AIDS Service Organization, which monitors and ensures that quality control of HIV/AIDS is achieved.

Public education of behavioural change

Raising awareness was the mainstay of the initial programme because people were instilled with fear for them to shy away from the disease, but it seemed not to work. Later political influence, mass media, fold media, and political personnel conducting mass campaigns with support of the community managed to promote awareness. Also, a new body of health educators was formed in all levels of administration, and the safe sexual practice of using condom was encouraged. A similar network established in schools significantly reduced the spread of the epidemic.

STD Management

Promotion of early and appropriate STD care has been part of social mobilization campaigns. The programme has continued to procure condoms and drugs.

Blood transfusion services

The national and regional blood banks have been strengthened and currently provide at least 70% of national requirements.

(Fighting, Continued on page 14)
Care and support for people with HIV/AIDS—The cumulative number of people living with HIV/AIDS in Uganda by December 2000 was 1,107,644, and due to the stigma associated with AIDS and poverty, patients are left without proper care. Therefore, the government has rolled out a plan to assist and care for the people with HIV/AIDS through trained personnel. Three-tier counseling services have been established. The drugs for opportunistic infections are available and free for patients. The joint ministry of health and UNAIDS drug access initiative is supplying drugs. The government, through access to nevirapine, has rolled out a plan to prevent HIV being transmitted from mother to baby, and also orphans are taken care of and supported by the government.

**Surveillance systems for HIV/AIDS**

Effective control and prevention of HIV/AIDS depends on the collection of reliable data on magnitude, trends, and distribution of HIV infections and AIDS disease. The STD/AIDS Control Programme used both passive and active surveillance systems to generate data for programme planning. Passive surveillance entails collection of data through formal reporting system, while active surveillance is conducted through sentinel sites where data are collected over time. The behavioral surveillance through population-based knowledge, attitudes, behaviours, and practice studies (KABP) repeated every 3 years has been conducted in each of 12 districts.

**Surveillance results**

(a) HIV Sentinel Surveillance

Antenatal screening
HIV prevalence rates in pregnant women have continued to decline at both rural and urban sentinel surveillance sites in the country

(b) STD Patient Screening

In the STD sentinel population at old Mulago Urban Hospital, the HIV prevalence rate declined from 44.2% in 1989 to 29.4% in 1998.

**HIV incidence rates**

The impact of HIV/AIDS on children and young people is a severe and growing problem, i.e., in 2008 430,000 children under 15 years were infected, although there are effective prevention and treatment interactions as well as research efforts to develop new approaches, medications, and vaccines. In many areas there is a reduction in incidence among young men and women, for instance, in Kyamulibwa.

**Behavioural Surveillance**

Repeat population-based KABP studies provide encouraging results on the priority prevention indicators and on selected key behaviours.

Note: Condom used with non-regular sexual partners has increased for all districts over the years.

**Discussion**

The reduction of new HIV infections seen in Uganda may be from changes in the human body or behaviour or arising from Uganda’s national response to HIV/AIDS, which is responsible for the reduction in new infection. HIV/AIDS epidemic may have spread at about the same time in the sub-Saharan countries but there are between-country variations in the trend of the HIV rate, and in some countries the rates are still raising.

Uganda has shown that for AIDS to be controlled, efforts need to be multisectoral and mainstreamed in the overall national development programme. It has proved possible to increase the coverage of services by decentralizing the HIV/AIDS control effort to the district and community level.

As we approach the end of the second decade of HIV/AIDS control, the Africa governments must avoid complacency and continue with frequent and targeted HIV/AIDS prevention and control messages. Also respect and the rights of those affected by HIV/AIDS must be fundamental in the national response.

Finally, we should remain receptive to newer strategies such as vaccine developments as they emerge as well as local HIV/AIDS variants to be used in development of new strategies.

**Conclusion**

Uganda’s experience suggests that multipronged prevention and control strategy can significantly influence behaviour and the prevalence as well as the incidence and rates. Mechanisms for the coordination of a multisectoral joint plan must be an integral part of the National HIV/AIDS policy of each country.
Two years ago, Marcia V. Ellis, GCAB ACTG Representative for Georgetown University Hospital, and Joseph Hall, CAB Leader for the INSIGHT CAB at the Veterans Affairs Medical Center (VA) Hospital, launched the first annual joint CAB Meeting aimed at providing important information from the Conference on Retroviruses and Opportunistic Infections. CROI is an annual conference where internationally renowned infectious disease researchers assemble to present and discuss the most recent developments in research devoted to defeating HIV. Marcia and Joseph, like many advocates, participate not only on each other’s CABs but also on other network CABs in DC. Both observed early on that each CAB had a presentation at CROI following the meeting and decided to make more efficient and effective use of our many CAB meetings by joining our CABs for news from CROI and possibly other cross-CAB themes and educational issues. CAB Liaison staff from both the Georgetown and VA sites, Karyn Hawkins and Melissa Turner, along with their site directors, Dr. Princy Kumar and Dr. Fred Gordin, endorsed and supported the idea. Last year the first meeting was piloted at the VA Hospital and proved to be a successful model.

This year on May 10, 2011 the second cross-CAB post-CROI meeting took place with features that further built upon the pilot event:

- Other network CABs, the George Washington University School of Public Health HPTN CAB and the DC Developmental Center for AIDS Research (DC-CFAR) CABs joined Georgetown and the VA in hosting the event.
- The meeting was expanded to include the entire DC community of HIV/AIDS activists and advocates. The meeting was held in the community and at one of the premier AIDS service organizations, Us Helping Us, People into Living that since 1988 has been providing critical services to black gay men. One of our visions is to spotlight the important work of one of the community agencies.

An exciting added dimension to this meeting was the fact that fellow CAB member and AIDS Research Advocate, Joseph Hall, was selected, through a competitive process, for a scholarship to attend CROI as one of the few community representatives in attendance. Through his participation in CROI he was able to bring a level of energy and enthusiasm and provide important leadership and a community lens and perspective at CROI.

The Planning Committee (Joseph Hall, Melissa Turner, and Marcia Ellis) began to meet regularly to jointly plan the event; the broader team included staff from both of our CABs, including Haidee Elvis from the VA and Annaliese Huesller from Georgetown. An illustrious panel of experts who attended or followed CROI closely was convened and topics were selected that reflected their own presentations, interests, and “take backs” from the conference. Marcia Ellis welcomed the participants and provided the context for the meeting. Melissa Turner introduced the panel and served as moderator. The panel and topics included the following, in the order of their presentations:

- **JOSEPH HALL**, kicked off the discussion on a very high and hopeful note by bringing to the panel and the audience the excitement at CROI around the issue of a **Cure** for HIV/AIDS as one of the major themes.

- **ANN LABRIOLA, MD**, is Associate Professor of Medicine at GWU, the Research Director of the Infectious Diseases Section of the DC VA Medical Center and Director of the HIV Silver Clinic Smoking Cessation Program at the VA. Her topic was **Antiretroviral Treatment (ART) for HIV Prevention**, one of the highlights from CROI.

- **IRENE KUO, MPH, PhD**, is Assistant Research Professor of Epidemiology and Biostatistics at the GWU School of Public Health. Her topic was **Community Viral Load and Updates in New HCV Drugs**.

- **PRINCY KUMAR, MD**, is Professor of Medicine and Microbiology and Senior Associate Dean of Students at Georgetown University School of Medicine, and Chief of Infectious Diseases and the Clinical Trials Unit at GUH. Her topic was **New Insights into Treatment**.

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KEITH CRAWFORD, PhD, is Chief of Public Health Research of the US Military HIV Research Program and Faculty Member at the Howard University College of Medicine in the Department of Pharmacology. Dr. Crawford provided a response, summary, and wrap-up of the meeting.

(Slides of the presentations are available for those who might be interested.)

Nearly 40 people from a cross section of the DC HIV/AIDS activist and advocacy community participated in this evening meeting and contributed to a lively discussion that followed the meeting. All the hosts of the event contributed the ample food and drinks and all other support. There was a lot of networking, cross-sharing of events, activities, and issues throughout the community that added to the success and richness of the evening.

Evaluation results reveal overwhelming support for the quality and importance of such cross-community meetings. In the DC community we, the Planning Committee, see it as a way to enhance the community capacity around HIV/AIDS research; create a space for open and critical analysis and learning between researchers and advocates; and to implement a model for improving the efficiency and effectiveness of CAB meetings and community education on HIV issues in general.

We thank our co-hosting institutions, VA Hospital, Georgetown, The DC Developmental Center for AIDS Research (CFAR), GWU, and Us Helping Us/People into Living Executive Director, Dr. Ron Simmons, and staff for graciously welcoming and supporting us; and very importantly, the community of allies, practitioners, and activists who have worked tirelessly over many years on behalf of all those affected by and infected with HIV who took the time to participate in and bring their knowledge and experience to an event we look forward to organizing again next year.

Our takeaway from this meeting is that the development of treatments for HIV/AIDS has been life-saving and quality-of-life enhancing and was not easily imagined many years ago. New and improved treatments are still needed to address the still toxic affects of the treatments and the co-morbidities. The idea of a community viral load is exciting and revolutionary. A vaccine may be closer at hand. And a cure for HIV/AIDS is no longer far-fetched. It, too, is attainable and achievable, but will require the same level of resources, education, advocacy, and activism, and hope...always the hope!
"Women and HIV/AIDS" - Their Vulnerability and Suggested Reforms of Policy That May Curb HIV/ AIDS Transmission

By Jacob K. Sitienei, Chairman CAB Mucrs - Eldoret

An Analytical Look at Women and Girls and Their Vulnerability to HIV/ AIDS Infection/ Transmission

The National AIDS Control Council has developed the Kenya National HIV/ AIDS Strategic Plan, published in October 2000 to cover the period between years 2000 to 2005. Therein, the mention of women and girls is to the effect that women’s attainment of healthy and fulfilling lives is influenced by factors operating at many levels of society, including traditional/ cultural, politics, and legislation, which do not allow full expression of women’s potential and abilities.

In addition, the majority of women have little control of their own sexual behaviour and less over the sexual behaviour of their husbands or sexual partners. Women are stigmatized if they insist on using condoms. In addition, women have biological factors that increase their risk of HIV infection and make it difficult to detect STD infections. Further, STDs are often asymptomatic in women, making them more difficult to be diagnosed than in men.

The risk of transmission from infected men to women is greater than from infected women to men.

Many women are powerless to take steps to protect themselves.

Women are also disproportionately responsible for the care and added burden of those infected and affected with HIV/ AIDS, often without sufficient information, medication supplies, counseling, and support.

Prevention strategies and messages, in particular, have focused on abstinence, reduction of sexual partners, fidelity within relationships, safer sexual practices (use of male condoms), and the treatment of STDs. Women need to be allowed to access all the available information on HIV/ AIDS.

Women should be empowered to enforce faithfulness within relationships. This will be done through improvement of their political, social, and economic status. We can assist by encouraging women to start associations that will enhance them economically and at the same time voice their political wants. Similarly, women politicians should be encouraged to take the stand and represent women's interests.

At the XIII International AIDS Conference, popularly referred to as Durban 2000, a justice of the constitutional court of South Africa, Yvonne Mokgoro, said “Stigma operates as a powerful barrier to disclosing HIV infection, even to partners placed at risk, a burden that falls particularly heavily on women in their intimate relationships.”

Thus, while physiology affects women’s greater risk of HIV transmission, it is women’s and girls’ lack of power over their bodies and their sexual lives, supported and reinforced by their social and economic inequality, that makes them such a vulnerable group in contracting and living with HIV/ AIDS.

Women’s Vulnerability to HIV/ AIDS

1. Poverty
   a. Commercial sex workers (not only for money - moonlighting)
   b. Migrants
   c. Refugees

2. Culture
   a. Silence that surrounds sex – a “good” woman is ignorant about sex and passive in sexual interactions
   b. The norm of virginity before marriage restricts ability to ask for information
   c. To preserve virginity, women practice alternative sexual behaviours
   d. Belief that sex with a virgin can cleanse a man of HIV infection

3. Intersection of poverty with culture
   a. No say over sexual relations
   b. Forced or arranged marriages, often at an early age
   c. Accepting that men should have many sexual partners
   d. May be denied equal rights to marital property
   e. May lack power to initiate or oppose divorce proceedings

4. Violence against women - coercive or violent sex

(Women, Continued on page 18)
5. Gender-specific roles combined with poverty and sociocultural attitudes toward women and girls; they bear the burden of caring for the sick and the dying
6. Limited access to risk and prevention education
7. Limited access to health and medical facilities

Key to Reform
1. Encourage behaviour change – responsible, respectful, consensual and mutually satisfying sex.
2. Efforts to work with couples as the unit of intervention, rather with individual men and women.
3. Enhancing of female autonomy so that they have the ability to decide when and whether to have sex, to engage in certain sexual practices, and to use contraceptives.
4. Increased opportunities to participate in the development of policy frameworks, laws and regulations that shape women’s access to and enjoyment of their social and economic rights.
5. Sufficient allocation of resources to effective policies and programs on gender equality.
6. A system of monitoring and evaluation to ensure that the gender-related objectives of the particular policy and program are met.
7. Increase access to female condoms and microbicides.
8. A focus on male attitudes and practices – early intervention to influence socialization of young boys to foster gender-equitable attitudes and behaviours.
9. Increase access to information about safe sex practices and reproductive health services.
10. Increase access to prevention of parent-to-child transmission.
11. Increase access to post-exposure prophylaxis for rape survivors.

These issues can be framed in terms of privileges or even rights and can form the basis of advocacy, research, educational and other strategies.

12. Ensuring a legal framework for protection against violence, and effective enforcement of the law. Currently there is a Sexual Offences Act in place in Kenya.

13. Ensuring an suitable legal framework for sex work (decriminalization, but without punitive measures).
14. Ensuring the right choice, both in terms of termination of pregnancy and in terms of the rights of HIV-positive women to have children.
15. Developing regulations for, and enforcement of, a right for rape survivors to be informed by the police/surgeon about the need to access antiretroviral drugs to prevent possible HIV transmission.
16. Undertaking legal action to obtain drugs to reduce parent-to-child transmission if it is possible in a national context to rely on the right to reproductive choice or the right to access to health care.
17. Ensuring access to resources and land through inheritance in customary law, which is purely based on the constitutional supremacy.
18. Ensuring a legal, social, and psychological framework of equal rights within the family, in marriage, divorce, guardianship, and custody of children.
19. Protecting the rights of HIV-positive women within relationships or the family, especially in relation to abuse, abandonment, and discrimination, say by use of an anti-discrimination law already in place.
20. Seeking an order of mandamus, meaning requiring the state to perform its functions, say of meeting the basic needs of its governed people.

Reducing Women’s Economic Dependence on Men
- Women need access to resources for economic advancement, including jobs, land, property, and credit.
- Legal reforms that target the lower levels of the economy, including the informal sector and small and medium enterprises, are critical to women’s greater empowerment.
- Anti-discrimination measures in the workplace must protect against discrimination on the basis of gender and HIV status.

Empowering women will not disempower men, rather more power to one invariably, in the long-term, means more power to all. Empowering women is not a zero sum game.
NOTE: Articles for the September Edition are requested by August 31, 2011