



**Presenter: Ron Rosenes**

## **"Challenges of living long with HIV: What don't we know and who has the answers?"**

Or "What don't we know and why can't I remember who has the answers?"

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Over the years working in this community and living with HIV for the past 28 or 30 years, I have made many wonderful friends. In the 1980s and 90s I lost many of these wonderful friends who, in retrospect, didn't live long enough to benefit from the incredible advances in treatment we now call HAART. I was at the Intl AIDS Conference in Vancouver in 1996 when many of us thought we had been saved, that HIV could in fact be eradicated. I remember being interviewed by the CBC and being photographed walking off into the sunset along English Bay. (I thought at the time that if I had a wheel chair, I would fling it into the Bay). As we now know, the David Ho dream of eradication was not to be. It was built on a faulty mathematical model that had not taken into consideration that HIV continues to hide in reservoirs and that to this day we are still not able to flush HIV out of those reservoirs, although there is work again being done in this area.

Here we are in 2010 and while many of us continue to do well on our meds, there is something ominous and troubling going. We are starting to see signals that all is not well with those of us who have had the good fortune to reach our golden years after many years on treatment for HIV.

We have just been to the celebration of the life of James Kreppner whom we might not have lost so soon had he been strong enough and able to receive a liver transplant. On the west coast, we learned of the sudden death of Brad Larson, barely 40 years old, from a massive heart attack. My friend and colleague Richard Baker, Secretary of our Board at CTAC, is fighting anal cancer in St. John's. (I am happy to report he is well enough to be with us in Montreal following extensive surgery). In Montreal, another former CTAC Board member in his early 50s, a giant of a man both physically and metaphorically, has suddenly been diagnosed with lung cancer and brain cancer and given a few months to live. Less serious, but of equal concern, is the complaint of another friend who tells me he increasingly goes in search of words he knows well and seems to have misplaced. For a man in his 50s, cognitive impairment seems to be happening much sooner than expected.

For me so far, knock on wood, things have been going OK (so, a little sciatica recently put me on crutches.....). Diagnosed with Osteoporosis almost 10 years ago, I am fortunate that it was diagnosed and I remain on treatment that has reversed it. Along with physiological amounts of testosterone and a vigorous yoga practice. Sometimes I feel like a "belligerent Buddhist" but that's another talk. Living in



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Toronto, I have also had a baseline screening for cognitive function as well as a follow up 4 years later which knock on wood so far so good. But how many of us are being screened for bone density or memory tested if we are living with HIV outside of a major urban centre?

There is, in my opinion, a second wave of premature death and dying going on right now in our community and it is time to sit up and pay attention, to start actively listening for those signals – so I am pleased that we are here today. Those of us living long term with HIV and on HAART have recognized this for some time and have begun to talk about it, to write about it, and more importantly to start asking questions of our health care providers, our epidemiologists, the research community, and ourselves. In the USA, Jules Levin of NATAP (North American Treatment Advocacy Project) has been pushing the issue daily on his listserv. The NATAP listserv coughs up at least 20 research reports each day and those reports can sound somewhat grim. They are confirming what we have suspected for some time now: that the population with HIV is aging at an accelerated rate with more frailty, non-AIDS related cancers, bone, heart, metabolic disease (diabetes) and cognitive impairment (as well as depression) when compared to the general population. The retrospective data being gathered from large cohorts around the world are compelling in terms of the picture that is now emerging BUT it is a picture of ASSOCIATIONS, one which leaves us in pretty much in the dark when it comes to understanding the CAUSAL relationships.

At CTAC we are currently working on a paper that will focus on the bio-medical issues associated with HIV and aging. This is consistent with our mandate to ensure access to therapies for people with HIV. It is of course only one piece of the puzzle and I know you will hear from others on the need for services and supports for those aging with HIV in our community.

Meanwhile, the statistics are compelling.

From 2000 to 2004, the Centers for Disease Control reported that the proportion of AIDS patients who are  $\geq 50$  years of age rose from 19% to 27% and that the number of adults  $\geq 50$  years of age living with HIV infection and/or AIDS more than doubled. Importantly, for that surveillance period, persons 40 to 49 years of age had the highest prevalence of HIV/AIDS and the steepest rise in prevalence. The number of older people with HIV/AIDS is expected to increase even further during the next decade. It is projected that by 2015, more than half of all HIV-infected individuals in the United States will be over the age of 50 [1].

An important point to remember here. Age isn't everything. The high rate of prevalence among older people confirms that many people unfortunately are continuing to seroconvert in their later years. And too many babies, children and youth are on treatment from an early age. Therefore, length of time on treatment will be a very important factor for researchers to consider along with HIV disease



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process and not just an individual's chronological age. Modifiable behaviours such as smoking, poor diet, and sedentary lifestyle, along with depression – all of which are disproportionately high in our community – play a role.

Time was we were succumbing to Opportunistic Infections (OIs) that we don't hear a lot about today in the age of HAART (since 1996). We are no longer dying of toxoplasmosis, disseminated cytomegalovirus, PCP pneumonia, MAC (Mycobacterium Avium Complex) or KS (Kaposi Sarcoma). Today, we are more likely to die from a cancer that is unrelated to HIV, (anal, colorectal, melanoma, liver, lung, Hodgkins lymphoma) from cardiovascular disease, bone disease or organ failure – end stage kidney or liver disease. There is a growing epidemic of Type II diabetes and co-infection with hepatitis C that only complicates matters further. These are the new OIs and cause of death may be reported on death certificates with no mention whatsoever of HIV. Clearly this is a challenge that must be taken up by epi surveillance and all who track the mutating course of the epidemic in our various cohorts across North America and internationally.

I am just back from the 2010 Conference on Retroviruses and Opportunistic Infections. The number of oral presentations and posters on the complications of ART in an aging population means that researchers are finally starting to pay attention to this issue. Let me read you the headlines:

**Do People with AIDS Develop Cancer at Younger Ages than the General Population?**

**Results:** The proportion of older persons (at greatest cancer risk) was far smaller among people with AIDS than the general population (3% vs 17% over age 60 years). Reflecting this difference, the observed median age at diagnosis for most cancers was around 15 to 30 years younger among people with AIDS than in the general population. After accounting for the age structure, we found no difference in observed and expected ages at diagnosis for most cancers. However, the observed median age at diagnosis for persons with AIDS was 3 to 4 years younger than expected for non-Hodgkin lymphoma, lung cancer and anal cancer (all  $P < 0.001$  and significant after adjustment for multiple comparisons).

**Conclusions:** For most cancers, age at diagnosis did not differ between persons with AIDS and the general population. Previous reports that did not account for large differences in underlying age structure incorrectly concluded that persons with AIDS develop cancer at a younger age. After controlling for differences in population structure, age at diagnosis remained slightly younger for only a few cancers among people with AIDS. These differences may reflect the effects of HIV/AIDS in accelerating development of some cancers, differences in cancer surveillance, or differences in the age at first exposure to other cancer risk factors (eg, HPV infection, tobacco).



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### **Incidence of Non-AIDS defining Malignancies in the HIV Outpatient Study (HOPS) Higher Than General Population**

Compared with the general population, Dr. Patel's group found that HIV-infected patients in HOPS were twice as likely to have lung cancer, 5 times more likely to have Hodgkin's disease, 10 times as likely to have anorectal cancer, and 3 times more likely to have melanoma.

### **T-cell Senescence and T-cell Activation Predict Carotid Atherosclerosis in HIV-infected Women**

#### **Conclusions**

Collectively, these observations are consistent with a model in which untreated HIV infection results in immune activation, accelerated immunologic aging and the emergence of a population of potentially dysfunctional immunosenescent T cells. Antiretroviral therapy-mediated suppression of HIV replication may only partially reverse or prevent this process. The presence of a large population of **activated and/or senescent T cells may be causally associated with the premature onset of CVD.**

What's all this about "senescence"? Aging is associated with emergence of senescent cells, typically defined as long-lived, apoptosis-resistant cells that have limited proliferative capacity and often have a secretory phenotype (Campisi Nature 2009). Senescence is stimulated by environmental stress, inflammation, and genetic instability (mutations, epigenetic changes).

(The hallmark of senescence is the decline in function of T cells: they age but they don't die sort of like a bad Gilbert and Sullivan opera: "they say goodbye but they don't leave"!)

### **Immune Senescence, Activation and Abnormal T cell Homeostasis Despite Effective HAART, A Hallmark of Early Aging in HIV Disease**

Immune activation drives T cell turnover and senescence in HIV-1 infected and uninfected aging individuals as indicated by significantly higher levels of activation (expression of CD38+HLADR+) on both CD4+ and CD8+ T cells of HIV-1 infected and uninfected aging individuals compared to young uninfected subjects.

Whether regulatory T cells play a role in controlling immune activation needs to be further elucidated. **Larger cohort studies are warranted.**

### **Baseline Liver Disease is Independently Associated with Risk of Death among HIV/HCV co-infected Adults with Histologic Staging**

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**Protein in Urine Presages More Severe Problems**

**HIV Infection May Make the Brain 15 to 20 Years Older:  
HIV slows cerebral blood flow and stimulus response in MRI study**

**Aerobic Exercise Improved Cognitive Function in Older Adults with Mild  
Cognitive Impairment**

**Diabetes 2 Caused Brain Atrophy in Older Individuals**

**Neurological Impairment Persists Despite HAART: "adjunctive therapies  
needed"**

**The clot thickens-oxidized lipids and thrombosis**

**HIV-1 INFECTION IS ASSOCIATED WITH ACCELERATED VASCULAR AGING**

**How Inflammatory Disease Causes Fatigue: chronic inflammation infiltrates  
the brain but can be blocked**

**Vitamin D deficiency, muscle function, and falls in elderly people**

**One Third With Undetectable HIV RNA Have  
Asymptomatic Neurocognitive Impairment**

**Effects of Aging on HIV-1 Pathogenesis: HIV causes inflammation & T-cell  
activation, reported here to be more in postmenopausal women**

**Lower Testosterone Levels Predict Incident Stroke  
and Transient Ischemic Attack in Older Men (mini stroke)**

**Sex Hormones and Frailty in Older Men: The Osteoporotic Fractures in Men  
(MrOS) Study**

Going forward, we will need to develop a better understanding of frailty in HIV. Frailty is defined as having 3 of the following: exhaustion, slowed walking speed, low activity, weakness, and weight loss. There are many similarities between the biology that underlies frailty and chronic HIV infection. Some HIV treatments appear to accelerate that biology.

It would therefore be useful to screen for biomarkers associated with frailty as a useful construct to identify the most at risk HIV+ older patients for future study and for interventions. We know from the data that we are at increased risk of fracture, the data is still unclear about the level of that risk but I think we need to plan based on the expectation we will see more frailty, at an earlier age depending on length of time on treatment. We need not just to screen for frailty but also to learn from those



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working in the field of anti-aging medicine, which interventions will be useful in treating early frailty in HIV.

We know what happens when HIV is left untreated. We know that treatment can do much to restore immune function but its ability to restore immune function is imperfect. Virus bounces back when treatment is stopped and the gains of many years can be lost within weeks. Even with perfect adherence, there is underlying disease progression that is only now beginning to be understood as the result of low-level viraemia, virus that may for example be escaping from latent reservoirs. There is the senescence of immune system cells which lead to activation of the immune system (think of a machine that is constantly left on and running, never turned off and generating heat in the process) and a state of ongoing inflammation (aye there's the heat and the rub!) which appears to lie at the heart of the acceleration of the aging process when compared to the general population.

(I remember in the 1980s when I started seeing a practitioner of Traditional Chinese Medicine (TCM), David Bray, he told me that in that paradigm, HIV is considered to be a disease of deep-seated heat and that he would work with me to cool me down. This was in the years preceding HAART)

These abstracts and presentations from CROI tell us several things:

1. It remains unclear just how much or how many of these co-morbidities we are likely to see going forward.
2. It remains unclear to what degree predisposition and modifiable behaviours such as smoking, diet and exercise may play a role
3. It remains unclear to what degree HIV disease progression and / or toxicities of HAART play a role
4. It is very clear that there is a lot we still don't understand
5. We will probably see a lot more going forward (higher incidence rates and growing prevalence) (the tip of the iceberg)
6. We need PROSPECTIVE trials designed quickly and soon in order to get better answers to outstanding questions
7. These trials must be designed taking into account gender and ethnoracial considerations (and well controlled for genetic predisposition, diet, smoking, exercise)
8. We need to be able as community to both influence the research agenda as well as advocate for access to early screening, diagnosis and therapeutic interventions where none yet exist.
9. Anti-aging doctors, specializing in geriatrics should be brought into the fold of HIV specialists to help screen, diagnose and treat age and HIV-related health conditions
10. We can and should start early screening for many of the age related problems we can now anticipate



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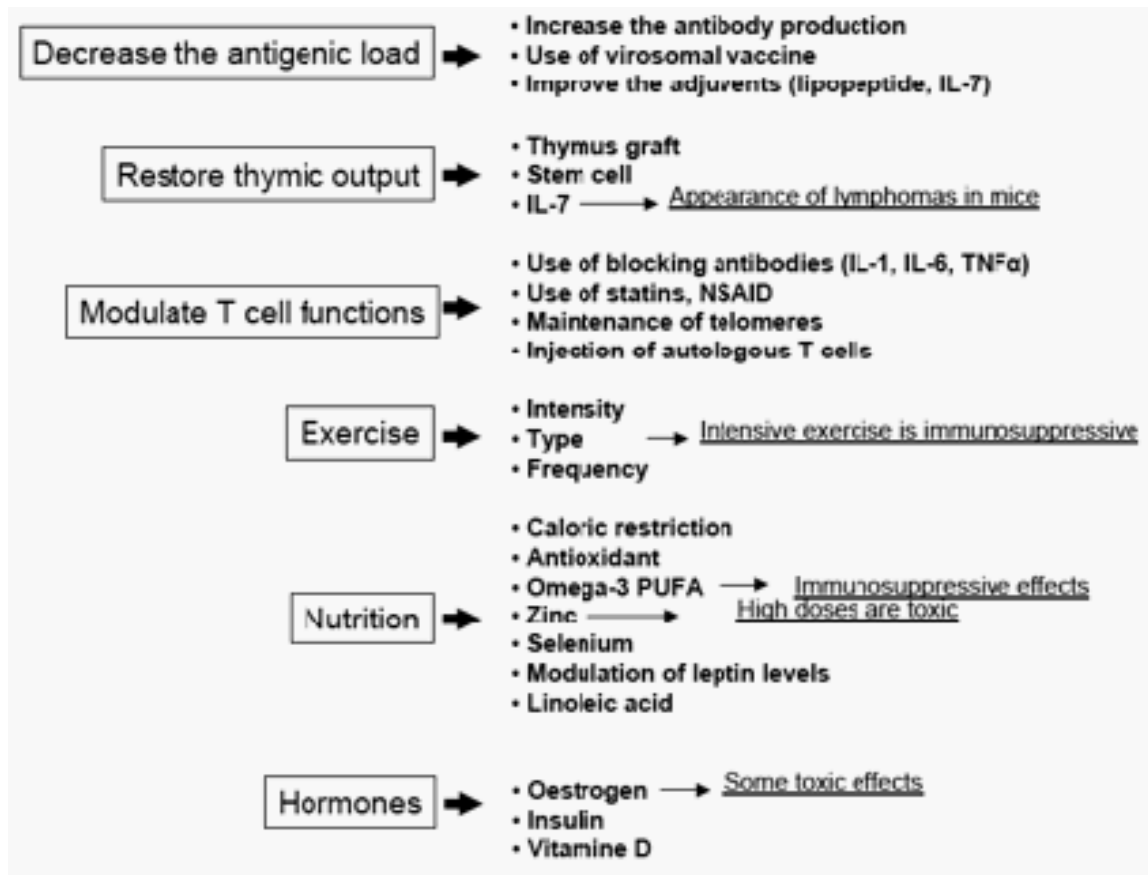
Here is a short list of examples of screening for which we should probably develop guidelines that would help both doctors and patients:

- DEXA scan for bone density
- Anoscopy for anal cancer
- Baseline cognitive function testing
- Better assessment tools for CV risk (Framingham plus?)
- Regular glucose tolerance tests
- 24 hour urine tests
- Improved assessment tools for kidney disease
- Same for liver disease
- Screening for non AIDS related malignancies
- The SENIEUR Protocol to screen for underlying illness

To name a few. And it's not just a question of having the right set of diagnostic tools, it's a question of making them available across the country and to people who live in rural or remote settings.

From screening, we need to move the research agenda forward with regard to the development of immunosupportive therapies.

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Refer to the MAINTAIN Study here.

The question is: what, if anything, can we do to prevent deleterious changes without dangerously dysregulating the precarious balance between supportive or productive immunity versus immunopathology or immune system disease? There are many potential new therapeutic means now available to modulate immunosenescence (therapies to prevent telomere shortening of chromosomes) and I expect we will hear more from the pharmaceutical industry in the future. But one problem in applying these experimental therapies is ethical: is aging in and of itself a disease? Should we be experimenting on the elderly who are frail but not sick and therefore do not require adventurous therapies with unpredictable side effects? I on the other hand might consider a therapy that would lengthen my life by lengthening my telomeres. My hope is that we will be able to discuss possible new therapeutic interventions one day soon in the appropriate ethical environment.

There was a lot of buzz at CROI once again around the possibility of eradicating HIV from the latent reservoirs and ultimately finding the long sought for cure. Until that



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time which feels as far off as the development of an effective vaccine, we need to ensure that we are all working together to minimize the toxicities of HAART, to support our communities to be able to make good decisions around modifiable risks, and to understand as we have said all along: HIV is not in recession, HIV does not take a vacation, HIV is only partially controlled by current therapies. HIV is still a serious disease, which can shorten our lives in ways we are only beginning to understand.

The Partners in Aging Forum gives us an opportunity to find ways together to create priorities going forward that will ensure we are part of the process to identify the gaps in knowledge and interventions needed to make sure that the gains we have made in treatment, care and support are able to carry us into our later years in a way that is more consistent with what we see in the general population.