Canadian Association for HIV Research
L'association canadienne de recherche sur le VIH

24th Annual Canadian Conference on HIV/AIDS Research

CAHR 2015 HIGHLIGHTS

MARK A. WAINBERG LECTURE

Decision Points in HIV – Re-evaluation of the Knowns and Unknowns

Dr Bill Cameron

With attention to lessons learned from history and personal experience, Dr Bill Cameron, senior scientist at the Ottawa Hospital Research Institute, offered a wide-ranging critique of various accepted practices in HIV research and medicine. Consistent with the conference theme of 'combining forces', greater cooperation and exchange of information with other areas of medicine and other health care disciplines may be useful to HIV researchers; and attention to HIV research, which has progressed so rapidly in one professional lifetime, may be instructive for other realms, he observed. "To address big problems we need big communities [and] communities are inclusive, not exclusive. Communities share ideas and experience freely with each other."

Dr Cameron noted that according to the "one health" concept, human health is highly related to animal health and the state of the world's ecology. That HIV has been such a challenging disease is a result of numerous epic changes, notably huge population growth and urban migration. High population density, commonly seen in megacities in disorganized and impoverished societies, is a key factor in the rise of parenteral disease transmission. "Zoonoses have been transmitted to human beings by parenteral transmission, have been amplified by their bloodborne nature, by a new ecology of bloodborne transmission, by crowding and sexual transmission, into the AIDS pandemic," he stated.

Prevention efforts such as blood screening and donor deferral might not have been enough to protect the blood supply even if they had been instituted far earlier on; and may not be adequate to prevent the emergence of other bloodborne diseases, he cautioned.

New Research Paradigm?

Widely accepted as the best practice for evaluating medical approaches and interventions, the placebo-controlled randomized clinical trial should be viewed with a more critical eye, he suggested. Evaluation of antiviral therapies that came after zidovudine all included placebo-controlled RCTs with death as an endpoint. "These sacrifices were seen as necessary due to equipoise, due to no alternatives for regulatory assessment, and for lack of methodological alternatives. But looking back, we can honestly say those drugs were potent enough against the virus that… we knew they were going to work. We simply had to prove it. And we proved it on the back of people's lives." Comparative trials, too, can relatively easily be designed to

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CANADIAN HIV VACCINE INITIATIVE

HIV Vaccine and Prevention Technologies: Forging a Path Forward

Drs Marc Gurwith and Frank Plummer

Global HIV prevalence has remained stable for about a decade. Development of effective preventive technologies to complement and supplement antiviral therapies remains an essential goal. Despite the myriad of challenges in preventing infection with this hypervariable retrovirus, the goal is believed to be attainable, whether through vaccination, antimicrobial administration, or other means, stated Dr Frank Plummer, Professor of Medicine and Medical Microbiology, University of Manitoba; and Scientific Director General, National Microbiology Laboratory, Public Health Agency of Canada.

Dr Plummer's work has focused on naturally developed immunity to HIV and correlates of protection that might be synthesized through technology. In the 1980s, he and his colleagues observed that although the majority of a population of female Kenyan sex workers had HIV, only a few had evidence of disease. Over time, it became evident that about 10% of the sex workers were resistant to the virus, probably through both biologic mechanisms and genetic factors producing an immune-quiescent phenotype. "We think [this leads to] an immune environment that doesn't permit efficient HIV replication," Dr Plummer indicated. Other populations of resistant or highly-exposed seronegative individuals have been documented around the world, he added.

Table 1 lists ways in which study of these individuals may contribute to new HIV-preventive measures. Study of female genital tract proteins in the resistant Kenyan population indicates some have direct anti-HIV activity or anti-inflammatory properties. Mechanistic studies are under way to determine how these factors work and whether this knowledge can help in development of a microbicide, Dr Plummer explained.

Dr Marc Gurwith of PaxVax, a biotechnology firm in Redwood City, California, observed that replicating vectors may have several advantages as candidates for HIV vaccines. These include replication without HIV reversion and the potential for replication at mucosal surfaces, leading to longer duration of exposure to the antigen and an adjuvanting effect. Moreover, replicating vector vaccines should combine the immunogenicity advantages of live attenuated vaccines with the safety of killed or recombinant-protein vaccines. On the other hand, he noted, they allow for less genetic room, viral interference is possible if multiple strains are included, and they are associated with potential concerns about persistence.

A number of attenuated vaccine viruses have been used as vectors, although to date few have been studied in humans. The Ad4/Ad7 platform employed by PaxVax is an oral adenovirus vaccine that has been administered to some 10 million US military recruits over 30 years. In numerous studies, an Ad4-pandemic influenza vaccine has served as a model for an AD4-HIV vaccine. A phase 1 study of its immunogenicity indicated good priming with three doses. The "take rate" rose from 50% to 96% with ascending doses, indicating successful vector replication, Dr Gurwith indicated. Although neutralizing antibody levels were initially low, there was a clear cellular response. Subsequent boosting with inactivated pandemic H5N1 vaccine led to a rise in neutralizing antibodies. Pre-existing Ad4 immunity affected the response, he observed. "You need to increase the dose to overcome vector immunity." Studies by NIH investigators suggest mucosal administration will be more efficient than oral dosing.

Based on these results, the NIH plans to evaluate an intranasally-administered HIV vaccine candidate, Dr Gurwith said. Additional studies of replicating vector HIV vaccines have produced promising data and clinical studies are planned or ongoing, as is research to refine the efficacy of adenovirus replicating vectors.

TABLE 1

Understanding HIV resistance: possible contributions to new vaccine/treatment

New epitopes or targets for vaccine (Th, CTL)
Microbicide (identification of natural HIV inhibitory molecules, systemic or at the female genital tract)
Novel approaches to immunization (Treg vaccine?)
Pharmaceutical induction of favourable immune environment at mucosal level
Adjuvants/immunoregulation (alternate gene expression?)

SYMPOSIUM

CIHR: Designing for the Future

Drs Jane Aubin and Marc Ouellette

The 2015-2020 strategic plan for the Canadian Institutes of Health Research (CIHR), "Roadmap II" (Figure 1), will follow through with the implementation of some significant changes to the organization and its practices as initiated in the previous plan "Roadmap I", explained Dr Jane Aubin, Chief Scientific Officer and Vice President of Research, Knowledge Translation and Ethics.

CIHR's first strategic direction in Roadmap II remains investigator-initiated research and the budget allotment for such programs (about 70% of funds available) reflects that fact, she emphasized. It was noted that more than half the funding for HIV/AIDS research comes from this envelope. Two funding schemes will be established to support investigator-initiated research, with the aim of decreasing researcher burden: the Foundation scheme and Project scheme. New peer-review processes include the establishment of a college of reviewers and review that is "application-based", which ideally will ensure effectiveness, consistency, fairness and sustainability of peer review. CIHR will also focus on training to ensure there are candidates for diverse and multiple careers in science and knowledge translation, she added.

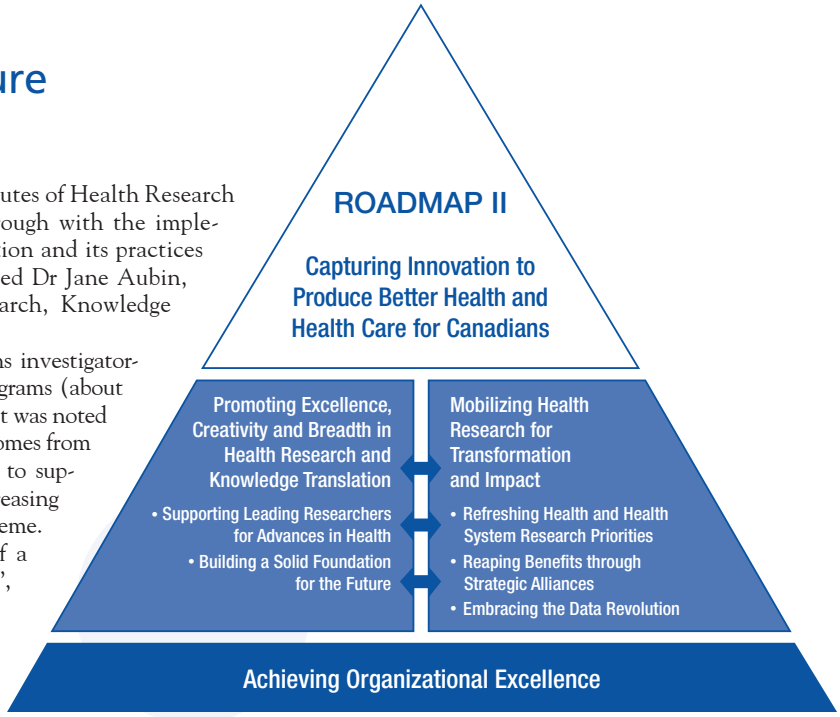

Figure 1) *Roadmap II. Source: CIHR*

The second strategic direction will ensure leadership and investment in high priority areas for Canadian health research. Table 1 lists the strategic research priorities of Roadmap II.

Dr. Marc Ouellette, Scientific Director of the CIHR Institute of Infection and Immunity, noted that the vision for the CIHR HIV/AIDS Research Initiative is that over the next five years, "Canadian-led research will have the most significant impact to date in alleviating the burden of HIV/AIDS in Canada and globally." Table 2 is an abridged list of its strategic directions for the next several years. Dr. Ouellette also described several new CIHR investments across a range of important HIV research topics.

TABLE 1
CIHR's refreshed priorities for Priority-Driven Research

RESEARCH PRIORITY A Enhanced patient experiences and outcomes through health innovation	This research priority focuses on accelerating the discovery, development, evaluation and integration of health innovations into practice so that patients receive the right treatments at the right time.
RESEARCH PRIORITY B Health and wellness for Aboriginal peoples	This research priority focuses on supporting the health and wellness goals of Aboriginal peoples through shared research leadership and the establishment of culturally sensitive policies and interventions.
RESEARCH PRIORITY C A healthier future through preventive action	This research priority focuses on a proactive approach to understanding and addressing the causes of ill health, and on supporting physical and mental wellness at the individual, population and system levels.
RESEARCH PRIORITY D Improved quality of life for persons living with chronic conditions	This research priority focuses on understanding multiple, co-existing chronic conditions, and on supporting integrated solutions that enable Canadians to continue to participate actively in society.

TABLE 2
CIHR-HIV/AIDS Research Initiative: Strategic Directions

1. Enable discovery research
   a. Develop new biomedical, behavioural and systems approaches to reduce HIV transmission
   b. Improve understanding of HIV to slow its progression and mitigate its impact
   c. Train and support a strong and diverse community of researchers
2. Mobilize research evidence
   a. Strengthen prevention of HIV and other sexually-transmitted and blood-borne infections in key populations
   b. Improve health outcomes for people living with HIV
   c. Strengthen the capacity of researchers, decision makers, front-line workers and organizations to apply evidence
3. Promote leadership in stakeholder engagement and accountability in HIV research
   a. Understand and address perspectives and priorities of key populations
   b. Enhance leadership in national and international partnerships
   c. Refresh the performance measurement and accountability framework

SYMPOSIUM

Updated HIV-HCV Co-infection Treatment Guidelines

Drs Curtis Cooper, Mark Hull, Marina Klein, Stephen Shafran, Alice Tseng, Alex Wong, Lisa Barrett and Pierre Giguère

There is now a strong likelihood of curing hepatitis C virus (HCV) infection with interferon-free, direct-acting antiviral (DAA) regimens. This finding, based on the results of several recent clinical trials, necessitated an update to the Canadian guidelines for HIV-HCV coinfection published in late 2014. The draft guidelines presented at CAHR were subject to additional comments and alterations but were scheduled to be published by the middle of 2015, noted Dr Curtis Cooper, Associate Professor, University of Ottawa, and Director, Ottawa Hospital and Regional Hepatitis Program.

All patients with confirmed coinfection with HIV and chronic HCV (Table 1) should undergo evaluation of their candidacy for HCV therapy. Appropriate assessment should take into account such potential barriers to success as substance abuse, addictions, mental health and housing and food security issues. Although the DAA regimens are generally shorter than those for interferon-based therapy, adherence remains crucial.

That short courses of HCV therapy may be sufficient means clinicians should consider initiating this treatment before antiretroviral therapy (ART) in patients with very high CD4 cell counts. Treating HCV first avoids drug-drug interactions and decreases ART-related hepatoxicity, said Dr Mark Hull, AIDS Research Program, St. Paul's Hospital, Vancouver. However, if HCV therapy that includes ritonavir boosting is planned, ART should be started first.

ART is effective, safe and well tolerated in HIV-HCV coinfection and helps slow liver disease progression, added Dr Hull. As such, the guidelines working group advises consideration of therapy in coinfected patients with CD4 cell counts above 500/mL if treatment for HCV is not imminent.

Table 2 summarizes the new proposed recommendations for drug treatment in HCV genotypes 1 through 4. All the regimens recommended are well tolerated and have an excellent safety profile, stated Dr Stephen Shafran, Professor and Director, Division of Infectious Diseases, University of Alberta, Edmonton. Three regimens are no longer recommended as first line treatment in genotype 1 HCV, he added: double therapy with pegylated interferon and ribavirin, triple therapy with pegylated interferon, ribavirin plus any DAA; and sofosbuvir plus simeprevir.

In the setting of coinfection, attention to drug-drug interactions and ongoing monitoring is crucial to avoid suboptimal virologic response, development of resistance, and drug toxicities, noted Dr Alice Tseng, Faculty of Pharmacy, University of Toronto.

TABLE 1
Diagnosis and Initial Assessment

Evaluate patients with confirmed HCV antibody with HCV-RNA PCR • Patients with a positive HCV RNA should undergo HCV genotyping • Those with negative HCV-RNA should undergo repeat testing to confirm spontaneous clearance (15-20% of cases)
Screen patients for hepatitis A and B and offer vaccination if non-immune
Evaluate patients for other conditions which may result in chronic liver disease; counsel regarding alcohol reduction/abstinence
Perform baseline evaluation of liver fibrosis (transient elastography advised); consider abdominal ultrasound
ALT level alone should not be used to determine the need for treatment initiation

TABLE 2
Proposed Treatment Recommendations

Genotype	Treatment-Naive Individuals	Comments	Treatment-Experienced Individuals	Comments
1	Sofosbuvir 400 mg coformulated with ledipasvir 90 mg daily x 12 weeks [class 1 level B]	High rate of sustained virologic response; minimal concern of drug interaction with ART	Sofosbuvir 400 mg coformulated with ledipasvir 90 mg daily x 12 weeks [class 1 level C]	24 weeks of treatment in patients with cirrhosis
	Parateprevir/ombitasvir/ritonavir + dasabuvir + ribavirin x 12 weeks [class 1 level C]	Has been used with ART with raltegravir and atazanavir, likely compatible with dolutegravir and darunavir but not NNRTIs or lopinavir/ritonavir	Parateprevir/ombitasvir/ ritonavir + dasabuvir + ribavirin x 12 weeks [class 1 level C]	May be used in patients who failed pegylated interferon/ribavirin therapy but not recommended for those who have failed a regimen including a NS3 protease inhibitor
2	Sofosbuvir 400 mg daily with weight-based ribavirin X 12 weeks [class 1 level B]	Consider 16 weeks of therapy in patients with cirrhosis	Same as for treatment-naive patients	
3	Sofosbuvir 400 mg daily with weight-based ribavirin and pegylated interferon 180 ug weekly x 12 weeks [class 1 level B]		Sofosbuvir 400 mg daily with weight-based ribavirin x 24 weeks [class 1 level B]	
	Sofosbuvir 400 mg daily with weight-based ribavirin x 24 weeks [class 1 level C]	Slightly lower efficacy but better tolerability than option 1	Sofosbuvir 400 mg daily with pegylated interferon 180 ug weekly and ribavirin x 12 weeks [class 1 level C]	
4	Paritaprevir 150 mg daily, ritonavir 100 mg daily, ombitavir 25 mg daily, and weight based ribavirin X 12 weeks [class 1 level C]	Dasabuvir not required	Same as for treatment-naive patients	
	Sofosbuvir 400 mg daily with pegylated interferon and ribavirin x 12 weeks [class 1 level B]	Based on studies in HCV monoinfection		
	Sofosbuvir 400 mg daily and ledipisvir 90 mg x 12 weeks [class 1 level B]			
	Sofosbuvir 400 mg and weight-based ribavirin daily x 24 weeks			

PROGRAM SCIENCE SYMPOSIUM

Innovations and Pragmatic Approaches to End HIV Epidemics in Canada

Drs Nancy Edwards, Kenneth Mayer and James Blanchard

Researchers and research funders have long been frustrated by the fact that so many interventions that are proven efficacious do not quickly or easily work their way into practice. At the same time, policy makers and program developers are critical of research done in conditions that cannot easily be replicated in the real world.

In a unique collaboration, six agencies that fund and/or use research – the Canadian Institutes of Health Research (CIHR), the CIHR Centre for REACH in HIV/AIDS (REACH 2.0), the CIHR HIV Trials Network (CTN), the Canadian Foundation for AIDS Research (CANFAR), the Public Health Agency of Canada (PHAC) and the Ontario HIV Treatment Network (OHTN) – co-sponsored this inaugural CAHR session, which highlighted the need for a different, more integrated approach to research and practice.

"Implementation science or program science is a shift away from interventions that are structured entirely by researchers to a more inclusive approach that looks at the context where an intervention will be delivered," explained Nancy Edwards, Scientific Director of the CIHR Institute of Population and Public Health. "What works for whom and when? To answer those questions, researchers have to engage in meaningful ways with those with the deepest knowledge of the context." She described program science as bringing together different sciences – political, epidemiological, health and social sciences – with community, funders and others to solve problems. The solutions can be complex and varied, and may include task shifting, integrated teams, regulatory and policy changes, and specific efforts to address stigma, cultural factors and historical contexts, such as colonization.

Program Science is a way to bring the research and practice worlds together to, as Chris Bunting of CANFAR said, "help achieve our objectives more effectively and efficiently."

James Blanchard, Professor and Director of the Centre for Global Public Health, has been using a program science approach in his global work for some time. In his experience, the challenge of HIV is that "we have developed many efficacious interventions but still have equity issues in terms of how those interventions translate into practice. … Program science looks beyond implementing a single intervention to the broader set of questions required to develop an effective program that optimizes the population impact." According to Blanchard, "the challenge of the current approach to programs is that it's siloed, with a patchwork of interventions being funded and no one really getting the whole picture. In a program science approach, research would be embedded in the program and would look at a different set of questions generated by the program."

Kenneth Mayer, Medical Research Director at Fenway Health and Co-Director of The Fenway Institute in Boston, Massachusetts, is an example of an embedded scientist. He works with the practitioners at Fenway Health, a community health centre that serves the LGBT community, to try to seamlessly transition between the community, hospital and academic worlds. He led efforts to implement a PrEP program at Fenway Health, which demonstrated that – even when you have a intervention with proven efficacy – you can get very different levels of effectiveness depending on contextual factors such as the level of community understanding of and trust in a particular intervention, cultural factors, social factors such as violence, poverty and access to health care, provider attitudes and structural stigma.

"There are many reasons why an individual may not take prevention medications consistently," he explained. "We need implementation strategies that work with people where they are at because sexual behaviours and risks and understanding of risk can change over time." In the case of access to PrEP, Mayer and his team found that one of the biggest enablers to people accessing and using PrEP consistently was whether they felt comfortable talking to their health care providers about their sexual behaviours. At the same time, one of the biggest challenges was provider attitudes and the "purview paradox": "Specialists in HIV care – who are comfortable prescribing antiretrovirals – don't want to take care of uninfected individuals. They don't want to spend the time doing counseling. On the other hand, primary care providers say these are difficult drugs to use and they don't feel prepared to prescribe and monitor them." There is a still a lot of work to do with providers if PrEP is going to implemented in a way that will have both an individual and population impact – with is the goal of program science.

While implementing PrEP has been challenging, the work has helped demonstrated how to integrate new prevention strategies into existing systems and how to make space for new prevention modalities over time which, once again, is an integral part of program science.

The question remains, how effective will Canada be at shifting to this more pragmatic – and often time-consuming – approach to research? As Dr. Blanchard noted, "program science is a far more iterative process requiring a longer sustained engagement between the individuals and groups involved." As a result, funding needs to be more program-oriented. That shift is starting to happen, with CTN, REACH 2.0, CANFAR and the OHTN committed to a program science agenda, and CIHR announcing new funding opportunities to support program science. The plan is to have an annual session each year at CAHR to highlight program science work, progress and challenges.

Said David Hoe, Chair of the OHTN Board and a person living with HIV, "We are hopeful that program science will help us look at the whole system rather than just its components in isolation and see how things work in the real world – and bring us closer to the end of HIV epidemics in Canada."

CLINICAL SCIENCES PLENARY

HIV Latency in a Perinatal Infection: Opportunities and Challenges towards Remission and Cure

Dr Deborah Persaud

Reservoirs of latency present a substantial obstacle to cure of HIV infection. New therapeutic strategies combining broadly neutralizing antibodies and other immunotherapeutic agents offer the best hope to date, said Dr Deborah Persaud, Professor of Pediatrics and Infectious Diseases at Johns Hopkins University, Baltimore.

At present, antiretroviral treatment (ART) for HIV must be lifelong. Even in patients whose HIV infection has been suppressed for lengthy periods, cessation of therapy is associated with rebound viremia within two to four weeks. This pattern is explained by the persistence of HIV in a reservoir of latency in resting central memory CD4 T-cells, which is established very early on in infection, Dr Persaud noted (Figure 1). "The dominant source of virions in plasma of untreated patients is activated CD4 T-cells that turn over on a daily basis. But [the reservoir cells of replication-competent HIV] are a dominant source of low-level virus production in patients on combination therapy for decades. So they become the major source of rebound viremia when patients stop treatment." These cells undergo self renewal and homeostatic proliferation and are unlikely to express viral proteins. As such, they cannot be targeted by immune surveillance mechanisms, she noted. One infected cell per million resting CD4 T-cells is sufficient to reverse latency and cause continuous virus production.

There have been just a few examples of patients who have not relapsed within the time window of two to four weeks, Dr Persaud indicated. "The Berlin patient" is perhaps the single known example of a sterilizing cure. Following an allogeneic bone marrow transplant he has remained virus-free for more than seven years off therapy and appears to have no replication-competent HIV reservoir. Two other transplant recipients had rebound after 12 and 32 weeks. A child in Mississippi who went off ART did not experience return of viremia for 27 months. The child's condition might best be described as remission, Dr Persaud remarked. A group of patients known as the Visconti cohort has maintained virologic control for several years despite detection of HIV infected cells. No biomarkers have been identified to predict remission or cure.

In perinatal infection the latent HIV reservoir is established within two months. It is hoped that especially in children, very early treatment will help reduce or prevent the establishment of the HIV reservoir to ensure virus reduction and promote remission, she stated. "Infants start out life with less than 10% of the peripheral blood expressing memory T-cell phenotypes. If we can curtail virus replication before memory T-cell development, we can perhaps curtail spread into these reservoirs."

Still, accumulated knowledge in cure research suggests targeting the reservoir of latency is only a first step to virologic remission. Table 1 summarizes new strategies aimed at HIV remission and 'cure'. Combination regimens (e.g., latency reducing medications and broadly neutralizing antibodies) will likely be needed to ensure elimination of virus, Dr Persaud emphasized. In recent studies, for example, the HDAC inhibitor panobinostat reversed HIV latency and provoked virus production, while a single infusion of broadly neutralizing antibodies decreased plasma viral loads from 0.8 to 2. 5 logs, she observed. "We believe that's the future for this field....The overall goal of this new and emerging research is to change lifelong course of antiviral treatment to a time limited treatment," she concluded.

TABLE 1

New Strategies
Latency reducing agents (HDAC inhibitors, TLR-7 agonists)
Combination therapies: Latency reducing agents + therapeutic immunization (T-cell based vaccines, broadly neutralizing antibodies)
Immune checkpoint blockade: PD-1 inhibitors
Immune-modulating drugs: Sirolimus, interferon-alpha and inhibitors of interferon-alpha
Very early treatment +/- immunotherapies

Red Ribbon Award 2015

Elisse Zack

The 2015 Red Ribbon Award was presented posthumously to Elisse Zack, the founding executive director of the Canadian Working Group on HIV and Rehabilitation (CWGHR).

In accepting the award on Elisse Zack's behalf, her friend and colleague Stephen Tattle expressed that she "ranks among the most dedicated and devoted and bright individuals many of us had the pleasure of working with… People who had the opportunity to work with her were captivated by her dedication, enthusiasm, integrity and incredibly hard work." Initially involved in literacy promotion, Elisse Zack was a renowned leader in social justice, "a true visionary and pioneer who placed HIV and rehabilitation on the research map in Canada and internationally," he commented. She was also instrumental in the initiation of research on HIV and aging and worked tirelessly to find ways to improve quality of life for people with HIV. Under her direction, the CWGHR set up a virtual library accessible to clinicians, employers, insurers and people living with illness.

Lillian Zack, Elisse's mother, remarked that Elisse's devotion to others was evident at a very young age, and that the Red Ribbon Award was a "beautiful kind of thanks for a wonderful daughter."

The Red Ribbon Award has been presented since 2001 for outstanding service to individuals or groups whose research or related work has increased understanding of the treatment and prevention of HIV/AIDS while enhancing patients' quality of life.

EPIDEMIOLOGY AND
PUBLIC HEALTH PLENARY

Criminalization, Sex Work, and HIV: From Research to Action

Dr Kate Shannon

In Canada and around the world, sex workers are disproportionately affected by HIV compared with the general population. In low- and middle-income settings, for example, female sex workers are more than 13 times more likely to have the infection than women of similar age in the general population.

Biomedical and behavioural preventive approaches have had only modest effects. Sex workers' access to screening, care and counselling is hampered by several structural factors, prominent among which is criminalization, said Dr Kate Shannon, Associate Professor, University of British Columbia and Director, Gender and Sexual Health Initiative, BC Centre for Excellence in HIV/AIDS. Both epidemiologic data and community narratives can promote the development of supportive public opinion and policies and structural HIV prevention measures, she added.

A longitudinal study of sex workers' health access in Vancouver indicated street-based individuals (prevalence 14%) and informal indoor sex workers (20%) have the highest HIV rates, Dr Shannon stated. HIV prevalence is about 5% among those who work in "more formalized" indoor environments. The difference is at least partly explained by street workers' greater likelihood of engaging in unprotected sex, she observed.

Other factors linked to increased HIV rates or to reduced use of condoms among sex workers include criminal and punitive laws, stigma, food and residential instability and insecurity, and gender inequities, Dr Shannon stated. Early initiation into sex work and physical or social violence in the work environment are also associated with increased risk.

Gender empowerment, higher education and literacy can help mitigate risk, as can community organization and empowerment and supportive policies and practices among authorities and government, such as access to condoms and HIV testing at the site of work.

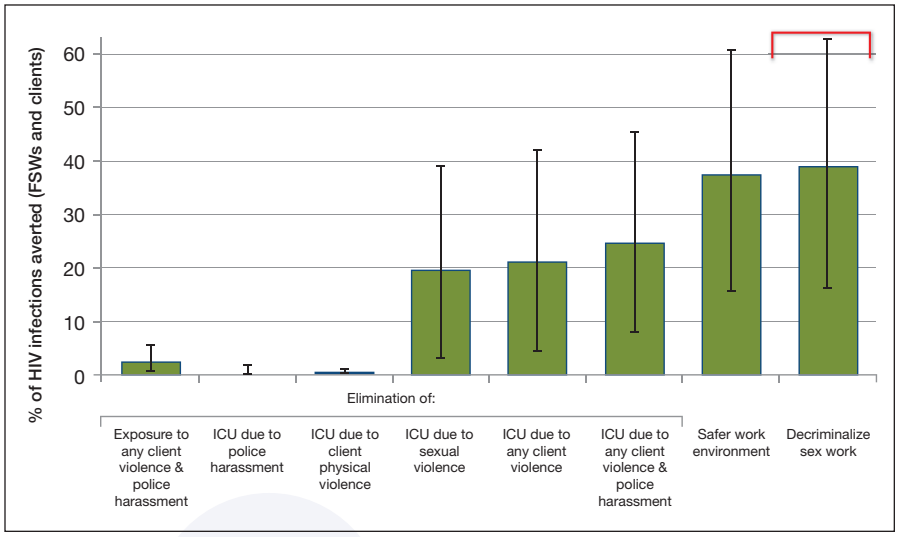

Figure 1) Decriminalization of sex work could avert 33-46% of HIV infections over the next decade

In Vancouver, criminalization of sex work had numerous consequences related to the health and human rights of sex workers, Dr Shannon remarked. For example, it "gave broad latitude to managers of housing programs to target marginalized groups." Restrictions on guests such as curfews and guest fees prevented sex workers from bringing clients into their rooms, which in turn reduced their access to safety precautions. In addition, "fear of disclosing sex worker status given the criminalized model has a direct impact on primary health access including regular STI and HIV screening."

The passage of Bill C36, which criminalized the purchaser of sex, has not altered risk for sex workers, she commented. Police intervention has targeted clients rather than sex workers, but as a result, sex workers often end up working in more isolated locations where they have reduced ability to screen clients and negotiate condom use. Spatial isolation also increases the risk of drug use, she noted.

The World Health Organization and UNAIDS have stressed the need to reduce HIV and other sexually transmitted infections in sex workers, Dr Shannon noted. "Decriminalization was clearly articulated as a cornerstone of the HIV response [but] the response has continued to be framed and hampered by criminalization and punitive approaches."

A report published recently by The Lancet indicated that a range of alterations to structural factors could significantly alter the course of the HIV epidemic.[1] In three settings studied – Kenya, India and Canada – decriminalization of sex work was likely to reduce overall HIV infections by 33% to 46% over 10 years (Figure 1). In Kenya, policy reform could help avert approximately one in three infections over the next decade, Dr Shannon stated. Scaling up treatment to meet WHO guidelines will not be adequately effective if current practices such as denying health services and ART to sex workers continue.

Similarly, according to Dr Shannon, organized support to sex workers living in a low-income housing program in Vancouver (client sign-in, access to condoms, testing for HIV and other STIs, communication with police) increased their health and safety.

An action agenda is required to counter backward steps, she concluded. Additional surveillance and epidemiologic data on structural determinants of HIV risk, especially in higher-income settings such as North America, are needed. "We really need to move. Combination prevention needs to include a structural approach and a community-led approach....One of the challenges we continue to face is how to engage with policy makers...to make sure the evidence has some traction."

Reference

1. Shannon K, Strathdee SA, Goldenberg SM et al. Global epidemiology of HIV among female sex workers: influence of structural determinants. *Lancet* 2015;385:55-71.

BASIC SCIENCES PLENARY

Targeting Antibody Functions for Improved Vaccine Efficacy

Dr Galit Alter

Unravelling the programming of antibodies in the natural immune response is a key to evaluating correlates of protection and the design or assessment of candidate vaccines against HIV, said Dr Galit Alter, Associate Professor of Medicine, Harvard University and an investigator at the Ragon Institute of MGH, MIT and Harvard, Charlestown, Massachusetts.

Vaccinologists have generally focused on inducing neutralizing antibodies that prevent HIV from accessing cells. However, antibodies generated in a natural immune response tend to target second-line and later epitopes expressed on infected cells, Dr Alter remarked.

Antigens expressed on the cell surface act as bait for antibodies, which then mark the cell as aberrant to provide a target and tether for cells from the innate immune system. They also direct the immune cells within a tissue compartment to initiate appropriate and rapid killing mechanisms for the specific infection (phagocytosis, T-cell mediated destruction, complement deposition etc.), Dr Alter explained.

These instructions emanate from the Fc domain, which has the capacity to alter the antibody's subclass (IgG 1 through 4) or modify its sugar to adjust interactions with immune cells. "If you think about the combinatory mathematics – four different subclasses in our immunological repertoire, 32 potential sugars we can add on – that gives about 125 potential functional states that we believe are the bar codes that tell the innate immune system how it should operate or kill," she noted. Given that billions of antibodies are produced and clustered during an immune response, "what we end up with is not two-dimensional bar codes but theoretically three-dimensional bar codes of unbelievable biological complexity, naturally recruited and programmed...to give better activity."

If you think about the combinatory mathematics – four different subclasses in our immunological repertoire, 32 potential sugars we can add on – that gives about 125 potential functional states that we believe are the bar codes that tell the innate immune system how it should operate or kill.

Systems serology, which examines variables controlling the biological activity of antibodies, provides a novel and accurate platform for evaluation of immune reponse and vaccine candidates, Dr Alter said. The method allows both biophysical and functional characterization of antibodies, including such aspects as their affinity for different Fc receptors, glycosylation profiles, and specific immune cells recruited. The aim is to learn "what is special about one population of patients versus another, or one vaccine profile versus another. This allows us to home in on correlates of immunological protection that we can follow up mechanistically," she added.

Using this system to study existing HIV vaccines, Dr Alter and her colleagues determined that the antibodies induced by the vaccine in the RV144 clinical trial (31% efficacy) elicited more functions than those in the Vax003 study (vaccine unprotective). "Those antibodies had a higher likelihood of recruiting multiple functions simultaneously, at least three if not more," she explained. Further study revealed that in RV144 vaccinees with the polyfunctional antibody profile, the vaccine selected for more IgG3 antibodies. This finding appeared to be a surrogate marker for activity by a larger pool of IgG1 antibodies with a unique glycan and robust killing properties, Dr Alter indicated.

Antibody glycosylation profiles are programmed naturally in response to various pathogens and antigens, Dr Alter continued. For example, glycan profiles in antibodies responding to influenza, tetanus and diphtheria are distinct. In the case of HIV, production of inflammatory and cytotoxic antibodies increases. "There is some sort of transcriptional regulation of single B cells that is actively promoting this different type of Fc effector activity required to control different pathogens...This offers a completely unique opportunity to target next generation vaccines, to induce antibodies that can kill more effectively." Different adjuvants have dissimilar effects on antibody glycosylation, which in turn affects immune cell recruitment. TLR adjuvants, for example, leads to antibodies that recruit NK cells, while mf59 leads to complement-mediated activation. Vaccine vectors probably also have the capacity to tune antibody activity she added.

There is some sort of transcriptional regulation of single B cells that is actively promoting this different type of Fc effector activity required to control different pathogens... This offers a completely unique opportunity to target next generation vaccines, to induce antibodies that can kill more effectively.

"What this tells us is that we can control [vaccine constituents] to target the functional antibodies we think are the most relevant... We have a spectrum of different opportunities out there that may get us where we want to go," Dr Alter concluded.

SOCIAL SCIENCES PLENARY

Interdisciplinarity and the Construction of Objects of Knowledge

Dr Viviane Namaste

Past and present analyses of and responses to the HIV epidemic are marked by certain oversights, noted Dr Viviane Namaste, Full Professor and Research Chair in HIV/AIDS and Sexual Health, Simone de Beauvoir Institute, Concordia University, Montreal. These gaps provoke questions about the ways in which evidence and knowledge are gathered and whether there are ways to rethink and improve these processes in future research efforts, she stated.

"I use the word oversight in two senses. One [is] what's been forgotten, what has been overlooked; and second, what has been overdetermined, what particular objects of knowledge come into being," she said. Considering what evidence, notions and concepts are or are not "on the radar" and others which are taken for granted is "useful not just for those of us who are located on the science or humanities spectrum... but also clinically useful," she asserted. "We have to think about what we see and what we don't see. And in an era of evidence-based medicine, more than ever, I think we need critical attention to what constitutes evidence itself [and to] how certain forms of knowledge and documents come into being while others remain hidden."

As examples, Dr Namaste noted that while women have recently been described as the "new face" of the epidemic, a historical analysis of the epidemic in Montréal reveals that there was a significant proportion of women among diagnosed AIDS cases in the early 1980s, and that many of these women were Haitian. Similarly, HIV research as well as public health prevention efforts have largely ignored the swinging community. There has been a particular focus on gay and bisexual men and relatively little attention to female partners of the latter, she observed.

She offered several suggestions for researchers as "points of orientation that might be useful for us to think about and rethink the construction of evidence."

Having humility involves acknowledging lack of knowledge and that success cannot be promised, she remarked. "You can't really say oh, I'm going to find the solution. You can say I'm going to try." A related point is the need to go beyond instrumentalist research, she suggested. "There's a challenge for the system in which we work because the funding of health research is very much – and more and more – oriented toward research which can promise an impact...If our knowledge response to this epidemic orients research in that way, we might be missing a piece of the puzzle."

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Deep reflection is needed on how objects of knowledge develop, both theoretically and methodologically, she proposed. It is necessary to consider how to develop completely new knowledge rather than simply employ existing methods or accepted concepts. To be successful in this step, "we need to slow down. Reflection can only happen when our work is careful, considered and intensely meditative." This is difficult in the modern academic and science milieu, she acknowledged, where speedy productivity is encouraged. "Less and less are we required to show how our work is methodical, laborious, painstakingly long and careful."

Training in languages can be crucial. In study of the HIV epidemic, knowledge of languages other than English assists appreciation of different cultural frameworks and promotes comparative thinking and evaluation, she suggested. "If interdisciplinarity includes the humanities in our response to HIV/AIDS...a commitment to interdisciplinarity means for humanities-based scholars a commitment to training across several languages." This measure, too, is time-consuming and challenging given that language training is not typically funded under research grants, she remarked.

University professors and other teachers can develop new pedagogy to encourage novel evidence and knowledge collection, Dr Namaste stated – for example, help students to "think through what happens when disciplines bump against each other...how do [various] disciplines construct their objects of knowledge and what might get left out of particular equations." The history of the AIDS epidemic has been described far differently by authors Jacques Pepin and Edward Hooper, she noted, because one placed greater reliance on documentary evidence and the other on oral history. "I'm encouraging us as teachers to create moments of pedagogy in which we demand of students, go back to the source; in which they think about the kinds of evidence mobilized to make a particular argument and in which they consider what are the forms of evidence that are excluded from a particular argument."

Dr Namaste acknowledged that her points of orientation involve systemic changes in academia and research. For example, in her view, longer, carefully considered work should be deemed as valid as rapid deliverables and numerous publications. But, she concluded, asking new questions allows the imagination of new possibilities for action.

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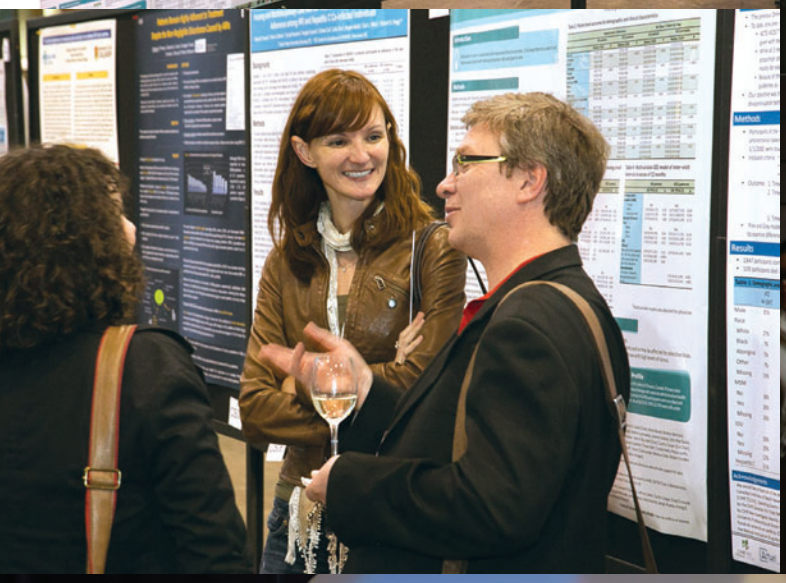


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favour one agent and "we have to be careful of that," he remarked.

An appropriate alternative for testing new therapies is a stepped-wedge study design, he proposed. "You can roll out a treatment for a disease for which you do not have equipoise and you do not have the capacity to start up everybody at one time." This design allows a staggered, stepwise introduction of a treatment or randomization of clusters of patients, he noted. It does require a pre-existing observational cohort and a biological specimen repository for that cohort, he explained. A similar design would work for evaluation of cancer therapies, he added. In fact, a biological specimen repository would permit etiological research into other common and deadly diseases.

Prevention Strategies

An effective vaccine against HIV always seems to be described as tantalizingly close but practically speaking remains well in the future, Dr Cameron stated. "The issues in vaccine technology, where we're back to the drawing board, are macrophages and long-lived latently-infected cells responsible for secondary spread, and early distribution of the virus due to its speed and mutability." Exploration of certain rapid immune system reactions, such as IgE-mediated anaphylaxis, might be of interest, he suggested. "There are branches of the immune system which have specificity and which have not been explored in terms of inducible specific immunity."

Other prophylactic measures against HIV, including treatment as prevention, present their own challenges. Prevention requires biomedical, psychosocial, behavioural and structural approaches, he stated. Medical and basic scientists have perhaps been resistant to forge the necessary partnerships with social scientists, given the tension between their dedication to objective data versus language and ideas. "But we need to use and learn each other's language if we're going to be able to collaborate with each other." The structural or contextual factors that are a barrier to HIV prevention also must be addressed. "In a chaotic society full of poverty, crowding, misery, debility, malnutrition, war, social disruption, you're not going to get anywhere with an organized and concerted response against HIV infection." To get to a point where diagnosis and treatment of HIV takes place faster than infection incidence, people at risk must feel comfortable enough to disclose their status. "We need to work on knowledge because that is the only proven intervention against stigma, which remains dominant in the field, if we are going to improve on diagnosis."

Dr Cameron further suggested that novel research paradigms may also help identify cause in other challenging diseases for which there is no known etiology, such as multiple sclerosis and breast cancer. "I believe that we will cure HIV infection if we persist in the research that's required to do so", he concluded.

CAHR bestows the honour of the Mark Wainberg Lecture to pay tribute to Dr Wainberg's ongoing contributions, and to recognize the efforts of others in the research community who exemplify the same traits of excellence, perseverance, and commitment to the cause of finding innovative and groundbreaking ways to address the epidemic.

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Pulsus Group Inc, 2902 South Sheridan Way, Oakville, Ontario, Canada L6J 7L6. Telephone 905-829-4799, fax 905-829-4799, pulsus@pulsus.com, www.pulsus.com