New Directions in Vaccines, Virology and Drug Treatments

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ALTRUISM AS A KEY FACTOR IN UNDERSTANDING WHAT MOTIVATES PEOPLE LIVING WITH HIV TO PARTICIPATE IN A THERAPEUTIC HIV VACCINE TRIAL

Louise Balfour [1]; Kimberly Corace [1]; John Kowal [1]; Valerie Krysanski [1]; Giorgio Tasca [1]; Cécile Tremblay [2]; Jean-Pierre Routy [3]; Jonathan Angel [1];
1-Ottawa Hospital-General Campus, Ottawa, Canada; 2-Centre Hospitalier de L'Université de Montréal (CHUM), Montréal, Canada; 3-Montréal Chest Institute, Montréal, Canada;

Plain Language Summary: The present study examines HIV patients' motivation for participating in a novel therapeutic HIV vaccine trial. Participants were adults (at least 18 years-old) with a documented HIV infection. Results indicate that altruism is a key motivating factor for trial participation. That is, participants feel that the potential social and personal benefits to participating in this therapeutic HIV vaccine trial outweigh the potential personal risks.

Objectives: Understanding HIV patients' motivation and concerns about participating in novel HIV therapeutic vaccine trials is important. Potential social and personal risks and benefits should be carefully weighed by patients when they enroll. The present study is a psychological sub-study of a larger, multi-site therapeutic HIV vaccine trial. The main goal of this psychological sub-study is to describe HIV patients' motivation for participating and to monitor patients' mood, coping, and quality of life throughout the study.

Methods: Eligible participants must be at least 18 years-old, have documented HIV infection, have an "undetectable" HIV viral load (< 50 copies/ml) for >2 years and a CD4 nadire >500 cells/uL, and currently be taking highly active antiretroviral treatment. All patients completed an 11-item vaccine motivation scale at study baseline as well as psychological measures of mood and quality of life. Data collection for the larger clinical trial is ongoing.

Results: All patients who enrolled in the larger study agreed to participate in the psychology-sub-study (N=46). Results indicate that altruism was a key factor in trial participation. All vaccine trial participants felt that their participation might yield social benefits (e.g., being one step closer to developing an effective HIV vaccine) and felt that their participation was a way of helping the HIV community. Most study participants (98%) reported also being motivated by personal benefits (e.g., to learn updated information about HIV), and 71% acknowledged that they accepted some level of personal risk (e.g., the therapeutic vaccine may cause some side-effects or future health problems). Depression scores were low and quality of life scores were high among study participants at study baseline.

Conclusions: Results from this study suggest that HIV patients who enrol in a novel therapeutic HIV vaccine trial are initially highly motivated by altruism. They feel that potential social and personal benefits to participating in this therapeutic HIV vaccine trial outweigh the potential personal risks. The issue of motivation, recruitment, and retention of patients in novel vaccine and clinical drug trials will be discussed.

Contact Information: Louise Balfour, Tel: 613-737-8037, Email: lbalfour@ottawahospital.on.ca

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PERCEIVED STRESS AND DEPRESSION SCORES REMAIN LOW THROUGHOUT 24 WEEKS OF PARTICIPATION IN A NOVEL HIV THERAPEUTIC VACCINE TRIAL

N. Parent [2]; L. Balfour [1]; J. Kowal [1]; V. Krysanski [1]; G. Tasca [1]; C. Tremblay [1]; J.P. Routy [1]; J. Angel [1];
1-University of Ottawa, Ottawa, Ontario, Canada; 2-Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada;

Plain Language Summary: This project is part of a psychological sub-study of a larger multi-centre HIV therapeutic vaccine trial. One goal of this sub-study is to monitor changes in participants' mood throughout the course of the larger HIV therapeutic vaccine trial. Participants in the trial self-administered validated depression and stress scales at each study visit. Results show that participants had lower levels of depression and stress at baseline than population norms and levels remained relatively low throughout the course of the trial to date.

Objectives: One goal of this sub-study was to monitor changes in participants' mood throughout the trial.

Methods: 27 HIV patients have completed through to week 24 of the 52 week trial. Study recruitment is ongoing and the aim is to recruit 60 participants in total. Criteria for eligibility include: > 18 years of age, documented HIV infection, an "undetectable" HIV viral load (< 50 copies/ml) for >2 years, a CD4 nadir >250 cells/uL, and currently on HAART. Patients are randomly assigned to receive either a therapeutic HIV vaccine or placebo starting at 4 weeks after baseline. All patients completed a validated 10-item perceived stress scale, and a validated 20-item depression scale, at each study visit, which includes study baseline (week -4), and weeks 0, 8, 20 and 24.

Results: All patients enrolled in the larger study agreed to participate in the psychology-sub-study. Preliminary results to week 24 (N=27) show that, on average, participants reported low levels of stress and depression in comparison to population norms. In addition, participants' levels of stress and depression remained low throughout the 24 weeks. No significant changes were found among mean depression and stress scores across time points as assessed by linear growth curve models (stress $p = 0.467$, depression $p = 0.429$).

Conclusions: Preliminary results suggest that participants in this HIV therapeutic vaccine trial reported lower levels of stress and depression at study baseline compared to population norms. For patients in this trial, receiving an HIV therapeutic vaccine or placebo also appeared to have no impact on psychological stress levels and mood throughout 24 weeks of study participation. Further follow-up is planned to continue to monitor participants' mood throughout the entire 52 weeks of the trial.

Contact Information: Nancie Parent, Tel: 519-204-3098, Email: nansout@hotmail.com

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INHIBITION OF HIV-1 ENTRY USING VECTORS EXPRESSING A MULTIMERIC HAMMERHEAD RIBOZYME TARGETED AGAINST THE CCR5 MRNA

Reza Nazari [2]; Sadhna Joshi [1,2];
1-Medical Genetics & Microbiology, University of Toronto, Toronto, Ontario; 2-Laboratory Medicine & Pathobiology, University of Toronto, Toronto, Ontario;

Plain Language Summary: HIV-1 needs a co-receptor in addition to the CD4 receptor to enter the cell. The co-receptor that R5 HIV-1 strains use to enter the monocytes/macrophages and T lymphocytes, is CCR5. We know that R5 strains are predominant in the primary infection, and that the CCR5 coreceptor is dispensable since people who are homozygous for a mutated CCR5 (CCR5-delta 32), are highly resistant to HIV-1 infections. Therefore, CCR5 down-regulation on the cell surface may prevent HIV-1 to enter the cells. Hammerhead ribozymes are small RNA molecule that can be designed to specifically recognize and cleave a target RNA. Multimeric ribozymes are more effective than monomeric ribozymes. We have developed a multimeric hammerhead ribozyme (Rz1-7), consisting of seven ribozymes that target the CCR5 mRNA. We have shown that the anti-CCR5 Rz1-7 expressed from a retroviral or a lentiviral vector rendered the susceptible (PM1) cells 99-100% resistance to an R5-tropic HIV-1 (Ba-L strain). Inhibition was observed for the duration of the experiment (2-3 months).

Objectives: Develop a retroviral (MSCV-based) and a lentiviral (HIV-1-based) vector expressing an anti-CCR5 multimeric hammerhead ribozyme (Rz1-7), targeted against seven unique sites within the CCR5 mRNA. Assess inhibition of HIV-1 replication in a human CD4+ T lymphoid (PM1) cell line, expressing this multimeric ribozyme.

Methods: Rz1-7 is designed to target seven unique sites within the human CCR5 mRNA. A mouse stem cell virus (MSCV)-based MGIN-Rz1-7 vector, as well as an HIV-1-based HEG1-Rz1-7 vector, was designed to express Rz1-7 in PM1 cell line. Expression of Rz1-7 and its activity in the stably transductants PM1 cells were determined by RT-PCR analyses. Untransduced and stably transductants PM1 cells were challenged with an R5-tropic HIV-1 (Ba-L). The inhibition of virus entry was determined by PCR analysis.

Results: The activity of Rz1-7 was demonstrated by cleavage reactions in vitro. The activity of Rz1-7 in transduced cells was shown by a decrease in the cellular CCR5 mRNA levels. While cells were permissive to an X4-tropic HIV-1 (NL4-3) replication, replication of an R5 HIV-1 (Ba-L) was shown to be inhibited. Inhibition was more prominent in cells transduced with the MGIN-Rz1-7 vector than the HEG1-Rz1-7 vector. Replication of HIV-1 Ba-L was 99-100% inhibited in the MGIN-Rz1-7-transduced PM1 cells for the duration of the experiment (2-3 months post-infection). Inhibition was shown to occur at the level of viral entry, as no HIV-1 provirus DNA could be detected by PCR.

Conclusions: These results demonstrate that Rz1-7 can effectively cleave the CCR5 mRNA and prevent R5-tropic HIV-1 infection at the level of entry.

Contact Information: Sadhna Joshi, Tel: 416-978-2499, Email: sadhna.joshi.sukhwal@utoronto.ca

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IMMUNE EVASION VERSUS VIRAL REPLICATION: EXAMINING THE BALANCE OF PRESSURES ON HIV-1 T-CELL EPITOPES

Natasha M. Christie [1]; David O. Willer [2]; Mark A. Luscher [2]; Eric J. Arts [3]; Kelly S. MacDonald [1,2,4];
1-Department of Immunology, University of Toronto, Toronto, ON, Canada; 2-Division of Clinical Sciences, University of Toronto, Toronto, ON, Canada; 3-Division of Infectious Diseases, Case Western Reserve University, Cleveland, OH, United States of America; 4-Department of Microbiology, Mt. Sinai Hospital, Toronto, ON, Canada;

Plain Language Summary: During the course of HIV-1 infection, certain areas of the viral proteins are targeted by the host immune response. These regions, called epitopes, can change in sequence due to the high mutation rate of the viral genome. When changes occur, the initial immune response can be lost, a phenomenon known as “Immune Evasion”. However, some of these epitopes may be in areas of proteins that are crucial in the virus' ability to replicate efficiently. Epitopes that are highly targeted by the immune system, but are also essential to the virus, would be the ones most useful to include in vaccine designs because the potential for immune evasion would be limited. The aim of this project is to determine whether immune evasion is restricted in favour of viral replication in the case of a well-characterized epitope called SLYNTVATL (SL9).

Objectives: To investigate sequence constraints imposed on the SL9 epitope by the requirement for HIV-1 replicative fitness.

Methods: Congenic plasmid clones of HIV-1 were constructed using an overlapping PCR approach to incorporate synonymous or non-synonymous mutations. Two panels of mutants were created: one substituting immunologically relevant positions of the epitope with amino acids testing the flexibility of these positions, the second representing variant SL9 epitope sequences that are seen in patients over the course of infection. All plasmids were transfected into 293T cells to allow for infectious virus assembly. Viruses were then purified using U87.CD4.CXCR4 cells and resultant virus was titered and subjected to mono-infection cell culture at equivalent multiplicity of infection (MOI). Viral growth in culture was monitored using a p24 ELISA.

Results: Upon transfection into 293T cells, viral proteins were produced from all constructs. All viruses representing natural variations in the SL9 epitope grew equivalently, with the exception of T8V, which showed a kinetic delay. In the artificially substituted viruses, all conservative substitutions lead to infectious virus that grew efficiently in culture. Non-conservative amino acid substitutions, as well as synonymous substitution throughout this epitope region, lead to non-viable viruses.

Conclusions: Although many of the variations of the SL9 epitope that occur in vivo do not appear to impair replicative capacity of the virus, the viability of artificially substituted viral variants illustrate that this sequence could allow for more variation at immunologically relevant residues. The lack of the appearance of these powerful escape mutations may be an indication of a functionally crippled T-cell response to this epitope.

Contact Information: Natasha Christie, Tel: 416-978-1605, Email: natasha.christie@utoronto.ca

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EVALUATION OF VACCINE VECTORS IMPLEMENTED WITH ANTI-APOPTOTIC MOLECULE M11L IN VITRO

Jin Su [1]; Christy Willert [1]; Timothy Irvine [1]; Grant McFadden [1]; Gregory Dekaban [1];
1-BioTherapeutics Research Group, Robarts Research Institute, UWO, London, Ontario, Canada;

Plain Language Summary: Apoptosis is a cell death process naturally exists in all living cells. Apoptosis is a key mechanism involved in HIV gp120-induced cell death and immune clearance of gp120-expressing cells, the process often reduces the immunogenicity of HIV vaccines. M11L is an apoptosis inhibitor expressed by a rabbit poxvirus called myxoma virus. In our study, we explored the possibility of incorporating M11L in HIV DNA vaccines to promote long-lasting antigen expression thereby augmenting the immune responses against HIV antigen. We found that Myxoma M11L modulates apoptosis by multiple independent strategies all of which contribute to the blockade of apoptosis. DNA vaccines implemented with M11L renders apoptosis resistant in cells resulting in enhanced expression of the HIV antigen.

Objectives: M11L is an apoptotic inhibitor encoded by a rabbit poxvirus, myxoma virus. In myxoma-infected or M11L-transfected cells, M11L localizes to mitochondria and blocks apoptosis of the host cell. This protection from apoptosis involves constitutive-forming inhibitory complexes with the peripheral benzodiazepine receptor and Bax on the outer mitochondrial membrane. In this study, we extended our investigation of the mechanism by which M11L interferes with apoptosis by examining Bax activation. Furthermore, we explored the possibility of incorporating M11L in HIV DNA vaccines to enhance the HIV antigen expression in vitro, thereby augmenting the immunogenicity of these vaccines in vivo. Our hypothesis is that DNA vaccine vectors containing M11L will possess an anti-apoptotic function that promotes long-lasting antigen expression.

Methods: The interaction between M11L and Bax, Bax conformational change and Bax localization were analyzed by immunoprecipitation and confocal microscopy. The anti-apoptotic function of M11L was confirmed by western blotting for the active form of caspase-3 and cleaved PARP. A rev-independent, codon optimized HIV clade B envelope sequence (gp140) was inserted into a novel DNA vaccine vector pHERO that is stably maintained in dividing cells. The genes encoding M11L and/or a murine CpG motif as vaccine adjuvant were inserted into the HIV pHERO vector. Mouse fibroblast L cells were transfected with pHERO constructs and the expression of HIV Env and M11L were confirmed by western blot. The level of apoptosis induced by HIV gp140 transfection was measured by a caspase activity assay in 96-well plates.

Results: In both human and mouse cells, M11L was found to block the conformational activation of Bax at the mitochondrial membrane thereby halting the apoptotic process at a mitochondrial checkpoint. Mouse L cells transfected with pHERO containing M11L exhibited resistance to the apoptosis induced by HIV gp140 transfection. Furthermore, a higher level of HIV gp140 was detected in the presence of M11L in comparison with those transfected with DNA without M11L.

Conclusions: Myxoma M11L modulates apoptosis by multiple independent strategies all of which contribute to the blockade of apoptosis within the mitochondrial pathway. DNA vectors implemented with M11L renders the transfected cells apoptosis resistant resulting in enhanced expression of the HIV antigen gp140. This may provide the basis of a novel strategy, incorporating anti-apoptotic function, to modify vaccines to fight against HIV infections and cancer.

Contact Information: Jin Su, Tel: 519-663-5777 x34239, Email: jsu@robarts.ca

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DEVELOPMENT OF VARICELLA ZOSTER VIRUS AS A PERSISTENT, REPLICATING SIV/HIV VACCINE VECTOR

David O. Willer [1,2]; James Brooks [3]; Paul A. Sandstrom [4]; Jocelyn Fournier [5]; Kelly S. MacDonald [1,2];
1-Division of Clinical Sciences, Department of Medicine, University of Toronto; 2-Department of Microbiology, Mt. Sinai Hospital, Toronto, Canada; 3-National Laboratory for HIV Genetics, Health Canada, Ottawa, Canada; 4-National HIV and Retrovirology Laboratories, Health Canada, Ottawa, Canada; 5-Health Products and Food Branch, Health Canada, Ottawa, Canada;

Plain Language Summary: Here, we describe the development and proposed testing of a novel vaccine vector for HIV based on the Varicella Zoster Virus (VZV).

Objectives: A fundamental problem of current HIV vaccine candidates is poor or short-lived immunogenicity. Varicella Zoster Virus (VZV) is an attractive, persistently replicating viral vector with the potential to deliver life-long immunity.

Methods: Here we outline the development and testing of a novel vaccine vector for HIV based on VZV. VZV, a herpesvirus, is the causative agent of chickenpox. The Oka strain (VZV-Oka), a live, replicating, attenuated vaccine strain of VZV, has been used safely in humans since 1974. VZV establishes a life-long infection in the host, with evidence of periodic reactivation and immunogenicity even in healthy individuals. This ability to self-boost makes it unique among the vectors currently in HIV trials. Furthermore, VZV-Oka induces broad reacting cellular and humoral immune responses and can induce mucosal immunity even following intradermal inoculation. In contrast to some attenuated SIV vaccine candidates, VZV is a non-retroviral, non-integrating persistent viral vector and can be used without fear of reversion to pathogenic vaccine virus variants. We have employed "PCR Assembly" using oligonucleotides to generate codon-optimized SIVmac239-derived sequences. These SIV gene products were targeted to a Bacterial Artificial Chromosome harbouring VZV via "Allelic Exchange" bacterial recombination.

Results: Here we highlight the construction of SIV antigenic sequences (Gag, Pol, Env, and a novel fusion protein NeTaRev) and the engineering of VZV-based SIV vaccine candidates.

Conclusions: This VZV-based SIV/HIV vaccine study will address the key issues of the immunogenicity and protective efficacy of this herpesvirus vector. The principal goal of this research is to develop a protective HIV vaccine, which can be tested in a non-human primate challenge model, and ultimately be transitioned into human clinical trials.

Contact Information: David Willer, Tel: 416-946-3732, Email: david.willer@utoronto.ca

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IMMUNE CORRELATES OF HIV SHEDDING: CMV-SPECIFIC CD8+ IMMUNE RESPONSES ARE NOT ASSOCIATED WITH REDUCED HIV OR CMV LEVELS IN THE SEMEN OF CO-INFECTED MEN

Prameet Sheth [1]; Sherzana Sunderji [1]; Roberta Halpenny [2]; Colin Kovacs [2]; George Moosa [3]; Tony Mazulli [3]; Rupert Kaul [1];
1-Department of Medicine, University of Toronto, Toronto, Canada; 2-Canadian Immunodeficiency Research Collaborative Inc., Toronto, Canada; 3-Mt. Sinai Hospital, Toronto, Canada;

Plain Language Summary: The majority of HIV is transmitted sexually, when HIV infected individuals shed virus in their genital secretions (i.e. semen or vaginal fluid). Generally, HIV levels in blood and semen are related although semen HIV levels tend to be 10-fold lower than blood HIV levels. However, we previously observed that HIV infected individuals co-infected with a common virus called cytomegalovirus (CMV) were shedding more HIV in semen, and semen levels of these two viruses were closely associated. As immune responses to CMV have been shown to be protective against CMV disease, we decided to investigate whether immune responses against CMV could control CMV semen shedding and indirectly also control semen HIV levels.

Objectives: In HIV-CMV co-infected men we evaluated the association between systemic CMV–specific CD8+ responses and localized CMV reactivation, as well as their association with levels of semen HIV.

Methods: Blood and semen samples were collected from 26 HIV infected therapy-naïve men and HIV RNA and CMV DNA in CD8+ immune MIP-1β and blood and semen were measured. CMV specific IFN-γ responses were measured by stimulating peripheral blood mononuclear cells with overlapping peptide pools to pp65 and IE-1 regions of CMV and analyzed using flow cytometry. CMV-specific CD4+ T cell responses were assayed by IFN-γ and IL2 production.

Results: Of the 26 HIV-CMV co-infected men, 18/26 (70%) were actively shedding CMV DNA in semen. There was a strong correlation between levels of HIV and CMV in semen ($P < 0.01$) and CMV shedding in semen was correlated with elevated levels of HIV-1 RNA in semen (log 10 semen VL 4.2 vs 3.0, p=0.03). 23/26 individuals had a measurable CMV specific CD8+ response against pp65 or IE-1. Individuals mounting a systemic CMV-specific CD8+ response tended to shed higher levels of HIV (Log 10 semen VL 2.7 vs 3.7, p=0.09) and CMV (Log 10 semen VL 2.4 vs 4.5, p=0.04) in semen. There was no association between CD4+ responses and HIV or CMV semen levels.

Conclusions: Systemic CMV specific CD8+ responses were associated with higher levels of HIV and CMV in semen, suggesting that these responses are reactive rather than proactive. These findings suggest that other CMV control strategies in semen warrant investigation.

Contact Information: Prameet Sheth, Tel: 416-946-7054, Email: prameet.sheth@utoronto.ca

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DIFFERENT MECHANISMS UNDERLY THE SUPPRESSION OF HIV-1 GENE EXPRESSION BY SRP30C AND HTRA2ß/ßΔN

Craig Platt [1]; Josip Nemet [1]; Alan Cochrane [1];
1-Dept. of Medical Genetics & Microbiology, University of Toronto;

Plain Language Summary: Control of HIV-1 RNA processing plays an important role in regulating viral protein production. Upon synthesis, the 9 kb viral transcript is converted into over 30 mRNAs by alternative splicing, regulated by both cis- and trans-acting factors. Evaluating how these factors interact and how their modulation alters HIV-1 gene expression may identify new means of disrupting viral RNA processing and of controlling the infection.

Objectives: To identify host factors that are able to modulate HIV-1 expression at the post-transcriptional level.

Methods: HEK293 cells were transfected with a HIV-1 proviral expression vector and plasmids expressing various members of the SR family of RNA splicing regulatory factors. Forty-eight hours post-transfection, cells were harvested and effects on HIV-1 Gag expression evaluated by Western blot. In parallel, alterations in viral RNA processing were also examined by Northern blotting and RT-PCR. To assess the role of known splicing modulatory sequences in the responses observed, assays were repeated using proviral constructs lacking these elements.

Results: Screening of multiple members of the SR protein revealed that overexpression of three factors, SRp30c, Tra2alpha/beta as well as an isoform of Tra2beta (Tra2ßΔN), yielded a strong suppression of viral replication as evidenced by reduced p24 expression. Subsequent analysis of their effect by Northern blot failed to reveal any significant alterations by Northern blot for SRp30c and Tra2ß, while Tra2ßΔN induced a marked increase in accumulation of the 2kb viral RNA species. RT-PCR analysis of the viral RNA species provided some explanation for the effects observed. While Tra2ß overexpression resulted in the loss of 2 kb RNAs encoding Rev, Tra2ßΔN overexpression induced an aberrant splicing event by joining of SD1 to SA7 and decreasing levels of RNA expressing Tat and Rev. Deletion of splicing regulatory sequences (ESE3, ESS3) in the terminal exon of the virus failed to alter the response to Tra2ßΔN, suggesting that it may be acting by suppressing recognition of splice sites elsewhere in the viral RNA.

Conclusions: We have been successful in identifying three members of the SR protein family whose overexpression can dramatically alter HIV-1 replication, some of which function by altering viral RNA processing. Analysis of their effects on viral RNA abundance and splicing reveal that each is functioning via different mechanisms to achieve the inhibition of HIV-1 gene expression observed. The differential expression of some of these factors in human tissues may underlie the variation in capacity to support HIV-1 replication observed.

Contact Information: Alan Cochrane, Tel: 416-978-4550, Email: alan.cochrane@utoronto.ca

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SAM68DC INHIBITS INCOMPLETELY SPLICED HIV-1 MRNA TRANSLATION BY REMOVING PABP: A NOVEL MECHANISM OF INHIBITION

Kim Marsh [1]; Alan Cochrane [1];
1-Department of Medical and Molecular Genetics, University of Toronto;

Plain Language Summary: Sam68DC is a potent inhibitor of HIV-1 replication. It has previously been shown to inhibit expression of the HIV-1 structural proteins. We have found that Sam68DC does not affect the abundance of these mRNAs or their composition. We have found that Sam68DC inhibits protein expression from these mRNAs by removing the protein PABP, which is required for protein expression. This represents a novel mechanism of inhibiting HIV-1.

Objectives: Sam68DC was previously found to inhibit protein expression from the incompletely spliced 9 and 4kb classes of HIV-1 mRNA. However, the exact mechanism of Sam68DC inhibition has remained elusive. The purpose of this study was to determine the mechanism of inhibition.

Methods: HIV mRNA localization was studied by fluorescent in situ hybridization. Total RNA from HIV transfected cells was fractionated over an oligo(dT) column and analysed by RNase protection assay. PABP containing RNPs were isolated, the RNA was analysed by RNase protection assay and the proteins were analysed by Western Blot.

Results: We established that Sam68DC inhibition of HIV-1 was not due to perinuclear bundling, but either alteration of the RNA or the RNP. Further experiments revealed that Sam68DC does not affect the abundance or the polyadenylation status of inhibited mRNAs, but that it does affect PABP binding.

Conclusions: This represents a novel mechanism to regulate HIV-1 gene expression.

Contact Information: Kim Marsh, Tel: 416-978-2500, Email: kim.marsh@utoronto.ca

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EFFECT OF GP120 AND CYTOKINES ON THE FUNCTIONAL EXPRESSION OF THE MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN 1 (MRP1), AN ATP-BINDING CASSETTE (ABC) EFFLUX DRUG TRANSPORTER, IN CULTURED GLIAL CELLS

Patrick T. Ronaldson [1]; Christopher Tran [1]; Vijay P. A. Rasaiah [1]; Reina Bendayan [1];
1-Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada;

Plain Language Summary: Mrp1 is a drug pump that can export anti-HIV drugs from the brain, which reduces their ability to treat HIV-1 encephalitis (HIVE). The goal of this study is to determine if toxic substances present in the brain during HIVE [i.e., HIV-1 viral envelope protein gp120, cytokines (i.e., TNF-α, IL-1β, IL-6)] can alter Mrp1 levels and activity. We observed that gp120 increased both Mrp1 levels and activity in astrocytes, a type of brain cell infected by HIV-1. We also showed that Mrp1 protein levels were increased by TNF-α but not changed by IL-1β or IL-6. These results imply that anti-HIV drug entry and distribution in the brain may be altered during HIVE.

Objectives: Brain immunological responses are well known to occur during HIV-1 encephalitis (HIVE). Using an in vitro model of HIVE-associated immune responses, we demonstrated that cytokine secretion (i.e., TNF-α, IL-1β, IL-6) is mediated by an interaction between gp120 and CCR5. An obstacle to HIVE pharmacotherapy is the functional expression of ABC transporters (i.e., P-glycoprotein, Mrp1) that export antiretroviral drugs from HIV-1 brain cellular targets (i.e., astrocytes, microglia). Our laboratory has shown that gp120 or IL-6 treatment decreases P-glycoprotein functional expression in cultured astrocytes. At present, it is unknown if gp120 or cytokine exposure can alter the expression of other ABC transporters. The goal of this project was to investigate Mrp1 functional expression in cultured rat astrocytes treated with gp120 or cytokines.

Methods: Primary cultures of rat astrocytes were incubated for the desired time (i.e., 6 h, 24 h) in the presence of 1.0 nM gp120 (subtype C, strain 96ZM651) or recombinant cytokines (i.e., 0.3-0.5 ng/ml and 10 ng/ml, TNF-α, IL-1β, IL-6). Gene and protein expression were determined by RT-PCR and immunoblotting analysis respectively. Transport properties of 2',7'-bis-(2-carboxyethyl)-5-(and-6)-carboxyfluorescein (BCECF), an established Mrp substrate, were investigated at 37ºC in cultured astrocytes grown as monolayers.

Results: RT-PCR and immunoblotting analysis demonstrated increased Mrp1 mRNA (2.3-fold) and protein (2.2-fold) expression in rat astrocyte cultures treated with gp120 respectively. Cellular retention of BCECF was significantly reduced (2.0-fold) in gp120-treated astrocytes, suggesting an increase in Mrp-mediated functional activity. Cytokine treatment showed that Mrp1 protein expression was increased by TNF-α (2.7-fold) but not significantly altered by IL-1β or IL-6.

Conclusions: Gp120 or cytokine treatment can modulate the gene and protein expression of Mrp1 in cultured rat astrocytes. Taken together with our P-glycoprotein work, these data suggest that complex drug-transporter interactions may occur during immune responses associated with brain HIV-1 infection.

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Contact Information: Patrick Ronaldson, Tel: 416-946-7523, Email: ptronaldson@sympatico.ca

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INVOLVEMENT OF THE MITOGEN-ACTIVATED PROTEIN KINASE (MAPK) PATHWAY IN THE REGULATION OF P-GLYCOPROTEIN (P-GP) EXPRESSION IN CULTURED RAT ASTROCYTES TREATED WITH GP120

Patrick T. Ronaldson [1]; Janica Chan [1]; Reina Bendayan [1];
1-Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada;

Plain Language Summary: P-gp is a drug pump involved in exporting anti-HIV drugs from the brain and reducing their ability to treat brain HIV-1 infection. Our laboratory has observed reduced P-gp levels and activity in astrocytes, a type of brain cell infected by HIV-1, in the presence of the HIV-1 viral protein gp120. However, the cellular processes involved in modifying P-gp levels are not known. The goal of this study is to investigate cellular processes that may be responsible for changes in P-gp levels. When we treated astrocytes exposed to gp120 with chemicals that interfere with the MAPK pathway, a cell system activated during HIV-1 infection, P-gp levels did not change. These observations suggest that the MAPK system may be involved in modifying P-gp levels during brain HIV-1 infection.

Objectives: Recently, our laboratory has shown decreased functional expression of P-gp, an ATP-dependent membrane drug transporter involved in limiting brain accumulation of antiretroviral drugs, in cultured rat astrocytes exposed to gp120 or interleukin-6, a proinflammatory cytokine. However, the intracellular signaling pathways involved in regulating this response have not been clearly elucidated. Studies have shown that proinflammatory cytokines may directly activate of the MAPK pathway, an intracellular system of enzymes known to be involved in signal transduction and regulation of gene expression during pathological processes (i.e., cell stress, inflammation). The goal of this study is to determine the role of the MAPK pathway in the regulation of P-gp expression in cultured rat astrocytes treated with gp120.

Methods: Primary cultures of rat astrocytes were incubated for 6 or 24 h with 1.0 nM gp120 (subtype C, strain 96ZM651) in the presence or absence of various MAPK inhibitors [i.e., MEK1 inhibitor PD98059 (50 μM), p38 MAPK inhibitor SB203580 (20 μM), c-Jun N-terminal kinase inhibitor SP600125 (20 μM)]. P-gp protein expression was measured by immunoblot analysis using the monoclonal anti-P-gp antibody C219.

Results: In primary cultures of rat astrocytes triggered with gp120, immunoblot analysis showed decreased P-gp expression (4.7-fold). In contrast, P-gp protein expression was not significantly altered in cultured astrocytes exposed to gp120 and specific MAPK inhibitors (i.e., PD98059, SB203580, SP600125).

Conclusions: These data suggest that the MAPK pathway may be involved in the regulation of P-gp expression during HIVE-associated immunological responses. Further studies are required to confirm the intracellular signaling molecules involved in the release of cytokines and in the alteration of antiretroviral drug transporter (i.e., P-gp) expression.

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Contact Information: Patrick Ronaldson, Tel: 416-946-7523, Email: ptronaldson@sympatico.ca

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DRUG TRANSPORT INTERACTIONS BETWEEN ATAZANAVIR AND RITONAVIR USING A HUMAN BRAIN MICROVESSEL ENDOTHELIAL CELL LINE

Jason Zastre [1]; Gary N.Y. Chan [1]; Manisha Ramaswamy [1]; Reina Bendayan [1];
1-Department of Pharmaceutical Sciences, Leslie L. Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada;

Plain Language Summary: Although limitations in brain penetration of HIV-1 protease inhibitors has been associated with drug efflux transporters, the co-administration of several protease inhibitors in HAART regimens may be of value to overcome efflux transport. Since both atazanavir and ritonavir have been previously characterized to be P-gp inhibitors, we hypothesize that co-administration may result in enhanced brain penetration of either protease inhibitor through inhibition of drug efflux transport.

Objectives: To investigate drug transport interactions between atazanavir and ritonavir using an immortalized human brain microvessel endothelial cell line, hCMEC/D3.

Methods: Cellular accumulation of atazanavir and ritonavir was evaluated using a newly developed immortalized human brain microvessel endothelial cell line, hCMEC/D3. Expression of drug efflux transporters by hCMEC/D3 cells such as P-glycoprotein, MRP1, and BCRP was confirmed by western blot analysis. Substrate and inhibitor properties of ritonavir and atazanavir for P-glycoprotein was evaluated using the P-gp substrate, rhodamine 6G (R-6G), and the P-gp inhibitor PSC833 in a P-gp overexpressing cell system (MDA-MDR1). For cellular accumulation studies, hCMEC/D3 cells were incubated (60 min, 37C) with 1 uM atazanavir or ritonavir in the presence of various concentrations of established drug efflux transporter inhibitors such as PSC833 for P-glycoprotein; MK571 for Multidrug Resistance Protein (MRP); and FTC for Breast Cancer Resistance Protein (BCRP). In addition, the co-administration of either atazanavir with increasing concentrations of ritonavir and vice versa was assessed for drug transport interactions by measuring the cellular accumulation into hCMEC/D3 cells.

Results: A significant decrease in cellular accumulation was found for atazanavir and ritonavir in a P-gp overexpressing cell line compared to wild type cells confirming the P-gp substrate properties of both ritonavir and atazanavir. Both ritonavir and atazanavir increased the accumulation of the P-gp substrate, R-6G in P-gp overexpressing cells, demonstrating P-gp inhibitory properties. Atazanavir and ritonavir cellular accumulation by hCMEC/D3 was increased by approximately 2 and 1.8 fold, respectively, in the presence of the P-gp inhibitor PSC833. However, the BCRP inhibitor FTC and the MRP inhibitor MK571 did not enhance atazanavir or ritonavir accumulation into hCMEC/D3 cells. In combination, neither ritonavir nor atazanavir was capable of enhancing each others cellular accumulation in hCMEC/D3 cells.

Conclusions: Although atazanavir and ritonavir appear to be substrates and inhibitors for the drug efflux transporter, P-gp, drug interactions between these two protease inhibitors with hCMEC/D3 cells do not appear to result in enhanced drug transport of either protease inhibitor. The lack of drug interactions between atazanavir and ritonavir with P-gp may be due to non-overlapping drug binding sites within P-gp or tissue specific differences in P-gp activity.

Contact Information: Jason Zastre, Tel: 416-946-4032, Email: j.zastre@utoronto.ca

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INTESTINAL TRANSPORT PROPERTIES OF THE HIV-1 PROTEASE INHIBITOR ATAZANAVIR BY CACO-2 CELLS

Jason Zastre [1]; Reina Bendayan [1];
1-Department of Pharmaceutical Sciences, Leslie L. Dan Faculty of Pharmacy, University of Toronto, Toronto ON, Canada;

Plain Language Summary: Currently, atazanavir is recommended in ritonavir boosted or unboosted HAART regimens for the treatment of HIV-1 infection. The co-administration of atazanavir with ritonavir has been demonstrated to result in improved atazanavir pharmacokinetics through metabolism inhibition. However, protease inhibitors have been shown to be susceptible to efflux drug transport in the intestinal tract which may further limit oral bioavailability. These studies were designed to characterize in vitro the intestinal transport of atazanavir and the effect co-administered protease inhibitors may have on its transport.

Objectives: To investigate the intestinal transport of the new HIV-1 protease inhibitor atazanavir using Caco-2 cells.

Methods: Cellular accumulation and transepithelial flux of atazanavir was evaluated using the human colon adenocarcinoma cell line, Caco-2, which undergoes spontaneous enterocytic differentiation, and is known to express several influx and efflux drug transporters. For cellular accumulation studies, Caco-2 cells were incubated (60 min, 37C) with 1 uM atazanavir in the presence of various concentrations of established drug efflux transporter inhibitors such as PSC833 and GF120918 for P-glycoprotein; MK571 for Multidrug Resistance Protein (MRP); and FTC for Breast Cancer Resistance Protein (BCRP). Co-administration of other HIV-1 protease inhibitors (i.e., amprenavir, tipranavir, and ritonavir) on atazanavir cellular accumulation was also evaluated. Transepithelial flux of 1 uM atazanavir with or without drug efflux transporter inhibitors in the apical to basolateral (AP-BL) or BL-AP direction was determined over 120 min at 37C using Caco-2 monolayers grown on Transwell membranes.

Results: Cellular accumulation of atazanavir by caco-2 was significantly enhanced (3-4 fold) in the presence of P-glycoprotein inhibitors PSC833 and GF120918. Transepithelial flux studies using 1 uM atazanavir resulted in an efflux ratio (Papp BL-AP/Papp AP-BL) of 22.1. In the presence of 1 uM PSC833, the efflux ratio was reduced to approximately 1.3. Together, this data clearly demonstrates P-gp mediated efflux transport of atazanavir. The BCRP inhibitor FTC had no effect on atazanavir accumulation, whereas the MRP inhibitor significantly decreased atazanavir accumulation. HIV protease inhibitors, amprenavir and tipranavir (0.01 – 50 uM) exhibited a biphasic interaction on atazanavir cellular accumulation, where atazanavir accumulation decreased approximately 2-3 fold and returned to baseline accumulation levels with further increases in amprenavir and tipranavir concentration. Moreover, amprenavir and tipranavir significantly reduced the enhancement in cellular accumulation of atazanavir by the P-glycoprotein inhibitor PSC833 when combined.

Conclusions: Transport of atazanavir by caco-2 cells appears to be mediated by P-glycoprotein. In addition, drug interactions with co-administered protease inhibitors suggest that an influx transporter may be involved in the uptake of atazanavir by the cell line system. Further studies will elucidate the nature of this drug transport interaction.

Contact Information: Jason Zastre, Tel: 416-946-4032, Email: j.zastre@utoronto.ca

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DEVELOPMENT OF A NANOPARTICLE DRUG DELIVERY SYSTEM FOR ENHANCED DELIVERY OF THE PROTEASE INHIBITOR (PI), ATAZANAVIR, TO THE BRAIN

Niladri Chattopadhyay [1]; Jason Zastre [1]; Ho-Lun Wong [1]; Shirley Wu [1]; Reina Bendayan [1];
1-Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada;

Plain Language Summary: The low brain permeability of currently used PIs can lead to the development of a protected viral reservoir which may result in the development of drug resistance, reinfection of peripheral macrophages following viral suppression as well as development of HIV-1 infection of the brain. Nanoparticle systems such as solid lipid nanoparticles (SLNs) have been shown to enhance the delivery of several drugs across the blood-brain barrier (BBB) as well as bypass efflux transporters such as P-glycoprotein which have been implicated in therapeutic failure of several neurological disorders, including HIV-1 infection of the brain. As a proof-of-principle study, SLNs were formulated using stearic acid and loaded with Atazanavir (Reyataz®, Bristol- Myers Squibb, NJ), a new PI.

Objectives: To develop and characterize a lipid based nanoparticle system for enhanced brain delivery of Atazanavir, using human brain microvessel endothelial cells (hCMEC/D3) representative of the BBB.

Methods: SLNs were prepared by a thin film hydration technique. The nanoparticles were analyzed for Atazanavir entrapment efficiency, particle size and zeta potential. Atazanavir release from the nanoparticles was determined by dialysis using PBS (pH 7.4, 37ºC) as the release medium. The viability of hCMEC/D3 cells in the presence of either free Atazanavir (0.1 to 1000nm) or Atazanavir loaded into the SLNs was evaluated by using a standard 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay.

Results: A high encapsulation efficiency of approximately 90% was achieved with a maximum Atazanavir loading of 5% w/w. The mean particle size was 167nm and the formulation had a narrow size distribution with a polydispersity index of 0.158. Surface charge of the SLNs was determined to exhibit a net negative charge with a zeta potential of approximately -18mV. Atazanavir release from nanoparticles demonstrated an initial burst release of approximately 17% by one hour with a gradual release up to 46% after 24 hours. Cytotoxicity experiments indicate that the nanoparticles exhibit no toxicity in hCMEC/D3 cells up to a concentration corresponding to 200 nM of Atazanvir.

Conclusions: Solid lipid nanoparticles with a high encapsulation of Atazanavir (90%) were successfully prepared using the thin film hydration technique. Initial cell viability studies indicate that the formulation presents low toxicity and could be a promising antiviral drug delivery system to target the BBB.

Contact Information: Niladri Chattopadhyay, Tel: 416-946-7523, Email: niladri.chattopadhyay@utoronto.ca

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EDUCATIONAL ATTAINMENT AND CLINICAL OUTCOMES FOR RECIPIENTS OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) IN ONTARIO

Luisa Frescura [1]; Ahmed Bayoumi [1,2,3];
1-Centre for Research on Inner City Health, St. Michael's Hospital; 2-Division of General Internal Medicine, St. Michael's Hospital; 3-Department of Medicine and Department of Health Policy, Management and Evaluation, University of Toronto;

Plain Language Summary: Educational status is closely linked to socioeconomic status, which has been linked with worse health outcomes for people living with HIV. We examined whether HIV+ patients taking HAART therapy in Ontario had different health outcomes according to their level of education. We used data from a cohort of patients in Ontario, and found that there were no significant differences in treatment outcomes by educational status.

Objectives: We examined the association between educational attainment and immunologic and virologic outcomes for patients receiving antiretroviral therapy in Ontario, Canada.

Methods: We used the Ontario HIV Treatment Network (OHTN) Cohort Study, in which trained abstracters collect data from consenting participants' medical charts at 6-month intervals. We supplemented viral load results with data from the Ontario Public Health Laboratory, which performs almost all tests in the province. We examined the time from initiation of the first HAART regimen to each of 3 clinically important outcomes: HIV viral load suppression to <500 copies/mL; virologic rebound to greater than 500 copies/mL after successful suppression; and an increase in the CD4 count of 100 cells/mm3 above baseline. We censored participants at the time of death or last data collection. We studied differences among groups using time-to-event-analysis and the Cox-proportional hazards method.

Results: Of 970 participants, 81% had completed high school or attained higher levels of education, 86% were male, 79% were white, 50% resided in Toronto, 12% reported a history of injection drug use, and 67% reported sex with men as a risk factor for acquiring HIV. The median age was 39 years. Most (855, 88%) participants experienced virologic suppression with a median time (interquartile range) of 79 days (43 to 210). Of these, 343 (40%) experienced virologic rebound at a median time of 857 days (440 to 1467). A CD4 cell increase of 100 cells/mm3 or greater was experienced by 833 participants (86%) at a median time of 153 days (63 to 335). In univariate analysis, higher education was associated with more rapid virologic suppression [Relative Hazard=1.26 (95% Confidence Interval 1.05-1.50)], and with less rapid virologic rebound [RH=0.79 (0.63-0.98)] but was not associated with CD4 increases [RH=1.10 (0.92-1.32)]. In multivariable analysis higher education was not associated with time to virologic suppression [RH=1.16 (0.93-1.36), virologic rebound [RH=0.84 (0.66-1.06), or CD4 increases [RH=1.07 (0.88-1.30)]. Early virologic suppression was associated with age [RH=1.18 (1.10-1.27); per decade increase], with having no previous AIDS diagnosis [RH=1.28 (1.03-1.59)], and with being treatment naïve prior to therapy [RH=2.14 (1.60-2.90)].

Conclusions: We found that lower educational attainment was not associated with more rapid virologic suppression, virologic rebound, or CD4 increases following initiation of HAART. Socioeconomic barriers to care may be less important in the context of universal public health insurance.

Contact Information: Luisa Frescura, Tel: 416-864-6060 x3345, Email: frescural@smh.toronto.on.ca

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NEUROCOGNITIVE SYMPTOM BURDEN IN HIV INFECTION: DOES LEVEL OF SOCIAL SUPPORT BUFFER NEUROPSYCHOLOGICAL STATUS?

Jana Atkins [1]; Sarah Rubenstein [1,2]; Teri Sota [1]; Sergio Rueda [1,2]; Sean Rourke [1,2,3];
1-St. Michael's Hospital; 2-University of Toronto; 3-Ontario HIV Treatment Network;

Plain Language Summary: Recent work in our research unit has demonstrated that elevated cognitive symptom burden is associated with depression and the presence of certain neuropsychological (NP) impairments. Given the link between the presence of social support in buffering depressive symptom burden, we were interested in exploring whether social support also had a role in buffering NP status.

Objectives: The aim of the study is to evaluate the relationship between cognitive complaints and social support and to determine if greater social support will not only buffer neuropsychological status, but also if it will reduce cognitive symptom burden.

Methods: A total of 357 adults with HIV (47% with AIDS) completed comprehensive NP testing, the Patient's Assessment of Own Functioning Inventory, and a brief social support inventory.

Results: A 2 x 2 ANOVA was conducted to evaluate the effects of two NP status conditions ("normal" vs. "impaired") and level of social support (low vs. high) on cognitive symptom burden. The ANOVA indicated no significant interaction between NP status and social support, but significant main effects were found for NP status, $F(1, 333) = 13.48$, $p = < .001$, and social support $F(1, 333) = 22.82$, $p = <.001$. The NP status main effect indicated that those who were NP impaired endorsed more neurocognitive complaints. The main effect for social support indicated that those who reported having less social support also reported higher cognitive symptom burden.
Conclusions: Although both NP status and level of social support

Conclusions: Although both NP status and level of social support were differentially associated with the level of cognitive symptom burden, social support was not found to be a buffer for NP status. These findings have important practical implications for the promotion of psychological well-being in PHAs, as the amount of perceived social support appears to be an important determinant of neurocognitive complaints (i.e., those with low levels of support tend to report higher cognitive symptom burden). It will be important to identify individuals with low social support and intervene appropriately in order to improve quality of life.

Contact Information: Jana Atkins, Tel: 416-864-6060 x6491, Email: atkinsj@smh.toronto.on.ca

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THE ROLE OF PSYCHOLOGICAL, BEHAVIORAL, AND PHYSIOLOGICAL FACTORS IN THE EXPERIENCE OF BODILY PAIN AMONG HIV, HCV, AND HIV/HCV CO-INFECTED PATIENTS

Lorraine Overduin [1]; Louise Balfour [1]; John Kowal [1]; Kim Corace [1]; Giorgio Tasca [1]; Paul McPherson [1]; Curtis Cooper [1]; Gary Garber [1]; Jonathan Angel [1]; Bill Cameron [1];
1-Ottawa Hospital-General Campus, Ottawa, Canada;

Plain Language Summary: The present study examines psychological, behavioral, and physiological factors that contribute to bodily pain in patients with HIV and/or HCV. Bodily pain in HIV or HCV patients may be a result of disease factors as well as medications used to treat these conditions. Analyses will be conducted to identify which factors are the strongest predictors of pain. Results will be used to inform treatment choices by helping to identify which factors are most beneficial to target as part of treatment strategies.

Objectives: Bodily pain, including neuropathic pain, is a possible side-effect of HIV and HCV medications, and can also be a result of the disease processes in each of these conditions. Such pain can contribute to a reduced quality of life. Psychological factors, such as depression, have been shown in the chronic pain literature to negatively impact the pain experience (e.g., increased pain intensity, increased interference of pain in daily activities; Keefe, et al., 1992). In addition, behavioral factors, including smoking, have been shown to correlate with bodily pain among individuals with HCV (Balfour et al., 2006). The objective of the present study is to examine psychological variables and health behaviors of individuals with HIV and/or HCV, and to identify those factors that most strongly relate to symptoms of bodily pain.

Methods: Participants eligible for inclusion in this study were at least 18 years-old, with a documented HIV or HCV infection. Participants with HIV were not currently on HAART. All 190 participants completed a series of psychological and behavioral measures as part of a routine visit to The Ottawa Hospital HIV or Viral Hepatitis clinic.

Results: A series of hierarchical regression analysis are planned to explore the relative contribution of psychological factors, health behaviors, and physiological measures in relation to bodily pain. Results from this study will inform treatment planning by identifying the best correlates of bodily pain.

Conclusions: As HIV evolves into a chronic illness, it is increasingly important to understand factors that impact quality of life, such as the presence and severity of bodily pain. Targeting treatment interventions toward factors that are modifiable (e.g., smoking, stress, depression) and that are most likely to negatively impact quality of life is therefore increasingly imperative.

Contact Information: Lorraine Overduin, Tel: 613-737-8036, Email: loverduin@ottawahospital.on.ca

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QUALITY OF LIFE AND DEPRESSION AMONG SOUTH ASIAN PEOPLE WITH HIV/AIDS (PHAS) IN URBAN TORONTO, ONTARIO

Rounak Khan [1]; Seema Opal [1]; Basanti Majumdar [2]; Robin Weir [2]; Gina Browne [2]; Jacqueline Roberts [2];
1-Alliance For South Asian AIDS Prevention (ASAAP), Toronto, ON, Canada; 2-McMaster University and Community - Linked Evaluation AIDS Resource Unit, Hamilton, ON, Canada;

Plain Language Summary: The South Asian community constitutes the second largest visible minority group in the Greater Toronto Area (Statistics Canada, 2005). However, there is little information available on how to address their HIV/AIDS prevention education and support needs. The few studies that have been published suggest that South Asians appear to be reluctant to speak about sex, which consequently interferes with the development of sufficient interpersonal communication skills to discuss and negotiate safe sex practices. Such reluctance to talking about sex must be challenged and strategies developed to enhance prevention and support. The Alliance for South Asian AIDS Prevention (ASAAP) is the only South Asian organization in Canada with a mandate to provide comprehensive HIV/AIDS education and prevention services in culturally and linguistically appropriate ways. This current project was a collaborative effort between the Community Linked Evaluation AIDS Research (CLEAR) Unit of McMaster University and ASAAP, where cultural sensitivity and respect had important roles.

Objectives: Primary objectives: 1. To compare the depression index between people living with AIDS (PHAs) and those who do not have HIVAIDS; 2. To compare the physical, mental and emotional health indexes of quality of life between PHAs and people without HIV/AIDS.

Methods: Quantitative and qualitative data were collected through a structured questionnaire, compared using t-test or Mann-Whitney test, and analyzed using SPSS 11.0. WHO's Quality of Life Measure (WHOQOL-HIV) and The Centre for Epidemiologic Studies Depression (CES-D) scale was used. Qualitative data was coded and themed. Three groups of participants were recruited (n=81): HIV+ASAAP Clients; HIV-/Not tested ASAAP staff/volunteers; Non-ASAAP HIV/Not Tested Persons.

Results: 71.6% of the entire sample scored ≥ 16, suggesting a clinically significant level of psychological distress. Depression and anxiety emerged as the predominant theme, with racism and stigma. More HIV+ ASAAP Clients identified depression as an issue compared to other groups. There was a significant difference between the three groups on quality of life: on measures of health perception ($p = 0.000$), physical function ($p = 0.009$), role function ($p = 0.000$), social function ($p = 0.002$), health distress ($p = 0.000$) physical health summary ($p = 0.000$), and mental health summary scores ($p = 0.001$). HIV+ ASAAP Clients scored lowest.

Conclusions: A high depression index score was found in all three study groups, as well as themes of depression, racism, discrimination and social issues, with HIV+ ASAAP Clients being most affected. Future goals: with increasing number of South Asians being diagnosed with HIV/AIDS, we need to address the issues faced by HIV+ South Asians living in Canada. Further research using a larger sample to explore levels of depression found among South Asian PHAs is required, as is creating and improving existing culturally sensitive support programs.

Contact Information: Rounak Khan, Tel: 416-599-2727 x223, Email: phasupport@asaap.ca

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HCV TREATMENT INITIATION AND OUTCOMES IN HIV-HCV CO-INFECTED PATIENTS FOLLOWED AT THE OTTAWA HOSPITAL VIRAL HEPATITIS PROGRAM

Meaghan McLaren [3]; Gary Garber [1,2,3]; Curtis Cooper [1,2,3];
1-University of Ottawa; 2-The Ottawa Hospital; 3-Division of Infectious Diseases;

Plain Language Summary: Despite demonstrated effectiveness in HIV-HCV co-infection not all patients start, complete or achieve success with HCV drug therapy. Our analysis suggests that preventing patient lose to follow-up, attention to substance abuse and addressing mental health issues should be the focus of efforts designed to increase HCV treatment uptake and success with currently available therapies

Objectives: Despite demonstrated efficacy in HIV-HCV co-infection not all patients initiate, complete or achieve success with HCV antiviral therapy.

Methods: All HIV-HCV co-infected consults received at The Ottawa Hospital Viral Hepatitis Clinic between June 2000 and September 2006 were identified using a clinical database [SPSS Version 13.0]. A descriptive analysis of primary and contributing factors accounting for why patients did not initiate HCV therapy, why patients interrupted treatment prematurely and therapeutic outcomes was conducted.

Results: 107 HIV-HCV co-infection consults were received. 73 patients (68%) did not initiate HCV therapy. 4 were HCV RNA negative and therefore not co-infected. For the remaining 69, key primary reasons for not initiating HCV therapy included: HIV therapy deemed more urgently needed (n=15; 22%), loss to follow-up (n=13; 19%), candidate deemed unlikely to progress to advanced liver disease (n=11; 16%), and patient refusal (n=7; 10%). Substance abuse (n=16; 23%) and psychiatric illness (n=10; 14%) were concurrent factors contributing to decisions not to treat. 28 of 69 patients (41%) have been lost follow-up. 5 patients not receiving therapy have died.

34 patients received 42 courses of therapy. 27 (64%) rounds of treatment were interrupted prematurely for reasons including: virologic non-response (n=20), psychiatric complications (n=4) and physical side effects (n=3).

Of all treatment recipients, 12 courses of therapy were completed and 3 remain on HCV medication. Seven percent of all referrals (n= 7) achieved a sustained virological response.

Conclusions: Not all HIV-HCV co-infected patients in need of HCV treatment are initiating therapy. Only a minority are achieving success. This analysis suggests that implementation of HIV treatment, patient retention, attention to substance abuse and addressing mental health issues should be the focus of efforts designed to increase HCV treatment uptake and success with currently available therapies.

Contact Information: Curtis Cooper, Tel: 613-737-8924, Email: ccooper@ottawahospital.on.ca

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CREATION OF AN HIV-RELATED FACIAL LIPOATROPHY RESEARCH PROGRAM

Darlene Ellenor [1]; Mona Loutfy [1,2]; Wendy Wobeser [3]; Frank Beninger [2]; Colin Kovacs [1,2];
1-Maple Leaf Medical Clinic, Toronto; 2-University of Toronto, Toronto; 3-Queen's University, Kingston, Ontario, Canada;

Plain Language Summary: Facial lipoatrophy (FLA) is perhaps the most distressing long-term adverse effect of antiretroviral therapy. FLA is characterized by profound visible depletion in facial fat. Because of its connection to HIV infection, FLA may be highly stigmatizing for patients, resulting in feelings of low self-esteem, social withdrawal and forced disclosure of HIV status. The aims of the research program are to: provide a comprehensive literature review of HIV-related FLA pathogenesis, research, and different treatment options; disseminate the findings of the review to the public; carry out FLA research studies; and secure health coverage for the FLA treatment procedures.

Objectives: 1. Review of FLA background, pathogenesis, research and treatments. 2. Disseminate findings of the review and treatment options to patients. 3. Development of FLA quality of life and treatment research protocols. 4. Policy development to guide reimbursement strategies and ensure access to treatment across Ontario.

Methods: Two meetings were held to discuss plans and progress of the Research Program. Participants consisted of people suffering from FLA, other PHAs, HIV-treating physicians, ASOs, CTN and OHTN members from across Canada. A research study is underway to determine the extent of HIV-related FLA in the community, and its effect on psycho-social issues and quality of life in patients from Kingston and Toronto. A proposal to carry out a clinical trial comparing common treatments for FLA was prepared in collaboration with the CTN. Several meetings have taken place with Ontario health policy advisors and their advice will guide the development of applications to secure Ontario health coverage of FLA treatment procedures.

Results: The FLA literature review has been posted on the Maple Leaf Medical Clinic Website (www.mapleleafmedical.com). At the Stakeholders Meetings, participants indicated preferred ways to disseminate treatment information on FLA: information seminars, peer-to-peer support and online discussions, all of which are in the implementation stages. The administration of the FLA quality of life questionnaires to the Kingston and Toronto cohort are almost complete. A letter of intent proposal was submitted to CIHR in October to conduct a clinical trial comparing common treatment procedures for FLA.

Conclusions: A research program on HIV-related FLA was created and is successful due to involvement from all stakeholders across Canada. The outcomes of the FLA Research Program including the literature review and research findings will assist in a proposal to the Ontario government to have HIV-related FLA treatment procedures considered reconstructive therapy and therefore qualify for coverage under the provincial health plan.

Contact Information: Darlene Ellenor, Tel: 416-465-5370, Email: darlene@mapleleafmedical.com

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IS OBESITY AND METABOLIC SYNDROME ASSOCIATED WITH HIV-NAFLD: A COMPARISON BETWEEN HIV-POSITIVE AND HIV-NEGATIVE MALES

Saira S. Mohammed [1]; Ellie Aghdassi [1]; Irving E. Salit [1]; Morris Sherman [1]; Ghazal Avand [2]; Jenny Heathcote [1]; Maha Guindi [1]; Johane P. Allard [1];
1-Department of Medicine, University Health Network; 2-Department of Nutritional Sciences, University of Toronto;

Plain Language Summary: Although obesity and metabolic syndrome (MS) are associated with non-alcoholic-fatty liver disease (NAFLD) in the general population, it is unclear whether a similar association is found in HIV- positive [HIV(+)] patients with NAFLD.

Objectives: To compare liver histology, metabolic, and nutritional parameters between HIV(+) and HIV-negative [HIV(-)] patients with NAFLD.

Methods: Twenty-six HIV(+) and twenty-five HIV(-) male patients with 1.5 times elevated liver enzymes, not taking antioxidant supplements, with alcohol consumption of less than 2 drinks per day and with liver biopsy-proven NAFLD were compared for liver histology (fibrosis staging, steatosis grading, steatosis %), blood biochemistry (glucose, insulin, c-peptide, HbA1c, lipid profile), insulin resistance (IR) using homeostasis method assessment (HOMA), anthropometry (BMI, waist circumference and arm muscle area), % body fat mass % using bioelectrical impedance analysis , dietary intake (7-days food record), and physical activity. Data were compared by unpaired t-test and considered significant if $P<0.05$

Results: The two groups were similar for age, gender, and severity of disease (simple steatosis versus non-alcoholic steatohepatitis). There was no difference in liver histology and HOMA between the two groups. However, HIV(+) patients had a lower BMI (26.3±0.5 VS 30.2±1.0 kg/m², p=0.001) with lower fat mass % (19.4±0.9 VS 22.7±1.2, p=0.026) when compared to HIV(-) patients. Although caloric intake was similar between the two groups, HIV(+) patients had a higher physical activity level (8.3±1.6 VS 4.1±0.8 units of exercise per day, p=0.029) when compared to HIV(-) patients. That was accompanied by a higher intake of vitamin B1 (10.5±3.7 VS 1.4±0.5 mcg/1000 kcal, p=0.017); vitamin B2 (13.4±4.6 VS 1.6±0.7 mg/1000 kcal, p=0.015); vitamin B6 (21.9±9.4 VS 1.0±0.2 mg/1000 kcal, p=0.032); potassium (1474±70 VS 1305±67 mg/1000 kcal, p=0.086); polyunsaturated fatty acids (5.9±0.4 VS 4.9±0.4 %, p=0.093) in HIV(+) patients. Blood triglycerides was significantly higher (3.14±0.39 VS 1.86±0.20 mmol/l, p=0.006) with a trend towards lower HbA1c (0.053±0.002 VS 0.057±0.002, p=0.099), HDL (1.06±0.05 VS 1.20±0.05 mmol/l, p=0.073), and LDL (2.64±0.21 VS 3.15±0.20 mmol/l, p=0.083) in HIV(+) when compared to HIV(-) patients.

Conclusions: Although the severity of liver disease is similar, HIV(+) patients tended to have better diet and exercise habits and less severe obesity and MS-related parameters than HIV(-) patients. This suggests that the metabolic abnormalities present in HIV(+)-NAFLD patients are more likely due to chronic infection and concurrent HIV medications. This study is funded by the Ontario HIV Treatment Network.

Contact Information: Saira Mohammed, Tel: 416-918-3235, Email: saira.mohammed@utoronto.ca

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THE ORAL CONSUMPTION OF URINE: IMPLICATIONS FOR ADVERSE DRUG REACTIONS, INTERACTIONS, AND THE FORMATION OF HIV DRUG RESISTANCE MUTATIONS

Patrick Hooey [1]; Dipen Kalaria [1,2]; Tobin Brown [1]; Elaine Lefaive [1]; Cathy Bailey [1]; Kara Piels [1]; Michael Silverman [1];
1-Positive Care Clinic, Lakeridge Health Whitby; 2-Pharmacy.ca;

Issue: In the arena of HIV/AIDS urine consumption has long been considered a benign practice with respect to health risks as the gaze was upon risk to HIV transmission. In the era of ART the presence of drugs or active metabolites excreted renally may pose significant risks to the consumer of urine.

Background: An HIV positive gay man on an ART regimen containing Tenofovir and with coronary heart disease participated in a “piss party” (group sex where urine is a shared fetish). After consuming approximately one liter of urine he developed an acute coronary syndrome. It is theorized that the person’s or persons’ whose urine he consumed may have taken stimulants (such as amphetamines or cocaine). As he also shared his urine with other participants and, given Tenofovir is excreted unchanged in urine, others were likely exposed to Tenofovir.

Implications: Given the social context of such groups there likely exist other participants with HIV infection; perhaps on ART, awaiting treatment, or unaware of their infection. Other HIV related drugs with significant urinary excretion include; didanosine, lamivudine, emtricitabine, stavudine, zidovudine, sulfonamides, and pentamidine. Ingestion of these may expose participants to risks of drug allergy, drug interactions or viral resistance mutation development. Potential risks are not solely specific to HIV populations or to a group sex context. As a practice urine consumption is more broadly located and socially silenced by hegemonic discourses about sex.

Recommendations: There is a need for investigation of; the nature and prevalence of urine consumption, risks for adverse drug reactions and interactions, and the formation of resistance mutations as a consequence of this practice. Urine consumption needs to be acknowledged, normalized and included in risk assessments for harm reduction. The challenge is to make risk more transparent in the negotiation of choice.

Contact Information: Patrick Hooey, Tel: 905-668-6831 x3120, Email: phooey@lakeridgehealth.on.ca

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THE PSYCHOLOGICAL IMPACT OF BEING SCREENED FOR ANAL CANCER IN HIV-INFECTED GAY MEN

Jill Tinmouth [1]; Irving Salit [2]; Michael Ali [2]; Lindsay Malloch [2]; Marie Sano [2]; Alice Lytwyn [4]; Bill Chapman [2]; Sean Rourke [3]; Linda Rabeneck [1];
1-Sunnybrook Health Sciences Centre, Toronto, Ontario; 2-University Health Network, Toronto, Ontario; 3-St. Michael's Hospital, Toronto, Ontario; 4-McMaster University Medical Centre, Hamilton, Ontario;

Plain Language Summary: HIV-infected gay men are at increased risk of anal cancer. Screening to prevent this cancer may be recommended in this population. We evaluated the psychological impact of being screened for anal cancer in a subset of gay men using questionnaires at various time points in the screening process. While psychologic distress increased from baseline immediately after undergoing the screening, this returned to baseline after receiving results. Participants also felt more positively about screening after receiving results. Persons with greater HIV symptoms were more likely to experience psychological distress.

Objectives: Patients being screened for cancer are at risk for anxiety; anxiety may be correlated with poorer screening compliance. We report the interim results from a study measuring the psychological impact of being screened for anal cancer in HIV-infected gay men.

Methods: Consecutive participants from a large trial of anal cancer screening were approached. At screening, anal Pap smear and high resolution anoscopy (HRA) were performed; after participants received results, treatment was offered where appropriate. Psychological impact was assessed at 3 times: prior to screening (time 1), after screening (time 2), and after receiving results (time 3) using the Impact of Events scale (IES), the Illness Intrusiveness Ratings Scale (IIRS) and the Psychological Consequences Questionnaire (PCQ). Mean differences between time points were tested using repeated measures analysis of variance. Stepwise multivariate linear regression was used to identify predictors of negative psychological impact. Age, CD4 count, viral load, education, HIV symptoms, anal cancer knowledge and baseline anxiety, depression and quality of life were included in the model.

Results: There were 99 participants at time 1, 88 at time 2 and 63 at time 3. Median age and CD4 count were 44 (25 – 62) and 423 (6 – 1260). Fifty four percent had undetectable viral loads and 79% were receiving antiretroviral therapy. Based on the IES, participants had significantly more psychological distress at time 2 than at time 1 or 3 (p=0.002). Based on the PCQ, participants felt more positively about screening at time 3 than at time 2 (p=0.003). HIV symptom score significantly predicted greater negative psychological impact at time 2.

Conclusions: HIV-infected gay men being screened for anal cancer experience more psychological distress in the week after screening but feel more positively about screening after receiving their results. Those with greater HIV symptomatology may require more emotional support during screening.

Contact Information: Jill Tinmouth, Tel: 416-490-5910, Email: jill.tinmouth@sunnybrook.ca

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SCREENING FOR HIV-ASSOCIATED ANAL CANCER (TRACE STUDY): TEST CHARACTERISTICS OF CYTOLOGY AND ONCOGENIC HPV TESTING FOR THE DETECTION OF ANAL DYSPLASIA

Irving Salit [1]; Jill Tinmouth [1]; Alice Lytwyn [2]; Janet Raboud [1]; Sandy Shen [1]; William Chapman [1];
1-University of Toronto, Toronto, ON, Canada; 2-McMaster University, Hamilton, ON, Canada;

Plain Language Summary: Anal cancer occurs at high rates in those with HIV. Screening can be done to detect pre-cancerous changes. The TRACE study detected high rates of advanced pre-cancerous changes by using Pap smears, HPV testing and High Resolution Anoscopy (HRA). Pap smears can be done as screening but HRA is the best method in a high-risk population of HIV-positive men who have had anal intercourse.

Objectives: TRACE is an anal cancer screening study using anal cytology, HPV detection and high resolution anoscopy with directed biopsy. The aim was to determine test characteristics of cytology and oncogenic HPV testing for detection of histologic high-grade squamous intra-epithelial lesions (AIN 2/3).

Methods: Subjects were HIV+ men who had anal receptive intercourse. Cytology was obtained by rotating a swab in the anal canal and by using liquid-based ThinPrepä. Oncogenic HPV detection was done by Hybrid Captureä. Cytology and biopsy specimens were independently assessed by 2 blinded pathologists. The reference standard was the consensus diagnosis of histologic HSIL (AIN 2/3).

Results: Results are presented on 357 subjects (median age=45, median CD4=400, median viral load <50, 90% on HAART). Cytology was abnormal in 61% of subjects: HSIL in 6%, low-grade changes (LSIL) in 40% and ASCUS in 15%. Anal biopsies were abnormal in 71%: AIN 2/3 in 23% and AIN 1 in 48%. The sensitivity (Sn) of any abnormality on cytology to detect AIN 2/3 was 72% (CI 60% - 81%) and the specificity (Sp) was 44% (CI 38% - 50%). Negative predictive value (NPV) was 84%, Positive predictive value (PPV) was 27% and cytology missed 23/81 (28%) AIN 2/3 lesions. HSIL on cytology was not strongly predictive of histologic AIN 2/3. Of 20 patients with HSIL on cytology, only 12 (60%) had AIN 2/3; Sn was 15% (CI 8% - 25%) and Sp was 97% (CI 94% - 99%). Oncogenic HPV was found in 85% of subjects. The presence of HPV had Sn of 100%, Sp of 18% (CI 13% - 24%), NPV of 100% and PPV of 21%. The detection of HPV did not fail to detect any AIN 2/3.

Conclusions: High rates of dysplasia have been detected during anal cancer screening. Oncogenic HPV testing was highly sensitive but had poor specificity in detecting AIN 2/3. A negative HPV test is very useful in excluding AIN 2/3. Abnormal anal cytology was sensitive but not so specific in detecting AIN 2/3.

Contact Information: Irving Salit, Tel: 416-340-3697, Email: irving.salit@uhn.on.ca

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SCREENING FOR HIV-ASSOCIATED ANAL CANCER (TRACE STUDY): CORRELATION OF HPV GENOTYPES, P16 AND E6 TRANSCRIPTS WITH ANAL PATHOLOGY

Jim Mahony [2]; Irving Salit [1]; Sylvia Chong [2]; Janet Raboud [1]; Sandy Shen [1]; Alice Lytwyn [2]; William Chapman [1]; Marie Sano [1];
1-University of Toronto, Toronto, Canada; 2-McMaster University, Hamilton, Canada;

Plain Language Summary: In the TRACE anal cancer screening study, over 400 HIV+ men with a history of anal- receptive intercourse had anal cytology (Pap smears), HPV testing, and high resolution anoscopy with directed biopsy. The objective of this study is to determine whether HPV types, p16 and E6 are correlated with high grade pre-cancerous changes. The HPV 16 viral load and number of HPV genotypes correlated with the presence of high-grade anal pathology in HIV-positive men. E6 and p16 transcripts did not correlate with high-grade anal changes.

Objectives: The objective of this study is to determine whether HPV genotypes, p16 and E6 transcripts are correlated with anal dysplasia in HIV+ men with a history of anal-receptive intercourse.

Methods: In the TRACE anal cancer screening study, over 400 HIV+ men with a history of anal- receptive intercourse had anal cytology (Pap smears), HPV testing, and high resolution anoscopy with directed biopsy. Cytology and biopsy specimens were independently assessed by 2 blinded pathologists. The reference standard was the consensus diagnosis of histologic HSIL (AIN 2/3). HPV genotype was determined by PCR/Line Blot assay. Real-time PCR assays were done in the LightCyclerTM to determine: viral load, E6 transcripts for HPV genotypes 16, 18, and 31 and an assay was developed for p16.

Results: Results are presented on 221 subjects (median age=45, median CD4=400, median viral load <50, 75% on HAART). Cytology was abnormal in 73%: HSIL in 9%, low-grade changes (LSIL) in 50% and ASCUS in 14%. Anal biopsies were abnormal in 64%: AIN 2/3 in 25% and AIN 1 in 39%. HPV was detected in 94% of subjects with multiple HPV types in 92%. Oncogenic HPV types were found in 88%: HPV 16 (38%), HPV 18 (20%), HPV 31(16%), 33 (15%), HPV 53 (20%), HPV 52 (18%), HPV 68 (12%), HPV 56 (12%). Only the following types were significantly associated with high-grade cytology or histology: types 16, 18, 31, 33, 54, 56 and 68. The number of HPV genotypes per biopsy was higher for AIN 2/3 (median=5 types) (Interquartile Range (IQR) 4, 7) than non-AIN 2/3 (median=4; IQR 2, 6) (P=0.001). There were more HPV 16 DNA copies for AIN 2/3 (median 2472; IQR 585, 8666) vs 528 (IQR 105, 2880) (P=.007). When comparing AIN 2/3 to non- AIN2/3, there were no differences in the number of E6 transcripts (for types 16, 18 and 31) and no differences in p16 transcripts.

Conclusions: The HPV 16 viral load and number of HPV genotypes correlated with the presence of high-grade anal pathology (AIN 2/3) in HIV-positive men. E6 and p16 transcripts did not correlate with AIN 2/3.

Contact Information: Irving Salit, Tel: 416-340-3697, Email: irving.salit@uhn.on.ca

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DEMOGRAPHIC AND RISK FACTORS ASSOCIATED WITH ANAL CANCER PRECURSORS IN THE TRACE STUDY

Irving Salit [1]; Jill Tinmouth [1]; Alice Lytwyn [2]; William Chapman [1]; Janet Raboud [1]; Sandy Shen [1]; Marie Sano [1];
1-University of Toronto, Toronto, Canada; 2-McMaster University, Hamilton, Canada;

Plain Language Summary: TRACE is an anal cancer screening study using Pap smears, HPV detection and high-resolution anoscopy (HRA) with directed anal biopsy. Subjects were HIV+ men with a history of anal receptive intercourse. We examined the risks of developing advanced pre-cancerous changes in these subjects. Anal biopsies were abnormal in 66% with high grade changes in 22%. High grade changes were associated with lower CD4's and a history of STD's. In this population we did not uncover other demographic, behavioural or clinical associations with pre-cancerous anal changes.

Objectives: TRACE is an anal cancer screening study using anal cytology, HPV detection and high-resolution anoscopy with directed anal biopsy. The study aim was to determine the test characteristics of cytology and HPV testing for the detection of histologic high-grade anal intra-epithelial neoplasia (AIN 2/3).

Methods: Subjects were HIV+ men with a history of anal receptive intercourse. Anal cytology and HPV specimens were obtained by rotating a swab in the anal canal. Cytology and biopsy specimens were independently assessed by 2 blinded pathologists and the reference standard was the consensus diagnosis of AIN 2/3 from only the first visit. At this visit, subjects completed a questionnaire on demographics, symptoms and risk behaviours. Test results were obtained from the clinical charts. We determined association of these factors with AIN 2/3 by using logistic regression analysis.

Results: Results are presented on 384 subjects (median age=45, HIV+ for 14yrs). Anal biopsies were abnormal in 66%: AIN 2/3 in 22% and AIN 1 in 44%. The CD4 count was lower in those with AIN 2/3 compared to those with AIN 1 or normal histology: medians = 354 (Interquartile Range (IQR) 190, 491) vs 404 (IQR 270, 600) (P=0.03). For CD4 counts>500 the odds ratio (O.R.) for AIN 2/3 was 0.51 (CI 0.28, 0.94) (P=.03). AIN 2/3 was associated with a history of STDs (O.R. 2.74, CI 1.05, 7.17) (P=.04). There was no significant association of AIN 2/3 with HIV viral load, antiretroviral therapy, AIDS, duration of HIV, numbers of casual or steady partners, condom use, age at first intercourse, smoking, injection drug use, anal symptoms, anal surgery or treatment for warts.

Conclusions: In HIV+ men with anal receptive intercourse, AIN 2/3 was frequent and was associated with lower CD4 counts and a history of STDs. In this population we did not uncover other demographic, behavioural or clinical associations with AIN 2/3.

Contact Information: Irving Salit, Tel: 416-340-3697, Email: irving.salit@uhn.on.ca

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CARDIOVASCULAR RISK FACTOR PREVALENCE IN THE CANADIAN HIV VASCULAR STUDY COHORT VERSUS THE MCMASTER HIV CLINIC

Geoffrey So [1]; Kevin Woodward [1]; Sonya Buracond [1]; Philipe El-Helou [1]; Marek Smieja [1];
1-McMaster University, Hamilton, Ontario;

Plain Language Summary: Antiretroviral therapy greatly prolongs life expectancy of HIV-infected people, however, drug-induced hyperdislipidemia may predispose to cardiovascular (CV) disease. Use of lipid lowering agents (LLA), commonly statins, may be initiated in addition to lifestyle changes to control for risk of CV disease; however, factors such as age, male gender, and smoking also increase CV risk. This analysis reveals that these risk factors, with the exception of smoking, are somewhat over-represented in the Canadian HIV Vascular Study compared to the Special Immunology Services (SIS) Clinic, a McMaster University-affiliated HIV centre.

Objectives: The objective of this study was to assess cardiovascular risk factor prevalence among subjects in the Vascular Study compared with our general clinic population.

Methods: We summarized population characteristics in the Vascular Study and a sample of the SIS Clinic by age, gender, smoking status, CD4 lymphocyte count, viral load, lipid profile, and LLA use. We estimated a 10-year percent risk for coronary artery disease (CAD) by Framingham Risk Score and categorized risk levels as low, moderate, or high. Proportions of individuals reaching target lipid levels were calculated.

Results: A total of 594 individuals were enrolled in this study. The Vascular Study had 294 subjects with the following characteristics: mean age (SD) of 46.7 (7.9) years; 90.5% male; and 36.9% current smokers. Median CD4 count (IQR) of 420 (335) and 60.2% viral load (VL) below 50. SIS Clinic characteristics were: mean age of 40.1 (10.3) years; 60.6 % male; and 48.0% current smokers. Median CD4 count of 440 (325) and 45.0% VL <50. Statistically significant differences were observed between populations for age, male gender, smoking, and viral load; all are CV risk factors except the latter. Total:HDL cholesterol ratios (SD) of 5.0 (1.9) and 4.2 (1.4) and frequency of current statin use at 9.9% and 3.2% was observed in the Vascular Study and SIS Clinic respectively and also statistically different. The Vascular Study had 81.3%, 11.9%, and 6.8% persons in low, moderate, and high risk of CAD respectively; compared to 91.7%, 4.7%, and 3.5% in the SIS Clinic. Target Total:HDL cholesterol ratios for low, moderate, high CAD risk was reached in 61.9%, 3.1%, 0% and 77.6%, 3.5%, 1.2% in the Vascular Study and SIS Clinic respectively.

Conclusions: The Canadian HIV Vascular Study Cohort may not be fully representative of CV risk factors and lipid lowering agent use in the general clinic population. The study population is older, predominantly male, and has higher cholesterol levels, but under-represents smokers.

Contact Information: Geoffrey So, Tel: 905-522-1155 x5136, Email: gso@mcmaster.ca

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CD14+CD16+ MONOCYTES IN HIV-ASSOCIATED ATHEROSCLEROSIS

Ines Menjak [1]; Courtney Maskerine [2]; Jennifer Newton [3]; Denis P. Snider [4]; Kenneth L. Rosenthal [3]; Marek Smieja [4];
1-Faculty of Health Sciences, McMaster University; 2-Faculty of Medicine, University of Ottawa; 3-Viral Vaccine Division, Centre for Gene Therapeutics, McMaster University; 4-Pathology and Molecular Medicine, McMaster University, Hamilton, Canada;

Plain Language Summary: Heart disease is an important long-term consequence of anti-retroviral treatment. Monocytes, specifically the CD14+CD16+ pro-inflammatory subset, are key mediators of the process that leads to atherosclerosis. In order to determine how they relate to cardiovascular risk factors and progression of carotid artery thickening, we examined the proportion of these monocytes in HIV-infected patients. Preliminary results show a negative association between the CD14+CD16+ population and baseline estimates of atherosclerosis. In future studies, we will further characterize these monocytes and their effect on progression of atherosclerosis in larger populations.

Objectives: In order to develop a treatment risk model, we aim to further elucidate the pathways that lead to premature atherosclerosis in HIV patients. The objective of this study was to evaluate the association of CD14+CD16+ monocytes to baseline and one year progression of carotid artery thickening.

Methods: Peripheral blood mononuclear cells (PBMC's) were isolated from 30 HIV-positive patients enrolled in the Canadian HIV Vascular Study aged 35 years or older. Flow cytometry analysis using monoclonal antibodies was conducted. We measured carotid artery 12-segment mean maximal intimal medial thickness (IMT) by high-resolution ultrasound at study baseline and at one year. We assessed the association between CD14+CD16+ monocyte percentages and baseline and one-year IMT by linear regression. We also adjusted the analyses for age, smoking, and HDL and total cholesterol measurements.

Results: The patients had CD14+CD16+ monocytes making up 1.84% of the monocyte population (Q1: 1.13%, Q3: 3.88%). The proportion of the CD14+CD16+ population was negatively associated with baseline carotid artery thickness ($p<0.03$). This association remained significant after adjusting for smoking ($p<0.05$), and total:HDL cholesterol ratio ($p<0.03$). Tertile analysis of CD14+CD16+ monocytes also showed a negative association with baseline IMT for patients in the third tertile compared to those in the first tertile ($p=0.006$). These associations remained statistically significant after adjusting for age ($p<0.05$), smoking ($p<0.01$), and total:HDL cholesterol ratio ($p=0.007$). The CD14+CD16+ monocytes were not significantly associated with one year progression of carotid artery thickening.

Conclusions: In our preliminary study of 30 HIV patients, we found an independent negative association between the CD14+CD16+ monocytes and carotid artery thickness. The implications of these results on a treatment effect model will be developed in a larger cohort of patients. We continue to expand enrollment in the study, and measurements of artery thickening will proceed for five years. Other markers of monocyte activation are also being explored in order to further characterize this population.

Contact Information: Ines Menjak, Tel: 905-578-7884, Email: menjaki@mcmaster.ca

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CHARACTERISTICS OF COMPLEMENTARY THERAPIES USE AT A UNIQUE NATUROPATHIC SPECIALTY CLINIC FOR HIV/AIDS

Hal Huff [1]; Deborah Kopansky-Giles [2]; Kevin Challacombe [4]; Bill Merryweather [3]; Anna Travers [3]; Philip Decina [2]; Anthony Tibbles [2]; Robert Hudder [4];
1-Canadian College of Naturopathic Medicine; 2-Canadian Memorial Chiropractic College; 3-Sherbourne Health Centre; 4-Ontario HIV Treatment Network;

Plain Language Summary: Naturopathic medicine utilizes a number of complementary and alternative (CAM) therapies. The Sherbourne Health Centre Community PHA Naturopathic Clinic (CPNC) in Toronto provides a unique setting where naturopathic care and some Natural Health Products (NHPs) are free of charge. We utilized a modified version of the HIV Ontario Observational Database (HOOD 2) to determine demographic and treatment information about Sherbourne's CPNC.

Objectives: We conducted a pilot study to collect information about CAM use at Sherbourne Health Centre Community PHA Naturopathic Clinic through a database analysis.

Methods: We extracted clinical and demographic information collected by the database over a 7-month period in 2005. The database pairs treatment information with specific indications.

Results: The mean age of patients was 44yrs (Range: 26-61), and 82% were male. The mean CD4 count was 417 cells/mm3 (Range: 43-1248). Viral load ranged from 19 to 480,534 copies/ml (Mean: 35,650; Median: 349). The top ten pairings of specific NHP use for indications were: (in order of indication count, IC): intramuscular injection of vitamin B12 for fatigue (IC: n=183), vitamin/mineral combinations for HIV infection (IC: n=70), vitamin C for HIV infection (IC: n=38), acidophilus for diarrhea (IC: n=36), vitamin B12 for HIV infection (IC: n=34), acidophilus for unspecified gastrointestinal symptoms (IC: n=33), N-acetyl cysteine (IC: n=30), acetyl-L-carnitine (IC: n=30), alpha-lipoic acid (IC: n=30), vitamin B1 (IC: n=29) each for peripheral neuropathy. The top ten indications paired to acupuncture at the clinic were (in order): HIV infection (IC: n=161), peripheral neuropathy (IC: n=90), fatigue (IC: n=64), anxiety (IC: n=64), depression (IC: n=51), diarrhea (IC: n=45), erectile dysfunction (IC: n=37), sleep disturbance (IC: n=33), unknown (IC: n=32), and poor appetite (IC: n=32).

Conclusions: CAM use is varied in this unique setting and is used for HIV infection, HIV related illness, and to address adverse effects of HAART and other medications. The effectiveness of complementary therapy use in patients living with HIV is an urgent research priority.

Contact Information: Hal Huff, Tel: 416-498-1255 x392, Email: hhuff@ccnm.edu

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INCREASED RELUCTANCE OF DENTAL HYGIENISTS TO TREAT HIV PATIENTS IN ONTARIO COMPARED WITH OTHER REGIONS OF CANADA

Gillian McCarthy [1,2]; Tom Mara [1]; Larry Stitt [1];
1-Dentistry, Schulich School of Medicine & Dentistry, The University of Western Ontario; 2-Epidemiology and Biostatistics, Schulich School of Medicine & Dentistry, The University of Western Ontario;

Plain Language Summary: A national survey of 5900 dental hygienists in Canada was carried out to investigate dental hygienists' reluctance to treat patients with HIV in different regions of Canada. Rates of refusal to treat HIV patients (%): British Columbia/North West Territories (3); Prince Edward Island/Nova Scotia/New Brunswick/ Newfoundland (8); Alberta/Manitoba/Saskatchewan/Yukon (10); Quebec (9); Ontario (12). Taking into account the effect of year of graduation, continuing education (infection control), dentists' reluctance to treat HIV patients, ethical responsibility to treat patients with HIV and compliance with standard precautions; multiple logistic regression (MLR) confirmed hygienists' refusal to treat HIV patients in Ontario was four times higher than in British Columbia/North West Territories. More research is required to explain regional differences in access to dental hygiene services.

Objectives: The objectives of this national study were to investigate dental hygienists' reluctance to treat patients with HIV in different regions of Canada

Methods: A confidential survey was mailed to a stratified random sample of dental hygienists licensed by their provincial/territorial colleges in Canada (n=5,900) with two follow-up attempts. Weighted data were analyzed using Pearson's chi-square tests and MLR using SPSS.PC+.

Results: Response rate: 56%. Rates of refusal to treat HIV patients were significantly different ($p<0.005$). Rates of refusal to treat HIV patients (%): British Columbia/North West Territories (3); Prince Edward Island/Nova Scotia/New Brunswick/ Newfoundland (8); Alberta/Manitoba/ Saskatchewan /Yukon (10); Quebec (9); Ontario (12). MLR showed hygienists' refusal to treat patients with HIV in Ontario was higher than in any other province (Odds Ratio 4.2, reference group - British Columbia/North West Territories) Other significant variables in the model included: year of graduation, continuing education (infection control), dentists' reluctance to treat HIV patients, hygienists' ethical responsibility to treat HIV patients and compliance with standard precautions.

Conclusions: Discrimination was lowest in British Columbia/North West Territories and highest in Ontario. Hygienists' reluctance to treat patients with HIV was influenced by the dentists that they work with. Continuing education on standard precautions and ethics for both dentists and dental hygienists may improve access to dental hygiene services. These interventions are particularly necessary in Ontario. More research is required to explain regional differences in access to dental hygiene services.

This study was supported by the Canadian Institutes of Health Research.

Contact Information: Gillian McCarthy, Tel: 519-661-2111 x86122, Email: gillian.mccarthy@schulich.uwo.ca

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OCCUPATIONAL EXPOSURES TO HIV AMONG HEALTHCARE WORKERS IN CANADA: A PARTICULAR CONCERN FOR NURSES

Gillian McCarthy [1]; Ken Harris [1,2]; Michael John [1,2]; Larry Stitt [1];
1-Schulich School of Medicine & Dentistry, The University of Western Ontario.; 2-London Health Sciences Centre;

Plain Language Summary: National surveys of random, stratified samples of dentists (n=6440), surgeons (n=4000), dental hygienists (n=5900); and a random sample of Ontario nurses (n=5810) were conducted. Known HIV exposures in the previous year were reported by 0.5% (dentists), 0.4% (hygienists) and 0.9% (surgeons). 8.2 % (nurses) and 1.7% (hygienists) reported exposure to HIV at any time. This confirms low rates of occupational exposure to HIV among healthcare-workers in Canada. The largest population -nurses had the greatest frequency of exposure. Crude estimates of occupationally-acquired HIV (OAH) indicated that it is a rare event (approximately 20 nurses in Ontario since the epidemic began) - far higher than reports from Health Canada, but much lower than estimates from Workers' Compensation Boards of Canada (WCBC): >200 nurses in Canada since 1998. More research and interventions to reduce occupational exposures are required.

Objectives: To investigate occupational exposures to HIV reported by dentists, surgeons, and dental hygienists in Canada and nurses in Ontario.

Methods: National, confidential, mailed surveys of random, stratified samples of dentists (n=6440), surgeons (n=4000), and dental hygienists (n=5900); and a random sample of nurses in Ontario (n=5810) were conducted. SPSS/PC+ was used for weighted analyses. Extrapolation provided crude estimates of OAH to compare with estimates from Health Canada and WCBC.

Results: The response rates were 66% (dentists), 56% (surgeons, hygienists), and 60% (nurses). Known HIV exposures in the previous year were reported by 0.5% (dentists), 0.4% (hygienists) and 0.9% (surgeons). In addition, 8.2 % (nurses) and 1.7% (hygienists) reported exposure to HIV at any time. High-risk exposure was reported by 2.0% (dentists), 6.5% (surgeons) and 1.4% (hygienists) in the previous year; and 22% (nurses) and 4% (hygienists) -ever. Extrapolation indicated that >20 nurses in Ontario may have occupationally-acquired HIV infection since the start of the epidemic. WCBC reports >200 nurses were compensated for OAH since 1998.

Conclusions: These results confirm low rates of occupational exposure to HIV among HCWs in Canada. These may be underestimates because of reluctance to report exposure and frequent uncertainty about the serostatus of the source. Given the low infectivity of HIV, the efficacy of HAART and the availability of post-exposure prophylaxis; the risk of occupationally-acquired HIV infection is very small. However, published reports underestimate the problem particularly in nurses.

These studies were supported by the Ontario HIV Treatment Network, Health Canada, Medical Research Council of Canada and the Canadian Institutes for Health Research. Gillian McCarthy had a Career Scientist Award from Ontario MOHLC 1992-2002.

Contact Information: Gillian McCarthy, Tel: 519-661-2111 x86122, Email: gillian.mccarthy@schulich.uwo.ca

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RELUCTANCE OF ONTARIO NURSES TO CARE FOR PATIENTS WITH HIV/AIDS

Gillian McCarthy [1]; Larry Stitt [1]; Michael John [2]; Cornell Driessen [1]; Somaya Eid[1];
1-Schulich School of Medicine & Dentistry, The University of Western Ontario; 2-Clinical Microbiology, London Health Sciences Centre;

Plain Language Summary: A mailed, confidential survey of a random sample of 5810 nurses in Ontario was used to investigate reluctance to care for patients with HIV/AIDS. 60% responded. Data analyses included Pearson's chi-square test and multiple logistic regressions. Of respondents, 10% were reluctant and 8% would refuse care for HIV patients. Highest refusal rates were reported by nurses 60years or more (18%); casual full-timers (14%); those working outside hospitals (10%) – especially nursing homes (15%), in long-term care (13%), rehabilitation (11%), gerontology, maternal/newborn or home-care (10%); using additional infection control measures for HIV patients (10%). Best predictors of refusal were age of 60 years or more; fear of HIV infection; non-compliance with standard precautions for infection control and exaggerated perception of risk after an HIV-contaminated needlestick. Educational interventions may improve access to care-especially in long-term, chronic and maternal/newborn care.

Objectives: To investigate reluctance to care for patients with HIV/AIDS among registered nurses in Ontario.

Methods: A confidential survey was mailed to a random sample of 5810 nurses in Ontario, stratified by area of primary responsibility with two follow-up attempts. Weighted data were analyzed using Pearson's chi-square test and multiple logistic regressions (SPSS/PC+).

Results: Response rate: 60%. Respondents reported: reluctance to care for patients with HIV (10%) or AIDS (11%); refusal to provide care (8%); that their families would be concerned if they cared for patients with HIV/AIDS (71%); concerns about increased personal risk (65%); they had an ethical responsibility to care for patients with HIV (89%). Highest refusal rates were reported by nurses 60 years or more (18%) casual full-timers (14%); those working outside hospitals (10%) – especially nursing homes (15%), in long-term care (13%), rehabilitation (11%), gerontology, maternal / newborn or home-care (10%); using additional infection control measures for HIV patients (10%); or who believed the risk of HIV infection from an HIV-contaminated needlestick is 50% or higher (14%). Significantly different ($p<0.01$). Best predictors of refusal:

- Age of 60 years or more;
- Concerns related to personal risk;
- Non-compliance with standard precautions;
- Exaggerated perception of risk after an HIV-contaminated-needlestick.

Conclusions: 8**%** of nurses would refuse care for HIV patients. Educational interventions focusing on ethics, standard precautions, occupational safety, and knowledge of HIV are required to improve access to nursing care. As a priority, these interventions need to be directed at casual full-timers; or those working outside hospitals, or in nursing homes, long-term care, rehabilitation, gerontology, maternal/ newborn or home-care.

This study was supported by the OHTN.

Contact Information: Gillian McCarthy, Tel: 519-661-2111 x86122, Email: gillian.mccarthy@schulich.uwo.ca

231b

HBV IMMUNIZATION, POST-IMMUNIZATION SEROLOGY AND IMMUNITY AMONG HEALTHCARE WORKERS IN CANADA

Gillian M. McCarthy [1]; Michael John [2]; Ken Harris [1,3]; Larry Stitt [1]; Tom Mara [1];
1-Schulich School of Medicine & Dentistry, The University of Western Ontario; 2-Clinical Microbiology, London Health Sciences Centre; 3-Surgery, London Health Sciences Centre;

Plain Language Summary: Healthcare workers (HCWs) who perform invasive procedures may be exposed to blood and are vulnerable to infection with bloodborne viruses. Hepatitis B virus (HBV) is the most infectious but immunization is available. This study investigated HBV immunization, post-immunization serology and known immunity to HB among HCWs in Canada. National, mailed surveys of random samples of dentists (n= 6440), surgeons (n=4000), and dental hygienists (n=5900); and a provincial survey of nurses in Ontario (n=5810) were carried out. The response rates were 56-66%. HBV immunization was reported by 90% of dentists, 87% of surgeons, 81% of nurses, 98% of hygienists. HB antibody testing was reported by 72% of dentists, 86% of surgeons, 87% of nurses, 70% of hygienists. Immunity to HBV was reported by 14% of surgeons, 51% of nurses and 59% of hygienists. Despite relatively high immunization rates and recommendations that HCWs who do invasive procedures should know their HBV status, many HCWs do not know if they are immune to HBV. Interventions are necessary to clarify HCWs' immune status and reduce potential vulnerability to HBV. More research is also required.

Objectives: To investigate HBV-immunization, post-immunization serology, and knowledge of adequate antibody-HBs levels in HCWs in Canada.

Methods: Confidential surveys were mailed to stratified, random samples of dentists (n=6440), surgeons (n=4000), nurses (n=5810) and hygienists (n=5900), with at least two follow-up mailings. Data were weighted to allow for nonresponse and the probability of selection, and analyzed using SPSS/PC+.

Results: The response rates were: 66% (dentists), 60% (nurses) and 56% (surgeons and hygienists).

	Dentists (%)	(Nurses (%)	Surgeons (%)	Hygienists (%)
HBV immunization:	90	81	87	98
Post-immunization serology:	72	87	86	70
Anti-HBs titer greater than 10 mIU:	no data	51	14	59
Naturally-acquired immunity:	3	2	4	<1

Conclusions: Dental workers reported the highest rates of HBV immunization and lowest rates of post-immunization serology. Surgeons reported the lowest awareness of adequate anti-HBs. Despite HBV immunization rates of 80-98%, it appears that many HCWs do not know their HBV status and may be vulnerable to HBV. Interventions are necessary to clarify HCWs' immune status and reduce potential vulnerability to HBV. More research is also required. These studies were supported by grants from the Ontario HIV Treatment Network, Health Canada, Medical Research Council of Canada and the Canadian Institutes for Health Research. Gillian McCarthy had a Career Scientist Award from Ontario MOHLC 1992-2002.

Contact Information: Gillian McCarthy, Tel: 519-661-2111 x86122, Email: gillian.mccarthy@schulich.uwo.ca

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PREDICTORS OF HBV IMMUNIZATION IN DENTISTS, DENTAL HYGIENISTS, SURGEONS AND NURSES IN CANADA

Gillian McCarthy [1]; Michael John [1,2]; Ken Harris [1]; Larry Stitt [1]; Tom Mara [1];
1-Schulich School of Medicine & Dentistry; 2-Clinical Microbiology, London Health Sciences Centre;

Plain Language Summary: National, random samples of 6440 dentists, 4000 surgeons, and 5900 dental hygienists; and 5810 nurses in Ontario were surveyed to investigate predictors of HBV immunization. Response rates were 56-66%. Nurses reported the lowest HBV immunization rate (81%). The best predictors of HBV immunization included younger age (all groups), previous treatment of known-HBV patients, relevant continuing education and use of recommended infection control practices. Continuing education promoting HBV immunization and standard precautions may reduce the potential for cross-infection and improve access to care for patients with HBV and (HCV or HIV). These interventions should be a priority for older healthcare workers and nurses.

Objectives: To identify predictors of HBV immunization of healthcare workers in Canada

Methods: Stratified random samples of dentists (n=6440), surgeons (n=4000), nurses (n=5810) and dental hygienists (n=5900) were surveyed using confidential, mailed questionnaires with at least two follow-up attempts. Weighted data were analyzed using Pearson's chi-square analyses and multiple logistic regression (SPSS/PC+).

Results: Response rates were 56-66%. HBV-immunization reports: 90%-dentists, 81%-nurses, 87%-surgeons, 98%-hygienists.
Significant predictors of HBV immunization ($p < 0.05$) were: Dentists: younger age, more patients seen per day, appropriate use of masks, continuing education on infection control, and treatment of known-HBV patients in the past year. Surgeons: younger age, treatment of known-HBV patients in last year, use of protective uniform to protect against splatter in the clinic / office, treating all patients as if they are infected with HBV/HIV/HCV**.** Nurses: younger age, continuing education on hepatitis viruses, willingness to care for patients with HBV, history of occupational exposure, using a post-exposure protocol, double gloving, and avoiding recapping of needles. Dental hygienists: Graduation after 1980, age < 30years; working fewer years, or > 20 hours/week; use of protective eyewear and continuing education on hepatitis viruses.

Conclusions: The best predictors of HBV immunization included younger age (all groups), previous treatment of known-HBV patients, relevant continuing education and recommended infection control practices. Educational interventions promoting HBV immunization and standard precautions may reduce the potential for cross-infection and improve access to care for patients with HBV – this should be a priority for older healthcare workers and nurses.

Acknowledgements: Funding for these studies was provided by Ontario HIV Treatment Network, Health Canada, Medical Research Council and Canadian Institutes for Health Research. Dr. McCarthy had a Career Scientist Award from Ontario MOHLC 1992-2002.

Contact Information: Gillian McCarthy, Tel: 519-661-2111 x86122, Email: gillian.mccarthy@schulich.uwo.ca

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OCCUPATIONAL EXPOSURES TO HBV AND HCV AMONG DENTISTS, SURGEONS, NURSES AND DENTAL HYGIENISTS IN CANADA

Gillian McCarthy [1]; Ken Harris [1,3]; Michael John [2]; Larry Stitt [1];
1-Schulich School of Medicine & Dentistry, The University of Western Ontario, London, Canada.; 2-Clinical Microbiology, London Health Sciences Centre.; 3-Surgery, London Health Sciences Centre, London, Canada.;

Plain Language Summary: Occupational exposures to hepatitis B virus (HBV) and hepatitis C virus (HCV) were investigated using national mailed surveys of random samples of 6440 dentists, 4000 surgeons, 5900 dental hygienists; and 5810 nurses in Ontario. Response rates were 56-66%. On average, nurses reported 1.3 exposures to HBV and 1.1 exposures to HCV ever. Known exposure to HBV in the previous year was reported by 0.8% (15% uncertain) of dentists. Surgeons reported exposure to HBV (1.4%, 24% uncertain) and HCV (2.3%, 27% uncertain); and dental hygienists reported exposure to HBV (0.7%) and HCV (0.9%) in the previous year. These results confirm that HCV has become a greater concern for healthcare workers than HBV – especially as there is no vaccine. In addition, co-infections of HBV, HCV, or HIV may be present. Post-exposure counseling, testing and appropriate prophylaxes are recommended for high risk exposures.

Objectives: To investigate reports of occupational exposures to hepatitis B virus (HBV) and hepatitis C virus (HCV) among healthcare workers (HCWs) in Canada.

Methods: National surveys of random samples of 6440 dentists, 4000 surgeons, 5900 dental hygienists; and 5810 nurses in Ontario were administered with at least two follow-up attempts. SPSS/PC+ was used for analysis.

Results: The response rates were 66% (dentists), 56% (surgeons and hygienists), and 60% (nurses). Known exposure to HBV in the previous year was reported by 0.8% (15% uncertain) of dentists.
Among surgeons, 1.4% (24% uncertain) reported HBV exposure, and 2.3% (27% uncertain) reported exposure to HCV in the previous year.
Among dental hygienists, 0.7% reported exposure to HBV and 0.9% reported exposure to HCV in the previous year.
Nurses reported means of 1.3 known exposures to HBV, and 1.1 known exposures to HCV (ever).

Conclusions: Reports of occupational exposures may be underestimates because of reporting bias and/or uncertainty about the serostatus of the source. The rates of known exposure to HCV in the previous year were higher than exposure rates to HBV. These results confirm that occupational exposures to HCV have become a greater concern for HCWs than exposures to HBV –especially as there is no vaccine. In addition, co-infections of HBV, HCV, or HIV may be present – post-exposure counseling, testing and appropriate prophylaxes are recommended for high risk exposures. Exposures to HIV have been discussed in a separate abstract.

Acknowledgements: Ontario HIV Treatment Network, Health Canada, Medical Research Council and Canadian Institutes for Health Research. Dr. McCarthy had a Career Scientist Award from Ontario MOHLC 1992-2002.

Contact Information: Gillian McCarthy, Tel: 519-661-2111 x86122, Email: gillian.mccarthy@schulich.uwo.ca

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UPREGULATION OF INTERFERON-DEPENDENT STAT1 ACTIVATION AND APOPTOSIS IN MONOCYTES FROM HIV+ PATIENTS

Abdulkarim Alhetheel [1,4]; Yuriy Yakubtsov [1,4]; Khaled Abdkader [1,4]; Nadia Sant [1,4]; Jonathan Angel [4,5]; Ashok Kumar [1,2,3,4]; Francisco Diaz-Mitoma [1,2,3,4]; Marko Kryworuchko [1,2,3,4];
1-Infectious Disease and Vaccine Research Centre, Children's Hospital of Eastern Ontario (CHEO) - Research Institute; 2-Division of Virology, CHEO; 3-Department of Pathology and Laboratory Medicine, University of Ottawa; 4-Department of Biochemistry, Microbiology and Immunology, University of Ottawa; 5-Division of Infectious Diseases, Ottawa Hospital - General Campus, Ottawa, Ontario, Canada;

Plain Language Summary: Monocytes/macrophages are cells capable of killing microbial pathogens and play a critical role in inflammatory and immune responses. Their activity is strictly controlled by growth factors of the immune system called cytokines. We studied whether the impairment of monocyte/macrophage function in HIV-positive patients may be the result of defects in their responsiveness to cytokines.

Objectives: Cytokines (IFN-γ, IL-10, GM-CSF, and IL-4) regulate the phagocytic, anti-microbial, and antigen presenting function of monocytes/macrophages in large part via the Janus kinase (Jak) / Signal Transducer and Activator of Transcription (STAT) signal transduction pathway. Therefore, our objectives were to evaluate cytokine-dependent Jak/STAT signaling in monocytes from HIV+ patients and determine the biological impact and molecular mechanisms responsible for any alterations in signaling observed.

Methods: Patient study groups included HIV-negative controls, and two groups of patients chronically infected with HIV (individuals off therapy for > 6 months and those on sustained antiretroviral therapy (ART) for > 1 yr). The specific intracellular activation of STAT1, 3, 5, and 6 proteins by cytokines IFN-γ, IL-10, GM-CSF, and IL-4, respectively, was measured by flow cytometry, as was surface expression of IFN-γ receptors. Secretion of chemokines and the apoptosis-inducing ligand TRAIL was measured by cytometric bead array and ELISA, respectively. Interferon Regulatory Factor (IRF)-1 mRNA expression was measured by real-time RT-PCR while apoptosis was determined by propidium iodide staining and flow cytometry.

Results: In contrast to the STATs induced by IL-10, GM-CSF, and IL-4, STAT1 activation by IFN-γ was upregulated in HIV+ patients off therapy compared to HIV-negative controls and patients on sustained ART. However, IFN-γ receptor (R1 & R2) expression levels were not affected, suggesting downstream signaling alterations. The expression of a number of IFN-γ / STAT1 responsive genes revealed a differential response. Unlike the chemokines (CXCL9, CXCL10) and TRAIL, only IRF-1 gene expression followed a pattern similar to that of STAT1 activation. In addition to its capacity to enhance phagocytic activity, IFN-γ and STAT1 are capable of inducing apoptosis. Interestingly, spontaneous and IFN-γ-induced monocyte apoptosis was found to be elevated in HIV+ patients compared to HIV-negative controls. However, unlike in controls, IFN-γ-induced apoptosis could not be inhibited by IL-10 in the HIV+ patients tested.

Conclusions: Amplification of IFN-γ-induced STAT1 activation and apoptosis in HIV+ patient monocytes as well as the resistance of these cells to the protective effects of IL-10 are novel findings that may explain, at least in part, the functional impairment observed in these cells through the course of the disease.

Contact Information: Marko Kryworuchko, Tel: 613-737-7600 x2312, Email: MKryworuchko@cheo.on.ca

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THE EFFECT OF CYTOKINES AND IN VITRO HIV INFECTION ON CD127 EXPRESSION ON THYMOCYTES

Charlene Young [1,3]; Jonathan Angel [1,2,3];
1-Ottawa University; 2-Department of Infectious Disease, Ottawa Hospital; 3-Ottawa Health Research Institute;

Plain Language Summary: Thymocytes are a subset of cells that play a major role in host immunity. The cytokine interleukin-7 (IL-7) and its receptor CD127 are essential for the normal generation of thymocytes. HIV infection has been demonstrated to alter normal thymocyte function. We hypothesis that impaired thymic function in HIV infection is due to a decrease in CD127 expression on developing thymocytes

Objectives: Thymic function is altered in HIV infection leading to a dysregulation of the thymic epithelial network, reduced thymic output and therefore an impaired naïve T-cell pool. The IL-7/IL-7R (CD127) signaling pathway is critical for the maturation and differentiation of thymocytes. Since CD127 expression is decreased on circulating CD8 cells in HIV infection we hypothesize that impaired thymic function in HIV infection is due to a decrease in CD127 expression on developing thymocytes.

Methods: Thymii were obtained from children undergoing elective cardiac surgery and thymocytes were isolated using established methods. Thymocytes were cytokine treated with IL-7 (0-5000 pg/ml), IL-4 (1-1000ng/ml), IFN-□ (0-100 ng/ml) or GM-CSF (0-200 ng/ml) or HIV infected at an MOI of 0.001 with an X4 viral strain (HIVIIIB), a dual tropic viral strain (HIVCS204) or a replication incompetent viral strain (HIV8E5) prior to co-culture with allogeneic thymic epithelial cells. Expression of CD127 was determined by flow cytometry on the thymocyte subset representing the various developmental stages of T-cell maturation: triple negative CD3-CD4-CD8-(TN), immature single positive CD3-CD4+CD8-(ISP4), double positives CD3-CD4+CD8+(CD3-DP), CD3+CD4+CD8+ (CD3+DP) and single positive cells CD3+CD4+CD8-(SP4) and CD3+CD4-CD8+(SP8).

Results: Within the thymus the most prominent sub-population is the DP CD3-CD4+CD8+ subset. All thymocyte subsets express CD127, however to varying degrees, where SP8 express CD127 to the greatest degree. IL-7 decreased CD127 expression on all subsets. IL-4 resulted in a decrease in CD127 on CD3+DP SP4 and SP8 cells. However IFN-□ and GM-CSF treatment had no significant effect on CD127 expression. Thymocyte infection with HIVIIIB resulted in decreased expression of CD127 on cells within the SP4 and SP8 subsets but not on cells of the CD3+DP subset. In contrast, in thymocytes infected with HIV8E5 or HIVCS204 no downregulation of CD127 expression was seen.

Conclusions: CD127 expression on thymocytes varies with the different stages of development and is downregulated by HIVIIIB as well as IL-7 and IL-4 suggesting that HIV may play a role in impaired thymic function by altering the IL-7 responsiveness of thymocytes. These results may provide some insight into how HIV infection results in impair thymic function.

Contact Information: Charlene Young, Tel: 613-737-8160, Email: cyoung@ohri.ca

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HIV-1 SPECIFIC T CELLS ACCUMULATE IN THE LIVER IN HCV/HIV-1 CO-INFECTION

Bahareh Vali [1]; Feng Yun Yue [1]; David Wong [2]; Jenny Heathcote [2]; Colin Kovacs [3]; Mona Loutfy [2]; Robin Gray [4]; Roberta Halpenny [2]; Mario, A. Ostrowski [1,4];
1-Department of Immunology, University of Toronto, Toronto, ON, Canada; 2-University Health Network, Toronto, Canada; 3-Canadian Immunodeficiency Research Collaborative, Toronto, Canada; 4-St. Michael's Hospital, Toronto, Canada;

Plain Language Summary: Co-infection with human immunodeficiency virus (HIV-1) and hepatitis-C virus (HCV) is frequent given the shared routs of transmission. There is accelerated progression of liver damage in co-infected individuals compared to HCV mono-infected patients and the underlying immunopathogenic mechanisms are currently unclear. Liver inflammation is due to local immune responses from a subset of immune cells known as T cells, to destroy HCV-infected liver cells. So it is paradoxical that liver damage progresses faster in HIV-1 patients with suppressed immune system. In co-infected individuals, HCV specific T cells are recruited to the liver. Our findings demonstrate that significant numbers of HIV-1 specific T cells are also deposited in the liver of dual infected individuals and this may promote liver inflammation.

Objectives: We hypothesize that HIV-1 specific T cells accumulate in the liver of co-infected individuals, promoting liver inflammation through bystander activation. Our objective was to characterize intra-hepatic HCV and HIV-1 specific CD4 and CD8 T cell immune responses in HCV/HIV-1 co-infected versus HCV mono-infected individuals.

Methods: Liver biopsies were performed pre-treatment in 6 HCV mono-infected and 17 HCV/HIV-1 co-infected individuals. Ex vivo intra-hepatic lymphocytes were stimulated overnight with peptide pools spanning the entire genome of HIV-1 and HCV, and then assessed for the production of IFNg and TNFa by intracellular cytokine flow cytometry.

Results: Similar numbers of lymphocytes were present in HCV versus HCV/HIV-1 biopsies. However, lymphocytes from HCV/HIV-1 had fewer % CD4 cells. We found similar frequencies of HCV specific CD4 and CD8 T cells producing IFNg and TNFa in HCV versus HCV/HIV-1. In co-infected individuals we also observed the presence of HIV-1 specific CD4 and CD8 T cells producing IFNg and TNFa, similar in frequency to those that are HCV specific. In the HCV/HIV-1 biopsies the mean % of HIV-1 specific CD4 cells producing IFNg and TNFa were 7.0% and 11.0% of total CD4s, and the mean % of HIV-1 specific CD8 cells producing IFNg and TNFa were 6.0% and 9.0% of total CD8s. Comparison of the percentage of total virus specific hepatic T cells (HIV-1 plus HCV) producing the fibrogenic cytokine TNFa in both cohorts reveals significantly greater frequencies in the co-infected individuals, indicating a more intense inflammatory activity.

Conclusions: Significant numbers of HIV-1 specific T cells are deposited in the liver of co-infected individuals, resulting in an increase in intra-hepatic viral specific TNFa responses. This mechanism may explain the faster progression of HCV disease in HCV/HIV-1 co-infected individuals.

Contact Information: Bahareh Vali, Tel: 416-978-1605, Email: bahareh.vali@utoronto.ca

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THE RATE OF CD127 DECAY FROM THE SURFACE OF CD8 T-CELLS IS ENHANCED BY THE HIV TAT PROTEIN

Mark McVey [1,2]; Elliott Faller [2,3]; Paul MacPherson [2,3,4];
1-Faculty of Medicine, University of Toronto, Toronto, Canada; 2-Ottawa Health Research Institute, Ottawa, Canada; 3-Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Canada; 4-Division of Infectious Diseases , The Ottawa Hospital, Ottawa, Canada;

Plain Language Summary: Interleukin-7 (IL-7) signaling is essential for CD8 T-cell survival, proliferation and cytolytic function. Previously we have shown the HIV Tat protein down regulates expression of the IL-7 receptor alpha-chain (CD127) on CD8 T-cells in a dose- and time-dependent fashion. Here we show that Tat causes this down regulation by enhancing the rate at which CD127 is lost from the cell surface.

Objectives: Since the HIV Tat protein does not appear to alter the rate of CD127 gene transcription, we hypothesized Tat down regulates CD127 via a post-translational mechanism.

Methods: CD8 T-cells were purified from healthy HIV-seronegative volunteers and incubated with purified Tat protein (10 µg/ml), cycloheximide (100 µM), or lactacystin (10 µM) or combinations thereof for up to 72 hours. Surface CD127 expression was measured by flow cytometry.

Results: CD127 decays from the surface of resting CD8 T-cells at a very slow rate with a half-life of more than 72 hours. This rate of decay is enhanced by Tat protein which reduces the receptor half-life on the cell membrane to approximately 20 hours. As shown previously, when Tat is removed from the media CD127 rapidly recovers on the cell surface. This recovery does not occur if the cells are treated with cycloheximide indicating recovery is dependent on new CD127 synthesis. Inhibition of proteosome function with lactacystin reduced the rate at which Tat was able to induce CD127 loss from the cell surface. These data suggest that Tat may down regulate surface expression of CD127 by increasing the rate at which the receptor is internalized and targeted for degradation. Pulse chase experiments are currently being conducted to confirm these findings and to determine whether CD127 is internalized or shed from the cell surface.

Conclusions: Tat down regulates IL-7 receptor expression on CD8 T-cells by increasing the rate at which CD127 is lost from the cell surface. By decreasing IL-7 signaling, Tat likely contributes to CD8 T-cell anergy and impaired cell mediated immunity in HIV infected individuals.

Contact Information: Mark McVey, Tel: 416-575-1600, Email: mcveymj@yahoo.ca

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TRANSCRIPTION OF THE CD127 GENE IS DOWN REGULATED BY IL-7 IN CD8 T-CELLS

Juzer Kakal [1,2]; Ritesh Kumar [1]; Paul MacPherson [1,2,3];
1-Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Canada; 2-Department of Molecular Medicine, Ottawa Health Research Institute, Ottawa, Canada; 3-Division of Infectious Diseases, The Ottawa Hospital, Ottawa, Canada;

Plain Language Summary: Expression of the interleukin (IL)-7 receptor is tightly regulated throughout the life-span of a CD8 T-cell. We and others have shown that binding of IL-7 to its receptor results in a down regulation of the IL-7 receptor alpha-chain (CD127) on the cell surface. Our lab has also shown that the HIV-1 Tat (Tat) protein similarly down regulates CD127 surface expression. Here we show that IL-7 decreases CD127 gene transcription while HIV-1 Tat has no effect on mRNA levels.

Objectives: To determine whether IL-7 and/or HIV-1 Tat effect CD127 gene transcription.

Methods: CD8 T-cells were isolated from healthy HIV seronegative volunteers and incubated in RPMI 1640 plus 20% FCS either alone or supplemented with IL-7 (10 ng/ml) or purified Tat protein (10 ug/ml) for 24 hours. Total RNA was harvested and CD127 mRNA transcripts were quantified using Real Time PCR normalizing to RPS18 expression. Transcripts encoding CD127 were quantified using a forward primer spanning the junction of exons 2 and 3 as all forms of the protein contain these sequences. Since secreted CD127 has exon 6 spliced out, transcripts encoding this form of the protein were quantified using a forward primer spanning the splice site joining exons 5 and 7.

Results: There was no change in the level of CD127 transcripts in CD8 T-cells incubated with purified Tat protein for 24 hours. Neither the level of total transcripts nor the level of mRNA encoding the secreted form of the protein was different compared to media control. In contrast, CD8 T-cells treated with IL-7 showed a 3-fold decline in the level of total CD127 transcripts. Interestingly, the relative decrease in mRNA encoding the secreted form of the protein was 1.7-fold suggesting IL-7 may induce a shift towards secreted CD127 protein.

Conclusions: While Tat specifically down regulates the expression of CD127 on the surface of CD8 T-cells, it does not appear to do so by suppressing CD127 gene transcription or by biasing splicing to the secreted form of the protein. IL-7 on the other hand strongly down regulates CD127 gene transcription, as has been shown in mice. Interestingly while the total level of CD127 transcripts declined in response to IL-7, the relative decline in transcripts encoding the secreted form of CD127 was less suggesting IL-7 may down regulate CD127 expression at both the transcriptional level and by biasing splicing to favour secreted CD127 protein.

Contact Information: Juzer Kakal, Tel: 613-737-8160, Email: jkakal@ohri.ca

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GAMMA-CHAIN RECEPTOR CYTOKINES DOWN-REGULATE IL-7 RECEPTOR-ALPHA (CD127) EXPRESSION ON CD8+ T-CELLS AND DIFFERENTIALLY AFFECT CELL CYCLING OF ACTIVATED CD8+CD127+ AND CD8+CD127- T-CELLS

Angela M. Crawley [1]; Tanya Katz [2]; Karl Parato [1]; Jonathan B. Angel [1,2];
1-Ottawa Health Research Institute; 2-University of Ottawa;

Plain Language Summary: Infection with HIV is initially controlled by a strong CD8+ T-cell response, however, progressive disease results in a loss of CD8+ T-cell cytotoxic activity. In untreated HIV+ patients, the expression of CD127 on CD8+ T-cells is decreased while antiretroviral therapy nearly restores expression. Interleukin-7, a member of a family of gamma-chain receptor cytokines (IL-2, -4, -9, -15, -21), is critical for T-cell development and maintains the number and survival of T-cells. The role of these cytokines in the regulation of CD127 and their role in cell division of cells expressing or lacking CD127 has not been described.

Objectives: The regulation of CD127 surface expression and secretion by CD8+ T-cells by gamma-chain receptor cytokines will be described and compared to the previously observed effects IL-7 which downregulates surface CD127 and induces receptor secretion. Secondly, the role of these cytokines in regulating the cell cycling and resistance to apoptosis of isolated CD8+CD127+ and CD8+CD127- T-cells will be described.

Methods: Isolated human CD8+ T-cells will be cultured with increasing concentrations of IL-2, -4, -9, -15, -21 for 24, 48 and 72 hours and the expression of surface CD127 will be assessed by flow cytometry. The secretion of CD127 by these CD8+ T-cells into culture supernatants will be quantified using a CD127-specific competitive ELISA after 24 hours of culture. Cell division of isolated CD8+CD127+ and CD8+CD127- T-cells will be analyzed by flow cytometry after the cells have be stained with CFSE and cultured with mitogen (PHA) and increasing concentrations of cytokines. The expression of Bcl-2 was also assessed in parallel, by flow cytometry.

Results: Most gamma-chain cytokines downregulate surface CD127 expression by CD8+ T-cells. Responses varied in magnitude and time dependency. Effector-memory-like cells (CD127-CD45RA+) divided more frequently in response to IL-4 + PHA while effector cells (CD127-CD45RA-) did not. The reverse was true for cells incubated with IL-15. Memory cells (CD127+CD45RA-) divided frequently in response to either IL-4 or IL-15. There was significantly more Bcl-2 expression in CD8+CD127+ T-cells compared to CD8+CD127- T-cells.

Conclusions: Thus, most human gamma-chain receptor cytokines share a common function in regulating surface CD127 expression, however they do not all induce receptor secretion. This research is the first to describe cytokine responses of isolated CD8+CD127+ and CD8+CD127- T-cells and suggests subset-specific responses that may influence CD8+ T-cell differentiation. This research may contribute to the design of therapies enhancing CD8+ T-cell function and controlling HIV viral replication.

Contact Information: Angela Crawley, Tel: 613-737-8673, Email: acrawley@ohri.ca

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IL-23, IL-27 EXPRESSION IN DENDRITIC CELLS AND THE EFFECTS OF HIV

Andreane Chenier [1,2]; Jonathan Angel [1,2,3];
1-Department of Biochemistry, Microbiology and Immunology, University of Ottawa; 2-Department of Molecular Medicine, Ottawa Health Research Institute; 3-Department of Infectious Diseases, Ottawa Hospital;

Plain Language Summary: Dendritic cells are important in the initial response of the immune system to infection. Their role in HIV infection remains unclear. We hypothesize that HIV will affect dendritic cell maturation and function by downregulating cell surface markers and signaling molecules. This impaired maturation will prevent the activation of the adaptive immune response and as such is a mechanism that prevents the successful clearance of HIV.

Objectives: Dendritic cells (DCs) are potent antigen presenting cells whose role in eliciting immune responses in the context of HIV-1 infection remains unclear. We hypothesize that HIV-1 will modulate DC maturation, downregulating the production of IL-23 and IL-27 thereby keeping memory T cells quiescent and downregulating IL-12 production, respectively.

Methods: DCs were isolated from skin obtained from patients undergoing paniculectomy. Langerhans cells (CD1a+) were obtained from the epidermal layer and dermal dendritic cells (CD1c+) were obtained from the dermal layer after overnight dispase digest and microbead isolation. Blood-derived DCs were isolated by CD1c+ microbeads. Monocyte-derived immature DCs were cultured for 6 days with IL-4 and GM-CSF. Cell purity was analyzed by flow cytometry. Monocyte-derived DCs were then infected with a pLXIN constructed containing the HIV-1 tat wt gene or the empty vector for 24h, before a 4h LPS (1□g/mL) stimulation. IL-23p19 and IL-27EBI3 and p28 mRNA expression were evaluated by qRT-PCR.

Results: After 6 days, monocyte-derived DCs were positive for CD1c, CD1a, CD11C, MHCI and MHCII, CCR5 with low levels of CD1d, CD80 and CD86. The loss of CD14 expression supports the differentiation of monocytes into dendritic cells. The cells obtained from microbead isolations (skin CD1a, CD1c, and blood CD1c) showed a similar phenotype consistent with an immature dendritic cell phenotype. Preliminary results of IL-23p19 and IL-27 EBI3 expression indicate a decrease in EBI3 and p19 mRNA by pLXiN HIV-1 tat wt vector. Dose response experiments to recombinant tat and to HIV-1CS204 are ongoing.

Conclusions: We have effectively isolated DCs from blood and skin (epidermal and dermal layers) have generated immature dendritic cells from blood derived monocytes. Preliminary data suggests an inhibition of EBI3 mRNA expression and an upregulation of p19 mRNA expression when treated with intracellular expression of HIV-1 tat wt. Understanding the function of cytokines expressed and secreted by dendritic cells to initiate T cell polarization may lead to better understanding of HIV-1 pathogenesis and the development of novel therapies for HIV infection.

Contact Information: Andréane Chénier, Tel: 613-737-8160, Email: achenier@ohri.ca

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THE ROLE OF MITOGEN ACTIVATED PROTEIN KINASES IN INTERLEUKIN-12 SIGNALLING

Fiona Frappier [1,2]; Jonathan Angel [1,2];
1-University of Ottawa; 2-Ottawa Health Research Institute;

Plain Language Summary: We are interested in studying the cytokine IL-12 and its decreased production following HIV infection. IL-12 is critical for a healthy immune response to invading pathogens and, in its absence individuals are more susceptible to infection. Unfortunately, we lack basic understanding of how this molecule is produced and therefore need to clarify this mechanism in order to further our understanding of HIV-mediated inhibition of IL-12. Knowing the mechanism of IL-12 production will greatly enhance or ability to propose novel methods for immune based therapy for HIV infection.

Objectives: We have previously demonstrated that monocytes infected in vitro with HIV have decreased IL-12 subunit p40 promoter activity and decreased nuclear factor binding to three critical promoter sites Sp-1, AP-1, Ets-2 and NFkappaB. Phosphorylation of the upstream MAPK signalling molecules, p38 and JNK, is also inhibited in LPS stimulated monocytes infected with HIV (Chambers 2004). Our current objective is to explore the hypothesis that HIV inhibition of IL-12 synthesis is mediated by altering MAPK activity and the binding of nuclear factors to the IL-12p40 promoter.

Methods: To characterize intracellular mechanisms which regulate IL-12 production we first evaluated the role of mitogen activated protein kinases (MAPK) activation in IL-12 p40 production by monocytes using pharmacological inhibitors of MAPK and measuring IL-12 p40 by real time PCR and ELISA. Then we identified the nuclear factors binding the human IL-12 p40 promoter site, which are critical for the production of IL-12 in myeloid cells again using pharmacological inhibitors of MAPK and measuring nuclear factor binding by Electromobility shift and luciferase assays.

Results: In uninfected primary monocytes, inhibition of p38 and JNK decreased LPS-induced p40 protein production; consistent with previous results inhibition of ERK had no effect on p40 production. Both the p38 and the JNK inhibitors decreased AP-1, Ets-2 and Sp-1 binding activity while only the JNK inhibitor reduced NFkappaB binding. P38 and JNK inhibitors decreased promoter activity as demonstrated by the luciferase reporter construct.

Conclusions: Decreased production of IL-12 observed in HIV infected monocytes is result of changes in inhibition of LPS induced p38 and JNK MAPK signaling. Inhibiting MAPK function leads to dysfunctional nuclear factor binding to Sp-1, NFkappaB, Ets-2 and AP-1 as well as decreased p40 promoter activity and IL-12 production. Understanding the mechanism by which HIV alters this signaling pathway may lead to novel approaches in the treatment of HIV infection.

Contact Information: Fiona Frappier, Tel: 613-737-8160, Email: ffrappier@ohri.ca

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THE HIV TAT PROTEIN ACTS SYNERGISTICALLY WITH IL-7 TO DOWN REGULATE CD127 EXPRESSION ON THE SURFACE OF CD8 T-CELLS

Elliott Faller [1,2]; Ritesh Kumar [2]; Marko Kryworuchko [3]; Paul MacPherson [1,2,4];
1-Ottawa Health Research Institute; 2-University of Ottawa, Faculty of Medicine; 3-Children's Hospital of Eastern Ontario, Research Division; 4-Division of Infectious Diseases, Ottawa Hospital, Ottawa, Canada;

Plain Language Summary: Interleukin (IL)-7 and the HIV Tat protein have both been shown to reduce IL-7 receptor expression on the surface of CD8 T-cells. We show here that while IL-7 and Tat have very different effects on CD8 T-cell function, they act synergistically to down regulate surface expression of the IL-7 receptor alpha-chain (CD127).

Objectives: We have previously demonstrated that the HIV Tat protein down regulates expression of the IL-7 receptor alpha-chain on CD8 T-cells. We and others have also shown that IL-7 similarly down regulates CD127 expression. We hypothesized that Tat and IL-7 may act synergistically to decrease CD127 expression on CD8 T cells.

Methods: CD8 T-cells isolated from healthy volunteers were incubated with purified HIV Tat protein (0.5-2µg/ml) and IL-7 (50-200 pg) alone or in combination. CD8 T-cell responses to these factors including stimulation (CD25), viability (Bcl-2), proliferation (Ki-67) and intracellular signalling (STAT5) as well as CD127 expression were followed by flow cytometry. Changes in CD127 transcripts were measured by real time PCR.

Results: Tat and IL-7, when added at near physiologic concentrations where each alone has only a small effect on CD127 expression, demonstrate synergy when added in combination. While at 24 hours 2 ug/ml of Tat decreases CD127 by only 4% and 200 pg/ml of IL-7 induces only a 10% decline, these two together at these same concentrations cause a 41% drop in surface CD127 expression. Interestingly, whereas Tat and IL-7 act synergistically to down regulate CD127, they have an opposing effect on proliferation where Tat inhibits IL-7-induced Ki-67 expression. Further, while IL-7 signaling increases STAT5 phosphorylation and expression of CD25 and Bcl-2 and decreases the level of CD127 transcripts, Tat has no effect on these pathways.

Conclusions: IL-7 is an important co-factor in CD8 T-cell activation enhancing cell proliferation and survival. The HIV Tat protein, in contrast, appears to inhibit CD8 T-cell activity by amplifying normal feed-back mechanisms leading to IL-7 receptor down regulation and by antagonizing activation-induced CD8 T-cell proliferation. Through this mechanism HIV may be able to disarm CD8 T-cells leading to impaired cell mediated immunity in patients with progressive disease.

Contact Information: Elliott Faller, Tel: 613-864-3414, Email: efaller@ohri.ca

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REGULATION OF THE IL-12 FAMILY CYTOKINES IL-23 AND IL-27 IN RESPONSE TO HIV OF HUMAN MONOCYTIC CELLS

Ali Akbar Rahim Rahimi [2,3]; Katrina Gee [3,4]; Niranjala Gajnayaka [3]; Jonathan Angel [2,4]; Ashok Kumar [1,2,3];
1-Department of Pathology and Laboratory Medicine; 2-Department of Biochemistry, Microbiology and Immunology; 3-Division of Virology and Molecular Immunology, Research Institute, Children's Hospital of Eastern Ontario (CHEO), Ottawa, Ontario; 4-Ottawa Health Research Institute and the Division of Infectious Diseases, Department of Medicine, Ottawa Hospital, University of Ottawa, Ottawa, Ontario;

Plain Language Summary: HIV employs a variety of mechanisms to undermine the effectiveness of the host immune system including dysregulation of Th1 cytokines, such as IL-12, an immuno-regulatory cytokine involved in the development of protective cell-mediated immune responses (CMIR). Recently, two heterodimeric cytokines, IL-23 and IL-27 that are structurally and biologically related to IL-12 have been described. These two cytokines are abundantly produced by monocytic and dendritic cells. It is well established that IL-12 production is decreased in HIV-infected individuals and following in vitro HIV infection of monocytic cells. Whether IL-23 and IL-27 expression is altered following in vitro HIV infection of monocytic cells remains unknown. We hypothesized that IL-23 and IL-27 expression is altered in HIV infection and that this likely makes a significant contribution in the loss of CMIR, and to HIV disease progression.

Objectives: The overall aim of this research is to elucidate the molecular mechanisms by which HIV-1 alters the expression of the IL-12 family of Th1 cytokines IL-23 and IL-27. Specifically, we investigated the role of MAPK, PI3K, and the calcium-signaling pathways involved in the regulation of IL-23 and IL-27 in LPS-stimulated human monocytic cell lines and primary monocytes. In addition, we evaluated the effects of in vitro HIV infection on spontaneous and LPS-induced IL-23 and IL-27 production by human monocytes and monocytic cell lines.

Methods: Virus propagation: The dual-tropic HIV-1 clinical isolate, CS204, was a gift from Dr. J. Angel (Ottawa Hospital, Ottawa, Canada). This virus isolate was propagated in the THP-1 cell line.
In vitro HIV infection: THP-1 cells were incubated with cell-free HIV-1 for 6 h at 37°C. Cells were washed with fresh medium and resuspended in IMDM medium supplemented with 10% heat-inactivated fetal bovine serum, 100 U/ml penicillin, and 100 µg/ml gentamicin. Cultures were maintained for 7 days with replenishment of medium every 3-4 days.
Harvested cells were subjected to RNA extraction and Real-Time PCR to measure IL-12 family cytokines mRNA expression.

Results: Our results suggest that LPS upregulated the expression of IL-23p19 and IL-27p28 mRNA in THP-1 and HL-60 cells. Using specific pharmacological inhibitors, LPS-induced IL-27p28 RNA was shown to be regulated by the PI3K and the p38 MAPK activation. In contrast, IL-23p19 was found to be negatively regulated by the PI3K and the ERK MAPKs. Furthermore, infection of monocytic cells in vitro with HIV-1 enhanced the expression of IL-23p19 but did not affect the expression of IL-27p28.

Conclusions: The approaches directed at understanding Th1 cytokines regulation by HIV may be helpful in devising novel strategies to enhance CMIR and facilitate immune reconstitution and potentially eliminate virus from the body.

Contact Information: Ali Akbar Rahim Rahimi, Tel: 613-737-7600 x3919, Email: arahi080@uottawa.ca

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IMMUNOPHENOTYPIC CHARACTERIZATION OF MEMORY AND DOUBLE POSITIVE CD4+CD8+ T CELL LYMPHOCYTES IN CONTROL AND VACCINATED CYNOMOLGUS MACAQUES WITH HIV-1 PEPTIDES

Ali Azizi [1,2]; David Anderson [2,3]; Abdolkarim Alhetheel [1]; Francisco Diaz-Mitoma [1,2];
1-Infectious Disease and Vaccine Research Centre, Research Institute Children's Hospital of Eastern Ontario, Ottawa, ON, Canada; 2-Variation Biotechnologies Inc., Gatineau, Quebec, Canada; 3-Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, MA, USA;

Plain Language Summary: We have previously reported a strong cell-mediated immune response in cynomolgus macaques that were vaccinated with mixture of 176 lipidated and non-lipidated envelope and gag-HIV peptides. Here, we further characterized the immunophenotype of native and specific lymphocytes before and after stimulation with V1-V5 HIV-1 peptides or with a recombinant vaccinia vector containing HIV-1 gp120 and gag subtype B (rVV).

Objectives: To characterize and compare naïve, double positive (DP), central (CM) and effector (EM) memory lymphocytes before and after stimulation in control and vaccinated macaques.

Methods: PBMCs were isolated from whole blood of control and vaccinated macaques by Ficoll density gradient centrifugation. The frequencies of NK, naïve CD4+, CM CD4+, EM CD4+, naïve CD8+, CM CD8+, EM CD8+, and DP CD4+CD8+ T cells were characterized by flow cytometry. Intracellular cytokine staining was also employed to detect increase or decrease of specific lymphocytes in response to HIV-1 peptides or recombinant vaccinia virus containing HIV-1 gp120-gag subtype B.

Results: Higher percentages of EM CD4+ (CD28-CD95+) T cells were detected in immunized macaques compared to the control group. On the contrary, the amount of NK cells was higher in non-vaccinated macaques. The amount of both CM and EM CD8+T cells were comparable in both control and vaccinated groups. Furthermore, DP CD4+CD8+ T lymphocyte (CM and EM) populations were larger in the vaccinated group before and after stimulation.

Conclusions: We found that DP CD4+CD8+ T cells in the blood of vaccinated and non-vaccinated animals were mostly memory (CD95+) T cells. In addition, vaccination with a mixture of HIV-1 envelope and gag peptides is able to upregulate the amount of EM CD4+ and DP CD4+CD8+ T cells, which were detectable up to 1 year after vaccination. Furthermore, these data suggest that our HIV-1 candidate vaccine may downmodulate production of NK cells and in a related mechanism increase amount of specific immune responses. These results open a new door regarding the role of double positive CD4+CD8+ T cells in the control of HIV-1 infection.

Contact Information: Ali Azizi, Tel: 613-737-7600 x3911, Email: aliazizi555@yahoo.ca

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A JNK-DEPENDENT PATHWAY IS REQUIRED FOR HIV-VPR-INDUCED APOPTOSIS IN HUMAN MONOCYTIC CELLS: INVOLVEMENT OF ANTI-APOPTOTIC BCL-2 AND CIAP-1 GENES THROUGH THE ACTIVATION OF JNK MAPK

Sasmita Mishra [1,2]; Jyoti Mishra [1,2]; Ashok Kumar [1,2,3];
1-Division of Virology, CHEO Research Institute, Ottawa, Ontario, Canada; 2-Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Ontario, Canada; 3-Department of Pathobiology, University of Ottawa, Ottawa, Ontario, Canada;

Plain Language Summary: HIV-1 Vpr causes apoptosis in different kinds of cells including lymphocytes, monocytes, granulocytes and neuronal cells. Persistently infected monocytic cells serve as a major reservoir of HIV at all stages of disease. It is believed that one of the reasons for monocytes in vivo to be protected from apoptosis is by secretion of different kinds of cytokines in response to HIV infection. C terminal moiety of Vpr is known to cause apoptosis in variety of cell types including monocytes. Herein we have demonstrated that Vpr c terminal peptide (52-96) causes apoptosis in monocytes and monocytic cell lines and the process was caspase dependent. Further, knowing the role of MAPKs in signal transduction pathway and in regulation of cell death and survival, we determined the involvement of MAPKs in Vpr induced apoptosis in monocytes. Our results suggest that synthetic Vpr (52-96) and (1-45) peptides induced phosphorylation of all the MAPKs, whereas only Vpr (52-96) peptide induced apoptosis in monocytic cells. The results were confirmed by using JNK stealth RNA. Using a variety of strategies to manipulate JNK activity, we provided evidence that JNK activation is important in mediating Vpr induced apoptosis through mitochondrial pathway. Furthermore, Vpr induced apoptosis was mediated by downregulation of antiapoptotic genes Bcl2 and c-IAP1 through activation of upstream JNK MAPK. Understanding the mechanism of apoptosis induced by Vpr will be beneficial for the development of therapeutic approaches.

Objectives: 1.To study the molecular mechanisms involved in Vpr induced apoptosis in human mononuclear cells. 2. To study the involvement of pro/anti-apoptotic genes essential for inducing Vpr mediated apoptosis.

Methods: We used Vpr synthetic C terminal peptide (52-96 amino acid) to induce apoptosis, whereas N terminal 1-45 amino acid was used as control. We used PI, annexin/PI and JC-1 stain to detect apoptosis. We also determined signaling molecules such as MAPKs involved in inducing Vpr mediated apoptosis by using western blotting. We used RNase protection assay to detect the involvement of anti/pro-apoptotic genes in Vpr induced apoptosis by using BD Riboquant kit. We also performed electrophoretic mobility shift assay to detect the transcription factors in regulation of anti/pro-apoptotic genes.

Results: We have investigated the role of the mitogen activated protein kinases (MAPKs), and the transcription factors involved in the regulation of anti-apoptotic genes mediating Vpr-induced apoptosis. Our results suggest that Vpr 52-96 peptide induced apoptosis in normal human monocytes and promonocytic THP-1 cells. Although both Vpr1-45 and Vpr52-96 peptides induced phosphorylation of all the three p38, Erk and JNK MAPKs, Vpr52-96 peptide-induced apoptosis was regulated selectively through JNK activation. Furthermore, Vpr-induced apoptosis was mediated by the down regulation of anti-apoptotic genes Bcl2 and c-IAP1 through the activation of upstream JNK MAPKs.

Conclusions: This approach has allowed us to dissociate deleterious effects of Vpr from those of other viral genes and to dissect the signaling pathway at the molecular level. Understanding the signal transduction pathways that induce apoptosis in monocytes in response to extrenal Vpr may provide new insights into pathogenic mechanisms involved in HIV-1 disease and may contribute to the development of new therapeutic strategies.

Contact Information: Sasmita Mishra, Tel: 613-737-7600 x3919, Email: sasmishra@hotmail.com

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INVOLVEMENT OF ANTI-APOPTOTIC GENE C-IAP2 IN CYTOKINE INDUCED RESISTANCE TO HIV-VPR MEDIATED APOPTOSIS IN HUMAN MONOCYTIC CELL

Sasmita Mishra [1,2]; Jyoti Prasad Mishra [1,2]; Ashok Kumar [1,2,3];
1-Division of Virology, CHEO Research Institute, Ottawa, Ontario, Canada; 2-Department of Biochemistry, Microbiology, and Immunology, University of Ottawa, Ottawa, Ontario, Canada; 3-Department of Laboratory Medicine, and Pathobiology, University of Ottawa, Ottawa, Ontario, Canada;

Plain Language Summary: HIV causes apoptosis in lymphocytes, monocytes, granulocytes and in neuronal cells. Vpr, the accessory protein of HIV-1 is a potent regulator of the host cell. It has its effect on host cell proliferation and growth arrest in the G2/M phase of the cell cycle and that may be linked to the induction of apoptosis. Monocytes/macrophages play a central role in both innate and acquired immunity, and are a major source of inflammatory/growth cytokines following exposure to bacterial endotoxins / lipopolysaccharides (LPS). Herein, we demonstrate that LPS enhance monocytic cell survival through the induction of the antiapoptotic c-IAP2 gene in a human promonocytic THP-1 cell line. We also investigated the role of upstream signaling molecules including the mitogen activated protein kinases, phosphatidylinositol 3-kinase, and the calcium signaling pathways in the regulation of c-IAP2 expression and eventual survival of monocytic cells. Our results suggest that LPS/TNF-a induced expression of c-IAP2 is not regulated by activation of MAPKs and PI3K, however, the expression of c-IAP2 was regulated by calmodulin (CaM) through the activation of calmodulin-dependent protein kinase-II (CaMKII). In addition, CaM and CaMKII regulated c-IAP2 expression in LPS- stimulated cells through NFkB activation. Moreover, the CaM/CaMKII pathway also regulated LPS mediated inhibition of VPR induced apoptosis in these cells. Taken together, these results suggest that LPS induced c-IAP2 expression and its associated antiapoptotic survival signals in THP-1 cells are regulated selectively by CaM/CaMKII through NFkB activation.

Objectives: To study the signaling molecules and anti-apoptotic genes involved in cytokine induced protection to Vpr mediated apoptosis

Methods: We determined the involvement of antiapoptotic genes by western blotting. We also confirmed the involvement of antiapoptotic gene by using antisense oligonucleotides. To determine the signaling molecules involved in inducing LPS/TNF-a induced protection, we dissected MAPK, PI3K, and calcium signaling pathways by using specific pharmacological inhibitors. We also confirmed the involvement of transcription factors regulating the specific anti-apoptotic gene by electrophoretic mobility shift assay and by luciferase assay.

Results: We investigated the intracellular signaling pathways underlying LPS/TNF-a induced resistance to HIV-Vpr mediated apoptosis in human monocytes and monocytic cells. We demonstrated for the first time that LPS and TNF-a induced resistance to HIV-Vpr mediated apoptosis and it was due to upregulation of c-IAP2 through activation of CaMKII via calcium influx. Furthermore, Vpr52-96 peptide inhibited LPS/TNF-a induced calcium influx, activation of calmodulin and CaMK-II, and c-IAP2 induction as determined by western blot and luciferase assays. Vpr52-96 peptide also inhibited the binding of NFkB to its binding site on the c-IAP-2 promoter as determined by gel shift analysis. Taken together, our results suggest that c-IAP-2 gene plays a critical role in LPS and TNF-a-induced resistance to HIV-Vpr-mediated apoptosis in human monocytic cells.

Conclusions: LPS and LPS induced proinflammatory cytokine TNF-a play an important role in HIV pathogenesis. Since LPS/TNF-a induced resistance to HIV-Vpr mediated apoptosis in monocytes is mediated by c-IAP2 upregulation, manipulating signaling molecules involved in c-IAP2 regulation such as calcium, CAMKII may help in clearing the viral reservoir from monocytes.

Contact Information: Jyoti Prasad Mishra, Tel: 613-737-7600 x3919, Email: jyotitoronto@yahoo.com

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DIFFERENTIAL REGULATION OF IL-7 RECEPTOR (CD127) ON CD8+ T CELLS: IMPLICATIONS FOR HIV

Agatha Vranjkovic [1]; J.B. Angel [1];
1-Ottawa Health Research Institute, Ottawa, Canada;

Plain Language Summary: Interleukin (IL)-7 and its signalling via the IL-7 receptor complex is essential for optimal CTL activity. Our demonstration that significantly fewer CD8 cells from HIV infected patients express CD127 as compared to healthy individuals, implicates a role for the regulation of CD127 expression in HIV immunopathogenesis. Based on preliminary observations that IL-7 decrease CD127 expression on CD8 cells, we hypothesize that HIV infection alters CD127 expression on CD8 cells and does so by upregulating production of IL-7.

Methods: Since X4 and R5 strains of HIV appear to have differential effects on IL-7 production, PBMCs or isolated CD8 cell from healthy volunteers were incubated with either an X4 (HIVIIIB), R5 (HIVBaL), dual tropic (HIVCS204), or replication incompetent (HIV8E5) strain of HIV with or without antibodies IL-7. After various lengths of time (24-96h), CD127 expression on CD8 cells was evaluated by flow cytometry. CD127 expression on isolated CD8 cells cultured with infected PBMC via a transwell, and isolated CD8 cells cultured with supernatants of PBMC infected with HIV for 24h were also studied. The effect of HIV infection on CD127 RNA expression was evaluated by PCR. Infection of PBMC cultures was monitored by p24 ELISA.

Results: Incubation of PBMC with HIVIIIB, HIVBaL or HIVCS204 transiently decreased CD127 expression on CD8 cells, however, addition of HIV to isolated CD8 cell cultures had no effect on CD127 expression. HIV8E5 had no effect on CD127. Isolated CD8 cells exposed to either: 1) PBMC incubated with HIVIIIB, HIVBaL or HIVCS204 and cultured in a transwell, or 2) supernatants from HIV incubated with HIVIIIB, HIVBaL or HIVCS204 resulted in decreased CD127 expression. PCR analysis of RNA isolated from CD8 cells in HIV infected PBMC demonstrated no change in the levels of CD127 RNA. p24 ELISA confirmed that incubation of PBMC with HIVIIIB, HIVBaL or HIVCS204 results in productive infection.

Conclusions: As seen in vivo, HIV infection of PBMC in vitro results in the downregulation of CD127 surface expression on CD8 cells. This effect appears to be due to the activity of soluble factor(s) present in HIV infected PBMC cultures. Candidate proteins include IL-7, the roles of which are being evaluated with neutralizing antibody experiments. Further elucidating the mechanism(s) of CD127 downregulation will provide important insights into the immunopathogenesis of HIV disease.

Contact Information: Agatha Vranjkovic, Tel: 613-737-8160, Email: akomsic@ohri.ca

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PREVENTING HIV PREVENTION: STIGMA, HARASSMENT AND VIOLENCE AGAINST MEN WHO HAVE SEX WITH MEN IN CHENNAI, INDIA

Peter A. Newman [1]; Venkatesan Chakrapani [2]; Murali Shunumugam [2]; Michael Woodford [1];
1-Faculty of Social Work, Centre for Applied Social Research, University of Toronto, Toronto, Canada; 2-Indian Network of Persons Living with HIV/AIDS, Chennai, India;

Plain Language Summary: In-depth, qualitative interviews were conducted with MSM and service providers, along with a survey of 200 MSM recruited from public sex environments in Chennai, India. Pervasive stigma, discrimination, violence and forced sex, and high HIV risk suggest a strong need for multi-level prevention strategies for MSM targeting individuals, families, healthcare and criminal justice systems.

Objectives: India has the highest number of persons living with HIV/AIDS in the world (>5.2 million). Limited HIV surveillance data suggest men who have sex with men (MSM) may be at elevated risk. This study explored and assessed experiences and contexts of stigma, harassment, discrimination and violence, and HIV/STD risk among high-risk MSM in Chennai, India.

Methods: In-depth, semi-structured interviews were conducted with 18 MSM at high risk for HIV infection, and 3 key informants, recruited from community agencies and public sex environments using purposive sampling. Interviews were audiotaped and transcribed verbatim. Data were analyzed using narrative thematic analysis and N-VIVO software. Prolonged engagement, member checking, peer debriefing and triangulation of methods increased the trustworthiness of the findings. A 30-minute paper-and-pencil survey questionnaire was administered to 200 MSM (mean age=29 years) recruited using time-space sampling from a random sample of 20 public sex environments. Survey domains, informed by qualitative findings, included HIV risk, harassment, forced sex and HIV testing. Voluntary syphilis testing (VDRL) and free treatment were provided.

Results: Qualitative findings revealed multiple intersecting social and institutional contexts of stigma, discrimination, harassment and violence involving police, "rowdies" (bullies), healthcare providers, family members, heterosexual friends, and other MSM. Participants reported verbal and physical harassment by police for carrying condoms, under allegations of engaging in sex with men or sex work; and stigmatization from healthcare providers. Survey data indicate 12% VDRL reactive and 13% self-reported testing HIV-positive. Almost two-thirds (61%) reported harassment or blackmail at least once a month, one-fifth (19%) on a daily basis. Perpetrators included police (37%), "rowdies" (61%) and sexual partners (16%). Forty-one percent (n=82) experienced forced sex in the past year. One-third had never been tested for HIV; 29% didn't use a condom during last anal sex.

Conclusions: Multi-level HIV prevention strategies are needed among high-risk MSM in India: culturally appropriate behavioral- and knowledge-based interventions to increase condom use, HIV/STD testing and treatment; and structural interventions to combat stigma, harassment and discrimination in legal, healthcare and family systems, and to reduce sexual violence. Criminalization of "homosexual behavior" (Indian Penal Code-377) is antithetical to public health and HIV prevention.

Contact Information: Peter Newman, Tel: 416-946-8611, Email: p.newman@utoronto.ca

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SYSTEMATIC REVIEW OF BEHAVIOURAL SURVEILLANCE SURVEYS IN FEMALE SEX WORKER, MALE SEXUAL CLIENT AND GENERAL POPULATION IN INDIA

Li Chen [1]; Prabhat Jha [1]; Mathew Silvaggio [1]; Peggy Millson [1]; Prem Mony [3]; Rajesh Kumar [2]; Neeraj Dhingra [1]; Nicole Greenspan [1]; Michelle Chakkalackal [1]; Nico Nagelkerke [4];
1-Centre for Global Health Research, St. Michael's Hospital, University of Toronto, Canada; 2-Post Graduate Institute for Medical Education and Research, School of Public Health, Chandigarh, India; 3-St. John's National Academy of Health Sciences, Institute of Population Health and Clinical Research, Bangalore, India; 4-United Arab Emirates University, Community Medicine, AL-Ain, United Arab Emirates;

Plain Language Summary: This systematic review of behavioral surveillance surveys in India created a composite description on the knowledge of HIV/AIDS and sexual transmitted diseases (STDs), sexual behavior and demographic information for female sex workers, male sexual clients and general population from 2001 to 2002.

Objectives: This study aimed to create a composite description on the knowledge of HIV/AIDS and sexual transmitted diseases (STDs), sexual behavior and demographic information for female sex workers, male clients and general population in India.

Methods: A comprehensive literature review and search of the grey literature was conducted for all available Behavioural Surveillance Surveys in India. Contact with all major programs was made, as well as searches by major developmental partners. A meta-analysis based on the inverse-variance method was conducted to obtain the overall measurements.

Results: Twenty two studies conducted by the National AIDS Control Organization in 2001 to 2002 were included, in terms of the identical questions of knowledge, sexual behavior and demographic information among female commercial sex workers, male clients and general population. We compared the similar indicators among female sex workers and female general population in north and south of India, male clients and male general population in north and south of India. We also compared the female sex workers and male clients in the North with those in the South.

Conclusions: The comparison of the core questions indicated that the average education level of female sex workers and male clients was lower than general population, however their knowledge of HIV/AIDS and STI were more than in the general population. Female sex workers and male clients in the South were more knowledgeable of HIV/AIDS than those in the North. There was no significant difference involving STDs treatments between female sex workers, male clients and the general populations.

Contact Information: Li Chen, Tel: 416-864-6060 x3315, Email: Chenli@smh.toronto.on.ca

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DOCUMENTING THE GEOGRAPHIC VARIATION IN HIV-1, ITS DETERMINANTS AND INTERVENTION COVERAGE IN 115 DISTRICTS IN SOUTHERN INDIA

Chris Pupp [1]; Li Chen [1]; Mathew Silvaggio [1]; Neeraj Dhingra [1]; Ajay Khera [2]; Prakash Bhatia [3]; Rajesh Kumar [4]; Prem Mony [5]; Prakash Doke [6]; Prabhat Jha [1];
1-Centre for Global Health Research, St. Michael's Hospital, University of Toronto.; 2-National AIDS Control Organization, New Delhi, India.; 3-Osmania Medical College; 4-Post Graduate Institute of Medical Education and Research, Chandigarh, India; 5-Institute of Population Health and Clinical Research, St. John's National Academy of Health Sciences, Bangalore, India; 6-Maharashtra State AIDS Control Society, Mumbai, India;

Plain Language Summary: It is often noted that India's HIV epidemic is more advanced in the "southern" states of Andhra Pradesh, Karnataka, Maharashtra and Tamil Nadu. However these states are large. To characterize an entire state as "high prevalence" is likely too broad a characterization. We wish to better understand, at the sub-state geographic level of a district, the variation of HIV-1 and its potential geographic-level risk factors such as number of truck stops, proximity to national highway and presence or absence of a brothel. Understanding geographic patterns informs policy and program officers in the development of prevention programs.

Objectives: This study aims to document district-level geographic variation of HIV-1 and potential ecological level risk factors in the four southern high-prevalence states in India.

Methods: Data collection was initiated through contact with collaborating Indian institutions, and the Government of India. Data sources included, but were not limited to; surveillance data including all antenatal clinic, sexually transmitted infection clinic, and voluntary counselling and testing centre data; 2001 Census data for all demographic data; intervention and sex worker mapping data; and baseline behavioural surveillance surveys.

Results: Selection of variables was based on plausibility of their being determinants (or indicators of determinants) of the biological mechanisms that effect the reproductive number, as defined the mathematical model R0 = βcD. These potential determinants were divided into distal (contextual) and proximal determinants, according to Boerma and Weir's adaptation of a proximate determinants framework. In this framework, contextual determinants (such as sociocultural and demographic variables as well as interventions) are thought to influence transmissibility, duration of infection and exposure through their influence on proximate determinants. Risk factors were from secondary sources including geographic data, demographic data, sexually transmitted infection surveillance data, and mapping of high risk groups. Prevalence of HIV was estimated from antenatal clinic surveillance data. In the four southern states in 2004, district level HIV prevalence varied from 0.0 to 4.0% (mean=1.3%; median=1.2%) in 115 urban sites and 0.0 to 4.8% (mean=1.1%; median=0.8%) in 79 rural sites. Analyses on associations with proximal and distal factors are forthcoming.

Conclusions: Preliminary findings confirm a high level of heterogeneity between the 115 districts of both HIV-1 prevalence for any particular year, and change in prevalence. Local mapping efforts are a useful tool for program planning and evaluation.

Contact Information: Paul Arora, Tel: 647-407-4867, Email: p.arora@utoronto.ca

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SPATIAL STATISTICAL ANALYSIS FOR HIV PREVALENCE IN 115 DISTRICTS IN SOUTHERN INDIA

Li Chen [1]; Prabhat Jha [1]; Chris Pupp [1]; Mathew Silvaggio [1]; Neeraj Dhingra [1]; Ajay Khera [2]; Prakash Bhatia [3]; Rajesh Kumar [4]; Ajay Goel [5]; Nico Nagelkerke [6];
1-Centre for Global Health Research, St. Michael's Hospital, University of Toronto, Canada; 2-National AIDS Control Organisation, Ministry of Health Family Welfare, New Delhi, India; 3-Osmania Medical College, Hyderabad, India ; 4-School of Public Health, Post Graduate Institute of Medical Education and Research, Chandigarh, India ; 5-Immunization and Vaccine Development, World Health Organization, South-East Asia Regional Office, India; 6-United Arab Emirates University, Al Ain, United Arab Emirates;

Plain Language Summary: This study documented the geographic variation of HIV prevalence in 115 districts of the four southern states of India by spatial statistical modelling.

Objectives: The objective of this study is to document the geographic variation of HIV prevalence and identify district-wise risk factors of HIV transmission in 115 districts of the four southern high-prevalence states of Andhra Pradesh, Karnataka, Maharashtra and Tamil Nadu in India.

Methods: Spatial statistical analysis is employed to capture the HIV prevalence in each district based on district-level geographic and demographical variables which were thought to influence HIV transmission such as prevalence of sexual transmitted infections (STIs), proportion of male's circumcised, percentage of female commercial sex worker, average age at marriage, and percentage of people in HIV prevention programs.

Results: We developed a Bayesian hierarchical model to estimate the HIV prevalence at district-wise and identify risk factors. The spatial pattern, area effects, is an intrinsic Gaussian autoregressive error, which uses a Markov chain Monte Carlo computational method to obtain the joint posterior distribution of the model parameters. Simulation of the model indicated it fits well. Smoothed maps associated with HIV prevalence are produced by GIS ArcView.

Conclusions: There is a substantial geographical heterogeneity of HIV prevalence existing within the 115 districts of the 4 states analyzed. Our findings are robust with respect to the specification of the prior distribution. Prevalence of STIs in the previous year and average age at marriage are significantly associated with district-wise HIV infection.

Contact Information: Li Chen, Tel: 416-864-6060 x3315, Email: chenli@smh.toronto.on.ca

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ESSENTIAL HYPERTENSION, INFECTION AND HUMAN IMMUNODEFICIENCY VIRUS IN PYGMIES LIVING IN CENTRAL AFRICA

Maurice, D. Bouity-voubou [1]; Donatien Mavoungou [1]; Pavel Hamet [1];
1-Centre de recherche, Centre Hospitalier de l'Université de Montréal - Technopôle Angus, Montréal, Québec;

Plain Language Summary: Essential hypertension remains a factor of significant risk for the cardiovascular diseases and is one of the most common diseases of the industrialized countries. In developing countries, infections have been identified as risk factors for cardiovascular diseases via pro-inflammatory cytokines. We showed recently that Pygmies in Central Africa have the capacity to growth, while the interaction between the GH-IGF-I axis and the renin angiotensin aldosterone and immune systems is well documented. Resistance to malaria is always observed in Pygmies not in Bantu. The absence and or low incidence of the human immunodeficiency virus and resistance to few infections, including Plasmodium falciparum malaria, have been reported in Pygmies living as hunter-gatherers in rural area in close contact with Bantu.

Objectives: To investigate body mass index (BMI), blood pressure and the common infections in Pygmies living in Libreville.

Methods: 17 female and 12 male apparently healthy Pygmies ages 12 to 47 were included in the study. All subjects were from the same tribe and origin. BMI was estimated using WHO criteria while blood pressure (BP) was recorded by the same physician using an automatic BP monitor "microlife model 3BTO-H." Common infections such as Chlamydia trachomatis (Organics), Plasmodium falciparum (Cypress Diagnostic); Toxoplasma gondii, HIV-1 and syphilis (Biomerieux), Loa-Loa and Mansonella perstans (Knott`s technique) were analyzed in the same subjects. Statistical analysis was performed using student t' test, Prism 3,0.

Results: Results were expressed as mean ±SE. Height (m) was higher in male than in female Pygmies (P<.01). The percentage of females with BMI ≥ 25.0 kg/m2 was 3 times higher than in males. BP measurements were similar or lower than in Bantu (P<.01). From all studied infections, Toxoplasma gondii was present in all male and female Pygmies, contrasting with the absence of syphilis, Loa-loa, Mansonella perstans and Plasmodium falciparum (malaria) in the same subjects. Seven males and nine females were co-infected by Chlamydia trachomatis, and by HIV-1.

Conclusions: Pygmies living in the capital of Gabon maintained their resistance to malaria, and microfilaria exhibiting, however, high susceptibility to Toxoplasma gondii, Chlamydia trachomatis known to be involved in cardiovascular diseases and HIV-1 was observed. This is the first study showing the presence of HIV-1 and Chlamydia trachomatis in Pygmies in Gabon to be included in the local programme against AIDS and others sexually transmitted infections in that area.

Contact Information: Maurice Bouity-voubou, Tel: 514-890-8000, Email: maurice.bouity-voubou@umontreal.ca

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ANTIRETROVIRAL DRUG USAGE IN HIV SERO-POSITIVE PREGNANT WOMEN IN ONTARIO

Sarabjit Gahir [1]; Michael Ibrahim [1]; Stanley Read [2]; Micheline Piquette-Miller [1];
1-Leslie Dan Faculty of Pharmacy, University of Toronto; 2-Division of Infectious Diseases, The Hospital for Sick Children;

Plain Language Summary: About 18 million women of child bearing potential (15- 49 yrs of age) are HIV positive today. An increasingly large number of pregnant women are being put on antiretroviral (ARV) therapy, with a view to maintaining the health of the mother and curtailing vertical transmission of the virus to the child. The use of ARV therapy during pregnancy has yielded promising results in terms of reducing the transmission to below 2% in N. America. The current Canadian consensus guidelines issued in 2003 recommend the use of combinational therapy containing at least 3 different ARVs. It has been suggested that minimization of transmission may also be achieved via cesarean deliveries rather than via the vaginal route. That decision, however, lies with the mother to make. There is little known about the compliance with these recommendations.

Objectives: This study looks at the prescribing trends of physicians handling HIV positive pregnancies over a span of about 7 years in order to shed light on the evolving prescribing patterns with regards to sero-positive pregnant women. It also attempts to identify any trends in associated factors such as mode of delivery, birth weight, gestational age, maternal health and birth defects associated with the changes.

Methods: The data regarding ARV use in HIV positive mothers was collected by carrying out a retrospective longitudinal and cross-sectional patient chart review. 180 usable charts were obtained from the Motherrisk program at the HIV clinic, The Hospital for Sick Children. The data ranges from Jan 1st, 1998 to May 31st, 2005. Charts were mined for the above described data and the same analyzed.

Results: Trends in the prescribing pattern seem to shadow the guidelines for the management of pregnant women with HIV. A continuous change in the prescription practices can be seen over this period with increasingly more women being put on combinational therapy containing NRTIs with NNRTIs and/or PIs. Moreover an increasing number of women take ARV medication throughout the course of pregnancy. The majority of births are still via the vaginal route rather than cesarean which is the preferred mode.

Conclusions: The data suggests that prescribing patterns in Ontario, while dynamic, are in line with the issued guidelines. While there is room for improvement, the strategy seems to be working, with only one case of vertical transmission seen in all the cases available.

Contact Information: Micheline Piquette-Miller, Tel: 416-946-3154, Email: m.piquette.miller@utoronto.ca

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IMMUNE CORRELATES OF HIV SHEDDING IN THE FEMALE GENITAL TRACT

Chris Pettengell [1]; Sherzana Sunderji [1]; Anu Rebbapragada [1]; Bolette Bossen [1]; Kelly MacDonald [1,2]; Anne Biringer [1,2]; Lidia Casciaro [3]; Sharon Walmsley [1,3]; Rupert Kaul [1,3];
1-Department of Medicine, University of Toronto; 2-Mt. Sinai Hospital, Toronto, ON; 3-University Health Network, Toronto, ON;

Plain Language Summary: Most HIV is transmitted through sex. Women may have a higher risk of acquiring HIV through sexual contract than men, but little is known about what happens during transmission at the level of the genital tract. Since it is likely that immune factors in the genital tract are important in transmission, we performed a pilot study to compare differences in the genital immune environment between HIV-infected and uninfected women, and examined the immune associations of antiretroviral therapy (ART).

Objectives: To elucidate the mucosal immune associations of HIV shedding and susceptibility in the female genital tract (FGT).

Methods: This was a cross sectional cohort study performed in Toronto, Canada. Chemokines/cytokines levels were measured in undiluted vaginal secretions using the cytokine bead array. HIV RNA levels in the FGT/blood were measured by bDNA (Roche), and CMV/HSV2 levels in the FGT by QPCR. Endocervical immune cell populations were quantified by flow cytometry. RNA expression profiling of immune factors was performed by RT QPCR on a second cytobrush sample.

Results: In HIV-uninfected women, immature dendritic cell (iDC) numbers varied with menstrual phase (P=0.05), so analysis was restricted to women in the follicular phase. We enrolled 34 women: 10 were HIV uninfected; 12 were HIV-infected, therapy naïve; and 12 were HIV-infected, on ART. Blood HIV viral load was lower in ARV-treated than naïve women (3.4 vs 1.7 log10 RNA copies; P<0.001), but this difference was less pronounced in the FGT (3.3 vs 2.9 log10 copies; P=0.09). FGT CD1a+ iDCs tended to be decreased in HIV+ women (P=0.07), and there was no recovery on therapy. HSV2 infection was also associated with iDC depletion (3804 vs 32013/cytobrush; P=0.01). Levels of RANTES were elevated in the FGT of HIV-infected women, whereas the expression of intracellular Toll-like receptors TLR3 and 9 was decreased. HIV-associated immune differences in the FGT were not restored in ART-treated women.

Conclusions: HIV is associated with profound differences in the FGT immune milieu. These changes may persist despite antiretroviral therapy, which appears to have more impact on blood viral load than on HIV levels in the FGT.

Contact Information: Rupert Kaul, Tel: 416-978-8607, Email: rupert.kaul@utoronto.ca

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HIV-1 SHEDDING IN WOMEN CO-INFECTION WITH HSV-2

Sameer Kassim [1]; Phillipe El-Helou [2,3]; Lynn Kelleher [3]; Marek Smieja [1,2,3]; Fiona Smaill [1,2,3]; Mike Shih [4]; Dan Kolk [4]; Charu Kaushic [1];
1-Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario; 2-Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario; 3-Special Immunology Services Clinic, Hamilton Health Sciences Centre, Hamilton, Ontario; 4-Gen-Probe Inc, San Diego, California;

Plain Language Summary: Scientific research has shown a link between the HIV-1 and Herpes (HSV-2). When acting together, they alter the nature of the disease so that symptoms associated with one disease or the other is seen more often and with increasing severity. Here we have established a group of female patients in order to complete this objective. We have collected blood and samples from the genital tract. We have analyzed them to find the number of patients that have had a previous exposure to HSV-2, through testing for antibodies. We are now analyzing our patient's for HIV-1 and HSV-2 virus. Ultimately, this study will give us important information regarding co-infection and HIV transmission in women.

Objectives: It has been shown that HSV-2 positive status has been linked to increased HIV-1 acquisition and transmission and vice versa. Thus, the objective of this study will be to examine the risks associated with transmission of HIV-1 in co-infected women, as well as to examine the associated clinical and immunological correlates of co-infection.

Methods: Female SIS patients will be asked to donate serum and genital samples in order to determine HSV-2 sero-prevalence, and baseline levels of HIV-1, HSV-2 respectively. Women will then be divided into two sub-groups: HIV-1 infected and HIV-1/HSV-2 co-infected. Participants will be asked to provide genital samples daily for the duration of one menstrual cycle. HSV-2 and HIV-1 viral loads will be determined. Human Research Ethics Board approval has been granted.

Results: 50 women from the SIS clinic have been recruited into the study to date. Of the completed questionnaires 51% indicated they were born in Canada, 37% were born in Africa. The patient population is equally balanced in terms of ethnicity, 54% are black, and 40% are white. HSV-1/2 EIA and immunoblot have determined HSV sero-prevalence of 36 patients to be 50% and 64%, respectively. Further, HIV load was compared between two different kits for cervical and vaginal shedding. Our analysis revealed that the home-based kit had a more consistent and sensitivity in the collection of viral particles determined by Gen-Probe HIV assay. Also, from a sub-group of 15 women shedding of more than 100 viral copies/ml was detected and no dissimilarity was observed based on ethnicity. However, patients (n=7) on HAART showed marked difference in both cervical and vaginal viral load as compared to their untreated counterparts.

Conclusions: The results obtained from this study will be important to understand the risks associated with HIV-1 transmission. Studies such as this one will aid in formation of recommendations for clinical intervention within the STI community.

Contact Information: Sameer Kassim, Tel: 905-525-9140 x22589, Email: kassims@mcmaster.ca

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INTERACTION BETWEEN FEMALE GENITAL EPITHELIAL CELLS AND HIV

Sherie Fernandez [1]; Mike Bunce [1]; Aisha Nazli [1]; Charu Kaushic [1];
1-Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Canada;

Plain Language Summary: We are addressing the mechanisms of initial HIV transmission to the female genital tract, focusing on the role of female genital epithelial cells (ECs).

Objectives: Our objective was to investigate how female genital EC's interact with HIV. We are interested in determining whether ECs can transcytose and/or sequester HIV to infect target immune cells, and if ECs themselves become infected with HIV. We are also interested in determining whether different forms of HIV (cell free vs. cell-associated, X4 vs. R5 tropic strains) interact with ECs differently.

Methods: Human primary endometrial ECs grown on matrigel- coated cell culture inserts were exposed to cell- free or cell- associated X4 HIV virus strains. Exposures were performed in the presence or absence of the Jurkat target cell-line in basolateral compartments of cultures. Apical and basolateral supernatants were collected at various time points to detect new infectious virus particles using the U373-CXCR4 magi indicator cell line. Sybrgreen real time PCR was used to detect viral RNA and proviral DNA in cell lysates.

Results: In the cell-free X4 experiments, infectious HIV particles were found only in basolateral supernatants of EC's infected in the presence of target cells. This indicated that EC's could transmit cell-free X4 to target cells. These results were supported by the detection of higher levels of gag gene in target cells compared to EC's and the detection of proviral DNA in the target cell lysates. EC's exposed to cell-associated X4 were also able to transmit virus to target cells. The appearance of infectious virus in supernatants was faster and there was a higher output compared to cell-free virus infections. Endometrial ECs were able to sequester both cell-free and cell-associated X4 for at least 48 and 72 hours, respectively, to infect target cell lines. One of three EC cultures exposed to cell-associated X4 displayed proviral DNA integration, indicating that in some females, genital EC's themselves may become infected with HIV.

Conclusions: Our female primary EC culture model has provided us with useful information regarding initial HIV interactions with the female genital mucosa. We are currently evaluating R5 HIV transmission to determine whether R5 and X4 virus strains have differential abilities to cross the female genital mucosa to infect target cells. This model is also being used to gain better insight on HIV infection of the female genital mucosa following heterosexual transmission by using semen from HIV infected men as a source of virus.

Contact Information: Sherie Fernandez, Tel: 905-525-9140 x22589, Email: fernansa@mcmaster.ca

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A NEW APPROACH TO DEVELOP MICROBICIDES AGAINST SEXUAL TRANSMITTED VIRUSES (STVS) BY BOOSTING LOCAL INNATE RESPONSES IN GENITAL EPITHELIUM OF WOMEN

Aisha Nazli [1]; Sherie Fernandez [1]; Kenneth Rosenthal [1]; Ali Ashkar [1]; Charu Kaushic [1];
1-Centre of Gene Therapeutics, McMaster University, Hamilton, Ontario, Canada;

Plain Language Summary: The epithelial lining, the inside surface (mucosa) of the body such as genital and epithelial cells form an uninterrupted physical barrier preventing from infections. Genital epithelial cells express receptors called Toll-like receptors (TLRs) that detect potential microbes and secrete defensive cytokines and upregulate the expression of anti-viral factors. We want to exaggerate these defensive responses by using natural ligands to Toll-like receptors. These ligands consist of the chemicals similar to those present in different microbes. We are trying different ligands to see whether we can boost protective effect against HSV-2 infection. Similar approaches will be tried for protection against HIV-1. This may be a new and unique alternative to topical microbicides that uses body's own defense mechanisms.

Objectives: Determine whether treatment of primary genital epithelial cells with TLR ligands protects against infection with sexually transmitted viruses, HSV-2 and HIV-1.

Methods: Endometrial and cervical tissues were obtained from women undergoing hysterectomies with their informed consent. The epithelial cells were isolated from tissues and grown on transwells. Transepithelial electrical resistance measurements were used to assess the integrity of the confluent monolayer. Epithelial monolayers were then treated with different individual TLR ligands including Poly I:C, flagellin, a new and unique bacterial extramembrane protein, Lipoteichoic acid, and peptidoglycan (TLR-2 ligands) for 24h and then infected with HSV-2. Viral load was detected further 24h later in the supernatants from apical and basolateral side of the transwells by plaque assay.

Results: Primary epithelial culture model has provided us with useful information regarding the susceptibility of genital epithelium to HSV-2 and HIV-1 viruses. Flagellin, a bacterial protein and ligand for TLR-5 was effective in providing 65-80% protection from HSV-2 infection. Poly I:C, a TLR-3 ligand, was found to be more effective in controlling HSV-2 infection than flagellin and viral titers were reduced by > 90%. Unique bacterial extramembrane protein reduced HSV-2 infection to 70-78% in different tissues. The infection was reduced by 50% and 46% when epithelial monolayers were treated with the peptidoglycan and lipoteichoic acid respectively. The antiviral effect of these ligands was partly due to Type-1 IFN production by epithelial cells following treatment with TLR ligands.

Conclusions: These studies will provide important information regarding the usefulness of TLR ligands as topical anti-microbials that can protect against sexually transmitted viruses.

Contact Information: Aisha Nazli, Tel: 905-525-9140 x22589, Email: nazlia@mcmaster.ca

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RESEARCHING THROUGH DRAMA: PERFORMED ETHNOGRAPHIES ON ISSUES OF HIV/AIDS AND PREVENTION

Nidhi Punyarthi [1,2,3,4]; Joanne Murray-Ormandy [1,2,3,4]; Teisha Thompson [1,2,3]; Gabrielle Zilkha [1,2,3]; Sarah Switzer [1,2,3]; Emma Ardal [1,2,3]; Tara Goldstein [1,2,3,4];
1-New College Youth Advisory Board; 2-Gendering Adolescent AIDS Prevention Project (GAAPP); 3-Department of Women and Gender Studies, University of Toronto; 4-The Ontario Institute of Studies in Education, University of Toronto;

Plain Language Summary: Research findings and experiences about HIV/AIDS can be disseminated in many forms. Out of these various forms, the dramatic arts – in a form that we call "performed ethnography" or "ethnodrama" – have proven to be exceptionally successful. Our research shows that the use of plays and scripts engenders an active learning experience for all parties involved: the writers, the performers and the audience. Through this active (and interactive) learning process, educators have been better able to convey the complexity of social realities that surround HIV/AIDS. Each performance is followed by a discussion with the audience, and based on this step, multiple perspectives on the issues are discussed, and even recasted in future performances.

Objectives: The project aims to convey and interpret the complex social realities of lived experiences of HIV/AIDS. Another objective of the project is to surpass (to some extent) linguistic and scholarly barriers, and to be accessible to youth and to a wider sector of the public.

Methods: Data was collected from 17 focus groups in Ontario, 2 of which were based at the University of Toronto. Information and reflections based on this data were incorporated into three sessions of reflective writing. Based on these pieces of writing, plays and monologues were created, and later performed before live audiences. Each performance was followed by a discussion with the audience members.

Results: Lived and envisioned realities of HIV/AIDS came to surface in the discussions that followed the performances. Both the performers and the audience members emerged from the experience with a renewed understanding of what it means to live with HIV/AIDS, because of the simulation of social reality that is accomplished by the genre of theatre.

Conclusions: Performed ethnography or ethnodrama proves to be a valuable tool for education and research in the field of HIV/AIDS. It engages its intended audience in an active and accessible manner. Moreover, it is better able to simulate and convey an understanding of the complexities of living with HIV/AIDS.

Contact Information: Nidhi Punyarthi, Tel: 416-494-2563, Email: nidhi.punyarthi@utoronto.ca

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PROSPECTIVE EVALUATION OF A LOCAL HIV MEDIA CAMPAIGN TARGETING GAY MEN

Anthony Lombardo [1]; Thomas Lampinen [2,3]; Keith Chan [2]; Robert Hogg [2,3];
1-Department of Public Health Sciences, University of Toronto; 2-BC Centre for Excellence in HIV/AIDS, Vancouver, BC; 3-Department of Health Care and Epidemiology, University of British Columbia, Vancouver, BC;

Plain Language Summary: The Vancouver "Arouse" campaign aimed to counter gay men's attitudes that HIV medications are easy to take by highlighting the side effects of the drugs. An evaluation of the campaign was unable to show changes in high risk sexual behaviour with exposure to the campaign, and it found little evidence that campaign exposure changed views on the threat of HIV infection as related to the availability of HIV medication.

Objectives: The "Arouse" campaign ran in Vancouver, BC, from February through April, 2002. It attempted to counter optimistic views about HAART by demonstrating the reality of the drugs' side effects. The study aimed to relate exposure to the "Arouse" campaign with individual-level change in sexual risk behaviour and HAART optimism.

Methods: MSM enrolled in the Vancouver "Vanguard" study reported unprotected anal intercourse (UAI) and STD incidence at annual study visits, and reported retrospectively their exposure to the "Arouse" campaign. Treatment optimism was measured on beliefs about prevention in the absence of an HIV cure, as well as on the perceived threat of HIV infection, and worry about becoming HIV-infected, with the existence of HAART. Pre- to post-campaign changes in binary behavioural variables were assessed using match-paired methods.

Results: Among 289 men surveyed (median age, 30), most (69%) recalled seeing the campaign. No significant pre-post change in risk behaviour was observed among men who saw the campaign. However, 27% (54 of 195) of such men said the campaign influenced their thoughts or actions and these men were more likely to report engaging in UAI with casual partners post-campaign. A positive, though non-significant, dose response was observed between campaign exposure and change toward high risk behaviour and incident STD. There were no marked changes found in the treatment optimism measures.

Conclusions: The data from this group of young gay men enrolled in the "Vanguard" cohort do not suggest a shift in the expected direction: less sexual risk behaviour or lower treatment optimism scores among men who were affected by the campaign compared to those who were not. The study was unable to demonstrate a relationship between campaign exposure and significant reductions in high risk sex nor self-reported incident STD. Nor was it able to demonstrate significant reductions in treatment optimism scores. "Arouse" was the first Canadian campaign to directly address attitudes towards HIV medication, and its evaluation suggests direction for future work, such as the need for representative samples in evaluation and the use of broader evaluation endpoints.

Contact Information: Anthony Lombardo, Tel: 647-430-8221, Email: anthony.lombardo@utoronto.ca

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MEANINGFUL HIV/AIDS PREVENTION INFORMATION FOR ETHNO-RACIAL MSM: RESULTS FROM THE 2005 SEXUAL HEALTH PROMOTION RESEARCH NEEDS ASSESSMENT FOR MSM IN CANADA

Tarik Bereket [1]; Ted Myers [1]; Dan Allman [1,2];
1-HIV Social, Behavioural and Epidemiological Studies Unit, Faculty of Medicine, University of Toronto; 2-Centre for Research on Families and Relationships, The University of Edinburgh;

Plain Language Summary: To assist in the development of a national toll-free telephone survey, a national research needs assessment was undertaken. The main goal of this developmental study was to identify both new and ongoing areas of research need that would provide useful information for future community development and sexual health promotion programming for MSM. This study utilized a web-based platform throughout Canada. AIDS Service Organizations (ASOs), Community AIDS Organizations (CAOs), and/or members of the Canadian AIDS Society which deal with men's issues participated. The main highlights related to the specific contexts and issues around the availability of meaningful HIV/AIDS prevention information for ethno-racial MSM are discussed.

Objectives: To understand the specific contexts and issues around the availability of meaningful HIV/AIDS prevention information for ethno-racial MSM in Canada.

Methods: The study utilized a web-based platform (www.msm-health.ca) nationwide. AIDS Service Organizations (ASOs), Community AIDS Organizations (CAOs), and/or members of the Canadian AIDS Society which deal with men's issues participated. The questionnaire, available both in English and French, was widely disseminated to a total of 130 organizations, with a 64% response rate. Ineligible ASOs included networks, hospices, organizations dealing with women or children's needs exclusively, and ASOs with no prevention programs for MSM; comprising 31% of the total sampling frame. The study sought responses from persons in organizations responsible for sexual health promotion for MSM. In addition to responses to the survey, extensive follow-up telephone consultations with sexual health educators for MSM and other key informants from ASOs were conducted across the country. The information obtained is primarily quantitative, and descriptive in nature.

Results: A majority of ASOs responding (65.1%) indicated that lack of sensitivity to ethno-cultural differences is a challenge to the dissemination of HIV/AIDS prevention information for MSM. ASOs highlight that immigrant MSM with diverse ethno-cultural backgrounds (77.1%) or with diverse language backgrounds (75%), and ethno-racial MSM in general (72.5%) have specific unmet sexual health prevention program needs. While ASOs in smaller cities (73.5%) point out that refugee and newcomer MSM get 'very little' focus in the delivery of HIV prevention programs, ASOs from larger cities (56.3%) call attention to a similar lack of focus. Although there was much uncertainty around the factors making refugee & newcomer MSM more vulnerable to HIV, the following were identified: fear of rejection by families & communities (76.9%), living in isolation (72.5%), rejection from families (70%), and lack of ethno-specific MSM support groups (62.5%); while insufficient language-specific/ culture-specific HIV resources, living in poverty, not understanding HIV prevention messages in English or French, and isolation because of limited English/French language skills were equally stressed (65%) as factors enhancing vulnerability to HIV.

Conclusions: There is considerable uncertainty regarding issues among ethno-racial MSM across the country. The study identifies the need for further research and discussion to help better understand the sexuality of men within and between different ethno-racial communities, and the importance of these for HIV/AIDS programming in smaller and larger cities across Canada.

Contact Information: Tarik Bereket, Tel: 416-642-6486 x210, Email: tbereket@ohtn.on.ca

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AGE-RELATED TEMPORAL TRENDS IN INSERTIVE AND RECEPTIVE UNPROTECTED ANAL INTERCOURSE (UAI) AMONG MEN WHO HAVE SEXUAL RELATIONS WITH OTHER MEN (MSM) IN MONTREAL WHO WERE ENROLLED IN THE OMEGA COHORT STUDY

Clemon George [1]; Michel Alary [2,3]; Joanne Otis [4,5]; Robert Remis [6]; Eric Demers [2]; Benoit Masse [7]; Bruno Turmel [3]; Roger LeClerc; Jean Vinclette [8]; Raymond Lavoie [5];
1-Mental Health Services, St. Michael's Hospital, Toronto, Ontario; 2-Centre hospitalier affilie universitaire de Quebec, and Universite Laval, Quebec, Quebec; 3-Institut national de sante publique du Quebec, Quebec; 4-Universite du Quebec a Montreal, Montreal, Quebec; 5-COCQ-Sida, Montreal, Quebec; 6-University of Toronto, Toronto, Ontario; 7-Fred Hutchison Research Center, Seattle, WA, USA; 8-Service microbiologie, Centre hospitalier de l'Universite de Montreal, Hopital Saint Luc, Montreal, Quebec;

Plain Language Summary: This study complements our previously published study (George C, Alary, M, Otis J. et al. Nonnegligible Increasing Temporal Trends in Unprotected Anal Intercourse Among Men Who Have Sexual Relations With Other Men in Montreal (J Acquir Immune Defic Syndr. 2006; 41:365-370). It describes the temporal trend in UAI among MSM in Montreal

Objectives: To determine age-related temporal trends in unprotected anal intercourse among men who have sex with men in Montreal (1996 to 2003).

Methods: Trend analysis using the Generalized Estimating Equation is based on data collected in the Omega cohort study. Analyses were done for length of cohort membership (visit) and for calendar time for all visits (calendar time), per type of sexual partner. Analysis are stratified by insertive (I-) and receptive (R-) unprotected anal Intercourse. Odds ratios (OR) are per 6-month period.

Results: There was a notable increase in both I- and R- UAI by both visit and Calendar time periods. By Visit the following increases were noted: I-UAI Regular seronegative partner (Regular-ve) (OR 1.06, 95% CI 1.03 – 1.09); R-UAI (OR1.05, 95% CI 1.03 – 1.09), Any type of Partner (ANY); both I-UAI and R-UAI (OR 1.05, 95% CI 1.03-1.07), Casual partners (Casual); I-UAI (OR 1.05, 95%CI 1.01-1.10), R-UAI (OR 1.05, 95%CI 0.99 -1.11). By calendar time, there was a small increase in I-UAI with Regular-ve, ANY and Casual partners. However, for both Regular-ve and ANY categories, there were important differences in trend by age for younger men up to 20 years (Young) and those between 35 – 40 years (Mid-age) as follows: Regular-ve (OR 1.05, 95% CI 1.02-1.09) (young); (OR 1.04, 95% CI 1.01-1.08) (mid-age); ANY (OR 1.04, 95% CI 1.02-1.07) (young); (OR 1.04, 95% CI 1.01-1.07) (mid-age). For R-UAI, there was a consistent increase for Regular-ve but for Casual, there were also difference by age whereby the Young increased their R-UAI (OR 1.07 95%CI 1.00 -1.14) but the Mid-age and those 45 – 50 years ((OR 0.89, 95%CI 0.80 -0.99) and (OR 0.88, 95%CI 0.79 -0.98), respectively) reduced the proportion of R-UAI. There was a non-negligible and consistent increase in UAI among Omega participants, between 1997 and 2003. Young MSM may be at a higher risk for acquiring HIV.

Conclusions: There was a non-negligible and consistent increase in UAI among Omega participants, between 1997 and 2003. Young MSM may be at a higher risk for acquiring HIV.

Contact Information: Clemon George, Tel: 416-864-6060 x6493, Email: georgec@smh.toronto.on.ca

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HAART-RELATED BELIEFS AND UNPROTECTED ANAL INTERCOURSE WITH SERODISCORDANT OR UNKNOWN HIV STATUS PARTNERS IN A CANADIAN SAMPLE OF MEN WHO HAVE SEX WITH MEN

Trevor A. Hart [1]; Carolyn A. James [1]; J. Gary Myers [1]; Karen E. Roberts [1];
1-Department of Psychology, York University;

Plain Language Summary: Men who have sex with men (MSM) account for 69.6% of HIV cases in Canada. Beliefs about HAART were associated with increased risky sex among MSM in predominantly U.S. studies (cf. Crepaz, Hart, & Marks, 2004). The present study examined 4 types of beliefs as predictors of unprotected sex with serodiscordant or unknown HIV status partners in a Canadian sample of MSM: 1) transmissibility beliefs (HAART reduces HIV transmission), 2) optimism about non-transmission of HIV because of HAART 3) HAART increases side effects, and 4) HAART causes health improvement among HIV+ people.

Objectives: This purpose of this study was to examine whether beliefs about HAART were associated with increased risky sex among MSM in a Canadian sample.

Methods: The sample consisted of 554 adult MSM (M= 37.45, SD= 11.49) recruited at the 2005 Toronto Gay Pride Festival. 81.2% were HIV-negative, 13.7% were HIV+ (58.3% on HAART), and 5.1% were uncertain about their HIV-status. Participants completed an anonymous questionnaire about HAART beliefs and sex over the past 6 months with short-term (<6 month duration) and longer-term (≥6 month duration) partners.

Results: Among HIV+ participants, transmissibility beliefs were associated with increased unprotected insertive anal intercourse (UIAI), OR= 6.14, 95% CI= 11.40-33.07. Optimism about non-transmission was associated with increased UIAI, OR= 10.00, 95%CI =1.18–84.78, and increased unprotected receptive anal intercourse (URAI), OR= 3.52, 95%CI= 1.00–12.39. Side effect and health improvement beliefs did not predict risky sex. Among HIV- participants, 1) transmissibility beliefs, OR= 2.99, 95% CI= 1.10–8.13, and 2) health improvement beliefs were both associated with URAI with longer-term partners, OR= 2.83, 95%CI= 1.09-7.34. Optimism about non-transmission was associated with UIAI with casual partners, OR= 2.53, 95%CI= 1.27–5.03. Side effect beliefs did not predict risky sex.

Conclusions: The present study suggests that beliefs about HAART regarding HIV transmission may be more likely than beliefs about HAART-related HIV severity to predict unprotected anal intercourse with serodiscordant or unknown HIV status partners. Prevention messages should focus efforts on how HAART cannot totally prevent HIV transmission.

Contact Information: Trevor Hart, Tel: 416-736-2100, Email: thart@yorku.ca

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INNOVATIVE STRATEGIES IN REACHING OUT TO SOUTH ASIAN MEN WHO HAVE SEX WITH MEN (MSM) AND WHO DO NOT IDENTIFY AS GAY OR QUEER

Paras Junior Prashad [1]; Seema Opal; Firdaus Ali; Vijaya Chikermane; Dunstan Egbert; Rounak Khan; Vijay Saravanamuthu; Zavare Tengra;
1-Alliance For South Asian AIDS Prevention;

Plain Language Summary: This presentation will highlight the specific community-based outreach strategies used for South Asian MSM who do not identify as gay. In 1996, ASAAP began MSM programming due to the lack of culturally specific programs at mainstream organizations. In conjunction with peer service users, new services reflecting South Asian faces in South Asian languages such as Bengali, Gujarati, Hindi, Punjabi, Tamil, and Urdu were developed including safer sex and gay men's health brochures, anonymous HIV testing and counselling, support and social groups, websites, anti-homophobia/ STI / healthy sexuality workshops, and safe social spaces. Networking with other ethno-specific and mainstream agencies also shapes programming. Recently, media outreach has been targeted to the South Asian community to raise awareness and support around MSM issues.

Objectives: In Canada, MSM are the largest group affected by HIV and heterosexual exposure has increased by 38%. HIV+ clients at ASAAP have increased by more than 40%. Homosexuality is still not accepted in many segments of the South Asian community. Often, South Asian MSM enter heterosexual relations and also engage in unsafe same sex relationships due to homophobia, racism, sexism, poverty and language and cultural barriers. Stigma and discrimination make it difficult for MSM to make healthy sexual choices. To normalize MSM identities in ethno-specific communities, prevention education outreach must be culturally and linguistically specific to the target group

Methods: In order to reduce HIV transmission among South Asian MSM, ASAAP has developed innovative outreach strategies that provide support, education and advocacy. MSM outreach activities initiatives work to frame sexual health and well-being in a holistic and non-judgmental approach.

Results: ASAAP has developed social/support groups, Dosti and Snehithan for South Asian MSM to socialize and build supportive networks with other men who share the same culture and language. These groups provide South Asian MSM with the support they need in order to feel comfortable sharing their life experiences in safe, non-judgmental, and confidential environments. Service-users request accessible education and resources that are culturally reflective. A safer-sex and anti-homophobia brochure in seven South Asian languages was developed to meet these needs. This material is distributed in bathhouses, bars, schools, community centers and other South Asian spaces.

Conclusions: Support programs and materials developed along with specific outreach tactics have seen positive feedback from community members/service users.
Peer service users must be involved from planning to implementation for effective and effective outreach services to be created and delivered. Peers are integral for creating and delivery of services. Networking with other ethno-specific and mainstream organizations provides greater understanding of the commonalities and difference among MSM.

Contact Information: Paras Junior Prashad, Tel: 416-599-2727 x2, Email: desimen@asaap.ca

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RELIGION VERSUS ETHNICITY AS PREDICTORS OF UNPROTECTED VAGINAL INTERCOURSE (UVI) AMONG YOUNG CANADIAN ADULTS

C.A. James [1]; K.E. Roberts [1]; T.A. Hart [1]; L. Iwenofu [1];
1-Psychology Department, York University;

Plain Language Summary: Despite the fact that young adults are considered to be at increased risk for contracting HIV (e.g., Bryan et al., 2004), little research has been done to examine differences in sexual risk behaviours according to ethnic and religious background in this age group. Most of these studies fail to address the increasing ethnic and religious diversity in many urban areas of North America.

Objectives: The purpose of this study was to examine differences in sexual risk behaviours according to ethnic and religious background in young adults.

Methods: The current study examined the relation between ethnicity and religion and UVI in a highly ethnically and religiously diverse sample of 511 young adults (M = 18.62, SD = 1.09). Sexual behaviour in the past 6 months was assessed: 47.2 % of the sample had vaginal intercourse and 30.6% reported UVI.

Results: Entered simultaneously into a logistic regression, religion but not ethnicity predicted UVI, even when controlling for other demographic variables. Compared to Muslims, Catholics (OR = 4.99, 95% CI = 1.87-13.33), other non-Catholic Christians (OR = 3.69, 95% CI = 1.34-10.17), Jews (OR = 3.66, 95% CI = 1.20-11.15) and non-religious/agnostics (OR = 3.98, 95% CI = 1.40-11.35) were more likely to report UVI. Examining unprotected vaginal intercourse only among those who had any sex, Muslims were no less risky than other religious groups, suggesting that Muslims had less UVI because they were less likely to be sexually active. Catholics (OR = 2.98, 95% CI = 1.38-6.44) and other non-Catholic Christians (OR = 2.50, 95% CI = 1.04-5.99) were more likely than non-religious/agnostics to have engaged in UVI.

Conclusions: The present findings indicate that there may be important differences among individuals of different religious backgrounds that can have implications for HIV risk. Religion may potentially play a more important role than ethnicity in predicting UVI among young adults in North America.

Contact Information: Trevor Hart, Tel: 416-736-2100 x33975, Email: thart@yorku.ca

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A PRESENTATION OF THE 1ST EDITION HIV PREVENTION GUIDELINES AND MANUAL (HPG & M): A TOOL FOR SERVICE PROVIDERS SERVING AFRICAN AND AFRICAN CARIBBEAN COMMUNITIES IN CANADA

LLana James [1,2];
1-African and Caribbean Council on HIV/AIDS in Ontario; 2-Women's Health in Women's Hands;

Plain Language Summary: The 1st Edition of the HIV Prevention Guidelines and Manual is a unique population specific tool that has been developed to meet the needs of service providers that serve African and African Caribbean people living in Canada.

Objectives: The HPG & M is a key tool for reducing and eliminating HIV transmission and provides service providers with specific information about key factors in HIV prevention within this population, how to overcome barriers to HIV prevention and diagnosis, risk assessment and how to develop an HIV Prevention Plan with individuals in an appropriate manner that acknowledges the diversity within the African and African Caribbean communities residing in Canada.

Methods: The HPG & M was developed via literature review, working group, two day consensus building workshop, vetted by ACCHO, reviewed by 50 people ranging from clinicians, medical officier, HIV/AIDS specialist physicians, public health, community health providers etc.

Results: The HPG & M has recently been published and disseminated it is available in English and French in hardcopy and PDF on line.

Conclusions: The 1st HIV Prevention Guidelines and Manual appeals to a broad range of service providers in clinical and non clinical settings as well as community based settings. The HPG & M addresses issues pertinent to service providers whether or not their primary area of focus is HIV prevention and diagnosis. The HPG & M can assist service providers with recognizing opportunities for providing appropriate, client focused service provision.

Contact Information: LLana James, Tel: 416-593-7655 x229, Email: incwell@rogers.com

Health Services and Knowledge Transfer

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OPERATION HAIRSPRAY - AN INNOVATIVE COMMUNITY APPROACH TO HIV/AIDS EDUCATION WITH AFRICAN AND CARIBBEAN COMMUNITIES – RESULTS OF A 1 YEAR PILOT

Zhaida Uddin [1];
1-Ottawa Public Health, Multicultural Health Program;

Plain Language Summary: Operation Hairspray is an innovative peer-led health promotion initiative, which seeks to engage African and Caribbean hairdressers and barbers as a channel to reach people from countries where HIV is endemic. In 2001, HIV infections among people from African and Caribbean countries where HIV is endemic represented a quarter of all reported HIV cases in Ottawa. This trend is not limited to Ottawa, epidemiological data show a similar pattern of increase occurring provincially and nationally. Ottawa Public Health wishes to address these issues by implementing a peer-led health promotion strategy to ensure better access to knowledge and support for members of the African and Caribbean communities.

Objectives: Are Peer Volunteers, specifically, hairdressers and barbers from the African and Caribbean community an effective channel to provide HIV/AIDS prevention information to people from countries where HIV is endemic?

Methods: The project seeks to increase community capacity, increase access/reduce barriers to health information on STI's and HIV/AIDS prevention and evaluate the effectiveness of a peer-led model as a channel to increase knowledge about HIV/AIDS prevention within the African and Caribbean communities in Ottawa, Canada. Several studies and research projects have demonstrated that the peer-led model is an effective health promotion strategy. Hairdressers and Barbers, who provide services to the African and Caribbean communities, in Ottawa are recruited and participate in training to become peer educators. Through this training, participants acquire: 1) the knowledge and the skills needed to integrate STI and HIV/AIDS prevention education within their practice and; 2) the ability to recognise opportune moments to share this information within client conversations. Data collection tools include: Pre and post training questionnaires for Peer Educators, Log Sheets to track type and number of community contacts, Reaction sheets, Log Book.

Results: Since early 2005, fifteen peer volunteers have been recruited and trained to deliver HIV/AIDS education information to their clients. Preliminary analysis of data collected on the log sheets indicates that all trained peer volunteers have been able to have between 1-61 discussions per week about HIV with their clients. Building partnership and trust within the community takes a lot of investment of time, however, once the community is on board, many doors open to provide health education information.

Conclusions: This appears to be an effective health promotion strategy for disseminating information and raising awareness of HIV/AIDS and local services with Ottawa's African and Caribbean communities. Next steps -Partnerships development with local community health centres.

Contact Information: Zhaida Uddin, Tel: 613-580-2424 x20136, Email: zhaida.uddin@ottawa.ca

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EMBODIED KNOWLEDGE: THE UNIQUE CONTRIBUTION OF PEOPLE LIVING WITH HIV IN HIV TREATMENT KNOWLEDGE-BUILDING AND DECISION-MAKING

Tim Rogers [1]; Darien Taylor [1];
1-Canadian AIDS Treatment Information Exchange (CATIE), Toronto, Canada;

Plain Language Summary: The Canadian AIDS Treatment Information Exchange (CATIE) is a national organization which provides accessible, accurate and current HIV treatment information. CATIE plays an important national role in mediating between evidence-based HIV research, medical knowledge and clinical practice and the experiential, embodied HIV treatment knowledge of PHAs. Experience-based treatment knowledge is traditionally considered less important than evidence-based medical knowledge. Research has shown, however, that the creation of embodied knowledge, by translating biomedical information into experiential terms, is central to the learning strategies used by people living with HIV/AIDS (PHAs) for building treatment knowledge. Learning from the experiences of other PHAs and using services provided by peers have a positive effect on the sense of personal efficacy, empowerment, knowledge-building, informed decision-making and overall wellbeing of PHAs.

Objectives: Objectives of CATIE's delivery of accessible and credible HIV treatment information include: 1) the meaningful involvement of PHAs in guiding and delivering all of our programs and services; 2) the use of multiple learning formats and media; 3) the support of staff and volunteers development in adult learning methodologies; and 4) the translation of our treatment information resources into a variety of languages in order to reach out to as wide as possible an audience of PHAs in Canada, along with their service and health care providers.

Methods: Data was compiled from: 1) CATIE's workshop evaluations from 2003-2006, which included a satisfaction survey tool completed by over 3,000 PHAs, AIDS service providers and health care providers working in the field of AIDS across Canada; 2) the results of an 2004 evaluation of the readership of CATIE's "Positive Side" magazine; 3) a needs assessment on e-learning completed for CATIE in 2005 by the Ontario Institute for Studies in Education, and 4) evaluation results of an ongoing multi-phase research project conducted by the national Positive Youth Project.

Results: CATIE's evaluations show that people with HIV want treatment information from trusted sources, such as peers, local health care providers or local AIDS service organizations, with whom they have an existing relationship. Distance and e-learning strategies have the ability to reach out to large audiences of PHAs across Canada but these technologies can be somewhat depersonalized and detract from the benefits which CATIE has found to be associated with "embodied" treatment information provision.

Conclusions: Programs and services which are created from the point of view/s of PHAs and which are provided by PHAs are valued by service users who are themselves living with HIV/AIDS. This model of service provision has a positive effect on knowledge-building, decision-making and the wellbeing of PHAs, both those who provide and those who use these services. However, as technological advances offer the potential of greater electronic connectivity, CATIE must strive to maintain a degree of direct personal contact in the provision of its services.

Contact Information: Darien Taylor, Tel: 416-203-7122 x250, Email: dtaylor@catie.ca

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THE ROLE OF PEER-DELIVERED COMMUNITY DEVELOPMENT INITIATIVES IN BUILDING HIV TREATMENT LITERACY

Michael Bailey [1]; Darien Taylor [1];
1-Canadian AIDS Treatment Information Exchange (CATIE), Toronto, Ontario;

Plain Language Summary: The Canadian AIDS Treatment Information Exchange (CATIE) is mandated to supply people living with HIV/AIDS and the people and organizations that support them with accessible, unbiased and timely treatment information. Since the introduction of HAART, this role has changed greatly. In addition to changes in the treatment of HIV, the populations infected and affected by HIV have diversified, requiring greater cultural sensitivity, attention to service users' literacy levels and innovative strategies to make HIV treatment information accessible to marginalized populations. As a result, CATIE must work collaboratively with AIDS service organizations (ASOs) and other community organizations across Canada to address specific regional and community needs. In January 2005, CATIE launched an 18-month Capacity Building Project to integrate treatment information into existing community prevention, care and support programs in seven regions across Canada.

Objectives: The objectives of CATIE's community capacity-building initiative were: 1) To deliver and evaluate the CATIE Capacity Building model in 7 pilot sites; 2) To develop a manual for the Capacity Building Model that addresses the needs of specific marginalized populations and can be adapted to community and regional needs across Canada.

Methods: Program delivery was preceded by a needs/capacity assessment process including 4 components: community network assessments, organizational assessments, individual assessments and a process evaluation. The network assessment consisted of a 3-4 hour needs assessment workshop with each site's community network, examining the community's definition of "treatment integration", current models of treatment information integration and current needs/capacities. The organizational assessment included a site visit with review of key organizational documents and a 3-4 hour needs assessment workshop. Individual assessments involved a web-based survey for workshop participants assessing the perceived value of service integration, access to treatment resources, knowledge of HIV/AIDS treatment, and skills related to delivering treatment information. Customized interventions involving a 2-day training were then developed and implemented.

Results: Evaluation suggests that the assessment process is worthwhile and stimulates useful reflection and discussion. The assessment process reported different organizational strengths and weaknesses as well as some commonalities, such as acknowledgement of the need to better integrate HIV treatment information with other site programs and services, strong motivation to implement 'integration' despite a lack of human & physical resources and wariness around the complexities of HIV treatment information.

Conclusions: This capacity building model serves as the basis for CATIE to initiate and develop productive partnerships. As PHA treatment information issues evolve, CATIE should take a leadership role in addressing barriers of access such as culture, language, literacy level, drug use, location and poverty and work collaboratively with networks and ASOs to implement them. Building and supporting community HIV treatment capacity is essential to promote HIV treatment education and optimize community access to HAART. The community capacity-building model is time-consuming and involves building trust and mutual respect, as well as carefully outlining roles and expectations. The involvement of peers as treatment trainers is an important part of this model.

Contact Information: Darien Taylor, Tel: 416-203-7122 x250, Email: dtaylor@catie.ca

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CONNECT: BUILDING A CANADIAN HIV/AIDS INFORMATION GATEWAY

Terry Gould [5]; Erica Lee [1]; Susan Massarella [3]; Veronique Moal [2]; Tom Richardson [4];
1-AIDS Committee of Toronto; 2-AIDS Vancouver; 3-Canadian AIDS Treatment Information Exchange; 4-Canadian HIV/AIDS Information Centre; 5-Canandian HIV/AIDS Legal Network;

Plain Language Summary: Many voluntary sector organizations in Canada have excellent, specialized library collections that are often overlooked or underutilized by the health library community and the broader public. The CONNECT website is designed to boost the profile and use of several valuable collections. It draws together the library collections of 5 major HIV/AIDS organizations in Canada: AIDS Committee of Toronto; AIDS Vancouver; Canadian AIDS Treatment Information Exchange; Canadian HIV/AIDS Information Centre; Canadian HIV/AIDS Legal Network. Together, these organizations have a comprehensive collection of monographs, periodicals, government documents, grey literature, graphic materials, and multimedia dating back to the beginning of the epidemic in Canada. The poster will highlight the history of the CONNECT project, features of the website and database, key activities and lessons learned, and plans for the future.

Objectives: To help people living with HIV/AIDS, people working with HIV/AIDS, and other affected populations increase their awareness of and access to HIV/AIDS information in Canada, the CONNECT project aims to bring together the library collections of 5 major Canadian HIV/AIDS organizations through the development of a joint online library catalogue.

Methods: The project involved collaboration among community-based and national HIV/AIDS organizations in Vancouver, Ottawa and Toronto. The CONNECT team worked in partnership to create library database and cataloguing standards, the joint CONNECT catalogue database, and the CONNECT website.

Results: The CONNECT project resulted in a bilingual database and website, found online at http://www.hivinfovih.ca, that allow for coordinated access to the resource collections of the 5 partner agencies. The project also increased the communication and standardization between the libraries of the 5 partners.

Conclusions: The CONNECT catalogue is a tool that Canadians can use to search for and access a wide range of HIV/AIDS information. It is also a tool that has brought together 5 major HIV/AIDS library collections in Canada and improved the potential for continued future collaboration and service delivery.

Contact Information: Erica Lee, Tel: 416-340-8484 x303, Email: elee@actoronto.org

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WHAT RESEARCHERS NEED TO KNOW ABOUT RECRUITMENT AND DATA COLLECTION: LESSONS LEARNT FROM THE PUBLIC HEALTH FIELD

Ana Johnson-Masotti [1]; Liz Romero [1]; Debbie Sheehan [2]; Karen Verhoeve [3]; Heidy Choi [3]; Suzanne Newmark [2]; Fiona Newton-Brown [2];
1-Queen's University; 2-City of Hamilton Public Health Services; 3-Region of Waterloo Public Health;

Plain Language Summary: A pilot research study was conducted in partnership with two health units in Ontario to test a methodology to evaluate the cost-effectiveness of their HIV and Sexually Transmitted Infections prevention programs. Experience from researchers was documented to identify problems encountered and solutions implemented.

Objectives: To identify the most frequent problems faced by researchers while recruiting and collecting data and to create a library of cases.

Methods: We documented, in the form of case studies, the experience of researchers recruiting and collecting data from three public health programs. After reviewing the case studies, we identified problems related to recruitment, interviews, and incentives offered to participants, as well as solutions implemented.

Results: Illustrate the meaning of "Privacy and Confidentiality": Research subjects do not want the information they provide to be known to individuals in their immediate surrounding. This appears to be more important than any broad confidentiality issues. Privacy and confidentiality need to be focused within their context. Choose type of incentive carefully: We conducted preliminary one-on-one interviews with clients to find out their preferred type of incentive. We found that different types of incentives were preferred among the particular groups (e.g., Tim Horton's, supermarket coupons). Establish rapport with clients: We found that clients were immediately inclined to participate in the research. However, they seemed reluctant to provide personal information (e.g., number of sex acts and partners). It was not until their trust was gained that we were able to engage them. Balance research objectives and service delivery objectives: Researches tended to be concerned with collecting data, time frame, and budget, while health units tended emphasize the importance of preserving clinic flow. On one occasion, our recruitment strategy was creating a bottle neck. After an informal brainstorming session with staff we generated a mutually acceptable solution. Adapting research design to public health practice - the case of eligible clients: Often, what is established through research design cannot be implemented in real settings. In these circumstances, it is useful to collaboratively problem solve (e.g., researchers, public health staff). We found that it was not feasible to recruit first time needle exchange clients. Our design was changed to recruit returning clients.

Conclusions: Our experience can be useful to researchers initiating work in the public health field since previous experiences can help them to solve new problems. The case studies will become part of a library of cases that can be readily consulted by researchers.

Contact Information: Liz Romero, Tel: 1-888-488-7461, Email: romerol@post.queensu.ca

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LEARNING FROM THE GLOBAL VILLAGE EXPERIENCES: FRAMEWORK FOR EVALUATION AND PRELIMINARY INSIGHTS

Alan Li [1,3]; Chad Leaver [1]; Evan Collins [1]; Karen Foreit [1,2]; Vuyiswa Keyi [1]; Laverne Monette [1]; James Murray [1]; Nicci Stein [1]; Robb Travers [1,3];
1-Global Village Monitoring and Evaluation Committee, AIDS 2006 Toronto Local Host; 2-GlaxoSmithKline Positive Action; 3-Ontario HIV Treatment Network;

Plain Language Summary: The Global Village at the International AIDS Conference 2006 was developed as an innovative venue for community engagement and dynamic knowledge transfer exchange. A thorough monitoring and evaluation study was carried out to measure the effectiveness of the Global Village in achieving its objectives. The presentation will share the framework, developmental process, methodology, research instruments and some of the preliminary findings from the evaluation study.

Objectives: Traditional health conferences catered to academic and scientific communities offered limited access and opportunity for grassroot communities and frontline service providers to showcase their experiences and show their knowledge. The Global Village programme at the IAC 2006 was set up to bridge such gaps. The monitoring and evaluation study developed objective instruments to measure the effectiveness of the Global Village in achieving its original objectives of engaging marginalized communities; facilitating discussion on emerging issues; enabling/strengthening coalitions development; as well as how well the Global Village activities integrated with the overall conference activities.

Methods: Guided by a monitoring and evaluation committee made up of volunteers and staff of diverse backgrounds, 15 quantitative and qualitative research instruments were developed and used to collect data to measure different indicators of success of the GV in achieving its stated objectives. Over 1500 responses were collected from delegates, general public and organizers of different programs. An audit was conducted on all submissions to assess the diversity of regional and issue based representation. Data collected were presented to the study team to enable collective analysis and reflection.

Results: Preliminary results shows that the Global Village was equally effective in engaging conference delegates as well as general public. There were overwhelming positive feedback on the relevance and innovation of the GV as an agent for community engagement and knowledge transfer. Insights were gained on the community participants' expectations of the village and factors that enhanced and prohibited participation. Gaps were identified in the integration with the IAC in bridging with the scientific program and with media publicity.

Conclusions: Large sample data on multiple objective indicators collected in the Global Village showed that the GV was successful in achieving most of its stated objectives. The program development as well as the evaluation processes both provided useful lessons and insights that can inform the planning and evaluation of future conferences and other knowledge transfer forums locally and internationally.

Contact Information: Alan Li, Tel: 416-364-2261, Email: alanli@sympatico.ca

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MOBILIZING WHAT KNOWLEDGE? LESSONS LEARNED IN DOING COMMUNITY BASED RESEARCH (CBR) AMONG AFRICAN AND CARIBBEAN GAY, BISEXUAL AND OTHER MEN WHO HAVE SEX WITH MEN (BMSM)

Clemon George [1]; Winston Husbands [1,2]; Barry Adam [3];
1-African and Caribbean Council on HIV/AIDS in Ontario; 2-AIDS Committee of Toronto; 3-Department of Sociology, University of Windsor;

Plain Language Summary: Community based research (CBR) is a valid scientific model of research that enables communities to fully participate in knowledge gathering and translation. It is particularly suitable for research involving stigmatizing behaviours and stigmatizing conditions such as HIV/AIDS as it helps to empower communities with regards to their health. CBR is increasingly being promoted and special funding axes have been created for CBR within the Canadian Institutes of Health Research (CIHR) and the Ontario HIV Treatment Network (OHTN). However, given the current requirements for implementation of CBR, there remain critical barriers for successful implementation of this valuable research model.

Objectives: To enunciate some of the barriers in doing CBR and to find ways of overcoming such disabling factors.

Methods: This insight is situated within a CIHR CBR funded study for and by black gay, bisexual and other men who have sex with men (BMSM) in Toronto. The African and Caribbean Council on HIV/AIDS in Ontario (ACCHO) determined that there was a need for targeted research for BMSM as the epidemiological data show that these men are increasingly affected by the HIV epidemic. The study was designed by researchers from the ACCHO and other academic institutions. Through a lengthy REB review process, various issues were identified that affect how CBR may be implemented.

Results: The following were identified as barriers to creating partnerships between community based organisations and academic institutions: a. Lack of harmonization between the different REBs requiring duplication of resources that are not at the disposal of community organizations; b. Differences in community and institutional ideologies may confound the ethics review process; c. Partnerships between community based organizations and other academic institutions may create issues related to leadership and control.

Conclusions: While some funding agencies require academic partnership for CBR, these institutions may not have in place mechanisms to overcome the systemic barriers to recognition of the mutual benefit of CBR partnerships. Although work is being done by funding agencies to alleviate these barriers, there is a need to promote understanding and harmonization between persons doing CBR and academic institutions. It is hoped that this presentation will be the impetus in creating open and transparent dialogue between funding agencies, community based organizations and academic institutions on CBR process and principles.

Contact Information: Clemon George, Tel: 416-864-6060 x6493, Email: georgec@smh.toronto.on.ca

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'BEYOND TIRED OF DRIVING THAT FAR': LIVING WITH HIV/AIDS IN RURAL CANADA

Tiffany Veinot [1]; Roma Harris [1]; Leslie Bella [2]; Irving Rootman [3]; Judith Krajnak [4];
1-Faculty of Information and Media Studies, The University of Western Ontario; 2-School of Social Work, Memorial University of Newfoundland; 3-Centre for Community Health Promotion Research, University of Victoria; 4-Centre for Clinical Epidemiology and Evaluation, University of British Columbia;

Plain Language Summary: People with HIV/AIDS (PHAs) and their friends/family members face special challenges if they live in rural Canada. We conducted interviews with 16 PHAs and 14 friends/family members of PHAs in two rural regions of Ontario. We have learned about the importance of PHAs in stimulating local response to HIV/AIDS, the potential for rural communities to support PHAs and their friends/family, and the positive roles of some service providers and volunteers in facilitating access to HIV/AIDS information. However, we have also learned that information exchange can be inhibited by stigmatizing attitudes and a lack of open dialogue about HIV/AIDS. Some PHAs have also reported painful breaches of confidentiality, been exposed to misinformation about the disease, and face challenges because of the distances they must travel for appropriate health care and support.

Objectives: PHAs and their friends/family face particular challenges if they live in rural Canada. The presence of HIV/AIDS is often unrecognized by rural residents and, given conservative values in some areas, PHAs may be reluctant to reveal their status to avoid stigma and discrimination. Rural communities may also have limited capacity to provide HIV-related health care, services and support. This study aims to increase understanding about how information related to HIV/AIDS is exchanged in, and affects, rural communities in order to develop new approaches to providing useful and timely information in these settings.

Methods: Individual, in-depth, semi-structured interviews were conducted with 16 rural-dwelling PHAs and 14 friends/family members in a community-based research project in Ontario.

Results: Many rural-dwelling PHAs are selective in disclosing their HIV status to others, decisions reinforced by stigmatizing attitudes, lack of open dialogue and misinformation about HIV/AIDS in some rural communities. Nevertheless, PHAs who have disclosed their status can act as a catalyst for local response to HIV/AIDS, and some community-based AIDS organizations have arisen out local activism. Some participants have extensive, overlapping relationships with others and may draw support from religious affiliations, closely-knit families, health and service providers and/or friends living nearby and outside the region. Local connections may support PHAs, although they can also lead to painful confidentiality challenges. Other PHAs, particularly recent migrants to the regions, have smaller personal networks and rely heavily on health and service providers for support. Rural PHAs frequently encounter difficulties in accessing care due to under-resourcing of local services and/or limited income. Most PHAs rely on specialist health care available only in urban centres, necessitating time-consuming and expensive travel. Many PHAs and friends/family use e-mail socially, but few participants interviewed to date feel that the Internet helps them deal with HIV/AIDS. However, some PHAs who regularly share HIV/AIDS information with others are more enthusiastic about the Internet, relying on it more than other participants for HIV/AIDS information.

Conclusions: Rural-dwelling PHAs and their friends/family have unique experiences due to geographic isolation, densely-knit local communities, values-based stigma and limited local services. Through this research, we aim to achieve the long-term goal of increasing the capacity of rural communities to raise awareness of HIV/AIDS and support people who are affected by the disease, especially through e-health or IT-based strategies.

Contact Information: Tiffany Veinot, Tel: 416-698-7743, Email: tveinot@sympatico.ca

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HIV HEALTH PROFESSIONAL REFERRALS TO COMMUNITY SERVICES AND VIEWS OF SERVICE CHALLENGES IN A NATIONALLY-FUNDED HEALTH-CARE SYSTEM

Catherine Worthington [1]; Ted Myers [2]; Kelly O'Brien [2,3]; Rhonda Cockerill [4]; Stephanie Nixon [3,5]; Tarik Bereket [2];
1-Faculty of Social Work, University of Calgary; 2-HIV Social, Behavioural and Epidemiological Studies Unit, University of Toronto; 3-Department of Physical Therapy, University of Toronto; 4-Department of Health Policy, Management and Evaluation, University of Toronto; 5-Department of Public Health Sciences, University of Toronto;

Plain Language Summary: A national postal survey was conducted with HIV specialists in Canada. We asked them to describe their referrals, and views on HIV service delivery challenges for people living with HIV (PHAs). Most respondents referred their patients to services that addressed social participation restrictions, such as social service assistance, income support, drug coverage, and psychosocial issues. Challenges accessing or delivering services included waiting lists, funding issues, restrictive policies, HIV stigma, and lack of patient information. With the needs of PHAs becoming more complex, community-based services are being used to address social participation restrictions. New approaches are needed to improve the access and delivery of HIV rehabilitation services for PHAs in Canada.

Objectives: To examine HIV specialists' referrals, and views of HIV service delivery challenges in expanding prevention, treatment and social participation needs of people living with HIV (PHAs).

Methods: As part of a nationwide Canadian mail survey of health care providers on HIV and rehabilitation, the known population of HIV specialists (physicians, nurses, social workers, pharmacists, psychologists, and dieticians) was asked about referrals to community service providers and opinions on HIV service delivery challenges. The survey instrument was constructed and pretested with a national advisory committee including PHAs, HIV specialists, and rehabilitation professionals.

Results: The response rate was 55%, yielding 214 completed surveys. Respondents averaged 16 years in practice and had seen a mean of 54 HIV positive clients within the last month. Ninety-one percent were from urban areas, and 8% reported they worked in a northern region. Within the past year, 86% had referred HIV positive clients to a social worker, and 85% to a community-based HIV/AIDS service organization. The largest percent of respondents reported referring clients to services that addressed social participation restrictions, including social service assistance (88%), income support (80%), drug coverage assistance (79%), psychosocial issues (76%), and housing support (74%). Challenges related to HIV service access/delivery reported by respondents included waiting lists (61%), funding issues (high costs, under funding) (59%), restrictive delivery policies (57%), and HIV stigma and discrimination (53%). Challenges specific to rehabilitation service provision included availability (68%) and client lack of information (66%).

Conclusions: As service needs of PHAs become more complex, enhanced community-based services are required to address social participation restrictions (including income, housing, and psychosocial issues) impacting the social inclusion of PHAs within a broader determinants of health perspective. Even within Canada's universal healthcare system, significant barriers to HIV service delivery exist.

Contact Information: Kelly O'Brien, Tel: 416-978-0565, Email: kelly.obrien@utoronto.ca

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INTERPROFESSIONAL LEARNING IN REHABILITATION IN THE CONTEXT OF HIV: USING MULTI-SECTOR CONSULTATION TO INFORM THE EDUCATION OF REHABILITATION PROFESSIONALS ON HIV/AIDS IN CANADA

Gillian Bone [1,2,3]; Elisse Zack [1]; Debra Cameron [3,4]; Kelly O'Brien [2,5];
1-Canadian Working Group on HIV and Rehabilitation; 2-Department of Physical Therapy, University of Toronto; 3-International Centre for Disability and Rehabilitation, University of Toronto; 4-Department of Occupational Science and Occupational Therapy, University of Toronto; 5-Centre for Research on Inner City Health, St. Michael's Hospital, Toronto, Canada;

Plain Language Summary: We explored existing educational courses on HIV and rehabilitation. We asked individuals to describe the learning needs of rehabilitation professionals, identify relevant content to include, and the best ways to teach an interprofessional course on HIV and rehabilitation. Fifteen rehabilitation professionals (occupational therapists, physical therapists and speech-language pathologists) took part in a one and a half day course in Toronto on HIV and rehabilitation. The course was taught by PHAs and rehabilitation professionals, and included topics such as HIV 101, HIV-related disability, potential treatment strategies and issues related to attitudes, and sensitive practice. Course evaluations were positive showing an increase in participants' comfort and confidence in providing rehabilitation services to PHAs. This curriculum could be applied with other health professionals to better meet the rehabilitation needs of PHAs.

Objectives: To develop an interprofessional education curriculum for rehabilitation professionals on HIV/AIDS and rehabilitation in Canada.

Methods: We developed a conceptual framework of existing HIV curricula for health care professionals on HIV/AIDS. Curriculum resources, educational initiatives and programs on HIV and/or rehabilitation were explored. We conducted 7 focus groups and 31 key informant interviews with people living with HIV (PHAs), rehabilitation professionals, curriculum experts and other HIV and rehabilitation stakeholders. We asked individuals to describe the learning needs of rehabilitation professionals, identify relevant content and delivery methods for an interprofessional curriculum.

Results: A national interprofessional curriculum for rehabilitation professionals (occupational therapists, physical therapists and speech-language pathologists) was developed and piloted in Toronto in June 2006. Recommendations for key content areas included: HIV 101, HIV-related impairments, activity limitations and participation restrictions, potential intervention strategies and issues related to attitudes, and sensitive practice. Recommendations for curriculum delivery methods included: engaging PHAs as educators, providing useable resources in a practical form, interprofessionalism, case-based learning and creating opportunities for distance learning. Fifteen rehabilitation professionals participated in the course and faculty included 3 PHAs, 3 advisory committee members and 3 representatives from different rehabilitation professions. Evaluation indicated an increase in participants' comfort and confidence in providing rehabilitation services to PHAs.

Conclusions: Consultations with HIV stakeholders offered new and innovative considerations for education content and delivery. Key content areas and methods of curriculum delivery informed the development of the new interprofessional curriculum for rehabilitation professionals. Overall, this curriculum demonstrated effective content and delivery of rehabilitation in the context of HIV. This curriculum could be applied with other health professionals, both within Canada and internationally, to better meet the rehabilitation needs of PHAs.

Contact Information: Gillian Bone, Tel: 416-513-0440 x235, Email: gbone@hivandrehab.ca

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CHALLENGES IN IMPLEMENTING AN HIV POST-EXPOSURE PROPHYLAXIS PROGRAM FOR SEXUALLY ASSAULTED PERSONS IN ONTARIO, CANADA

T. Myhr [1]; H. Husson [1]; S. Balla [1]; T. Leeke [1]; J. Du Mont [1]; M.R. Loutfy [1,2]; S. MacDonald [4]; A. Rachlis [2,3];
1-Women's College Research Institute, Women's College Hospital, Toronto, Ontario; 2-Department of Medicine, University of Toronto, Toronto, Ontario; 3-Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, Ontario; 4-Ontario Network of Sexual Assault/Domestic Violence Treatment Centres, Toronto, Ontario, Canada;

Plain Language Summary: HIV post-exposure prophylaxis (PEP) has been recommended to prevent transmission of HIV following non-occupational exposure (CDC, 2005). In 2003 Ontario implemented a program offering HIV PEP following sexual assault. Health Care Providers faced implementation challenges but identified creative solutions to address many of the barriers encountered.

Objectives: To examine the challenges encountered in implementing a program of universal offering of HIV PEP to at-risk sexually assaulted persons presenting to Ontario's hospital-based Sexual Assault/Domestic Violence Treatment Centres (SATC).

Methods: As part of an HIV PEP Study operating from September 2003 to January 2005, Health Care Providers (HCP) who participated in the implementation of an Ontario-wide HIV PEP program were surveyed and invited to participate in focus groups to elicit their opinions of the program. In addition to formal data collection, opinions of the program were documented in written correspondence between the research coordinator and SATC HCPs. Using qualitative techniques, data were analysed for common themes around barriers to and supports for implementing and sustaining an HIV PEP program.

Results: An HIV PEP program was successfully implemented In 24 SATCs (70.6%) (staff resources, maintaining the follow-up schedule, and organisational resistance prevented implementation in 10 SATCs). Of implemented sites: 35.2% of HCPs responded to a general survey about the program; 80.1% of Follow-up Care Providers responded to a specific survey about the HIV PEP follow-up schedule; and 26 HCPs participated in 4 focus groups. Challenges encountered by SATCs that introduced the new standardised protocols for HIV PEP care fell within three areas: 1) Staff Resources: insufficient HCPs for 24/7 service, insufficient clerical support, insufficient time for client counselling, follow-up schedule; 2) Expertise: inconsistent HIV PEP knowledge (Nurse & Physician level), logistics of HCP training and ongoing education, insufficient HIV Expert support; and, 3) Commitment: staff resistance to new procedures, physician resistance to delivering HIV PEP, hospital administration resistance. Establishing local support networks, ensuring accessibility of HIV PEP information, and flexibility in program delivery were identified as solutions SATCs developed to address challenges.

Conclusions: While funding for staff resources was identified as a significant barrier to program sustainability by nearly 10% of respondents to the general survey, the majority felt that the program was sustainable within their current infrastructure. Findings indicate that despite challenges faced in implementing an HIV PEP program, HCPs were able to propose solutions to ensure HIV care was provided for their clients.

Contact Information: Heather Husson, Tel: 416-351-2538, Email: heather.husson@wchospital.ca

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ASSESSING RECENCY OF IMMIGRATION OF YOUNG ADULTS AND SEXUAL BEHAVIOR, HIV-RELATED KNOWLEDGE AND ATTITUDES TOWARDS HIV ANTIBODY TESTING

Maryna Zhuk [1]; Trevor A. Hart [1]; Carolyn A. James [1];
1-Department of Psychology, York University, Toronto, Canada;

Plain Language Summary: HIV has been shown not only to disproportionately spread in the developing countries but to disproportionately affect the minorities and the underprivileged in the developed countries. Newly arriving immigrants to developed countries often fall into the underprivileged group as they attempt to build their life in the new home country. In 2001, proportion of foreign-born Canadians was highest in 70 years and nearly 1 in 5 schoolchildren in Canadian urban centres were new arrivals.

Objectives: This study examined associations between duration of stay in Canada and sexual behaviour, HIV knowledge, and attitudes towards HIV antibody testing.

Methods: A sample of 519 young adults (AGES 17-24, M=18.3) in Toronto was divided into three groups: non-immigrants (59%), long-term immigrants (living in Canada more than 8 years, 19.7%) and recent immigrants (lived in Canada 8 or less years, 21.4%). The study was conducted through a self-reporting questionnaire.

Results: Non-immigrants were more likely to be sexually active (vaginal, anal, or oral) than recent immigrants (OR=2.14, 95% CI=1.37-3.34) but long term and recent immigrants did not differ in sexual activity. Prevalence of unprotected sexual activity did not differ among the three groups. Recent immigrants had less knowledge about HIV transmission and were more concerned with perceived friends' reaction to getting an HIV test than non-immigrants. Long-term immigrants were more concerned with the family's reaction to getting an HIV test than the non-immigrants or the recent immigrants. No significant differences were observed among the three groups with regards to concerns about the confidentiality of HIV testing.

Conclusions: These data suggest the need to create more specific HIV prevention programs targeting young newly arriving immigrants, who are less sexually active but with less knowledge about HIV. The data also suggest the need to examine differences among immigrants, as long-term and recent immigrants evidenced different patterns of sexual activity and HIV knowledge and attitudes.

Contact Information: Trevor Hart, Tel: 416-736-2100 x33, Email: thart@yorku.ca

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FEAR OF BEING JUDGED AND SOCIAL ANXIETY AS PREDICTORS OF LOW SELF-EFFICACY FOR GETTING TESTED FOR HIV

Karen Roberts [1]; Carolyn James [1]; Trevor Hart [1]; Rodney Blanco [1];
1-Psychology Department, York University;

Plain Language Summary: Previous studies suggest that social anxiety, or fear of being negatively evaluated in social situations, is a risk factor for unprotected sex (e.g., Hart & Heimberg, 2006). Social anxiety has been indirectly linked to HIV testing behaviours (e.g., Greene, Parrott, & Serovich, 1993), however, no study to date has investigated whether social anxiety can predict low self-efficacy for HIV testing.

Objectives: The objectives of the study were to investigate whether social anxiety can predict low self-efficacy for HIV testing.

Methods: 491 university students (80.4% female, 94.7% heterosexual, age = 17 to 24) reported their sexual activities, HIV testing histories and willingness to get tested, beliefs about being judged for getting an HIV test, and degree of social anxiety. 61.5% reported unprotected sex within the past 6 months.

Results: For the 90% of participants who had never been tested, those with high social anxiety were less likely to endorse that they could get an HIV blood test, OR = 2.01, 95% CI = 1.36-2.97, and were more unsure about their ability to get an HIV blood test, OR = 2.10, 95% CI = 1.38-3.18. The results were still significant when controlling for demographic and relationship variables and depression. Those with high social anxiety were more concerned about being judged for getting tested by their friends [OR = 1.72, 95% CI = 1.17-2.53], siblings [OR = 1.92, 95% CI = 1.28-2.89], family doctor [OR = 2.59, 95% CI = 1.53-4.37], grandparents [OR = 2.52, 95% CI = 1.54-4.11], people they work with [OR = 3.05, 95% CI = 1.63-5.70], and God [OR = 1.89, 95% CI = 1.12-3.17].

Conclusions: The present study suggests social anxiety may be associated with reduced confidence in untested persons to get an HIV test. HIV prevention programs should focus on promoting the social acceptability of getting tested for HIV. This could include informing communities, family doctors, and churches about their roles in this process.

Contact Information: Trevor Hart, Tel: 416-736-2100 x33975, Email: healthpsychlab@hotmail.com

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USING A MULTI-SECTORAL AND CROSS-DISABILITY DESIGN FOR POLICY CHANGE

Eileen McKee [1];
1-Episodic Disabilities Project, Canadian Working Group on HIV and Rehabilitation (CWGHR);

Plain Language Summary: Today, people with HIV who have access to treatment are living longer than ever before. There are many disabilities that are similar to HIV in that they are lifelong and episodic in nature. The unpredictable nature of HIV and other episodic disabilities, such as multiple sclerosis, mental illness and cancer present challenges to active labour force participation, stable income and social inclusion as fluctuations occur in a person's ability to participate in the labour force. The goal of the Episodic Disabilities Project, sponsored by the Canadian Working Group on HIV and Rehabilitation (CWGHR), is to determine program and policy changes for optimal labour force participation for PHAs and people with other episodic disabilities.

Objectives: The objectives were to: 1. Develop progressive solutions for optimal labour force engagement, income and benefit supports for people with episodic disabilities; 2. Determine the cost of the primary recommendations; 3. Determine knowledge, skills and training needs of human resources professionals about episodic disabilities.

Methods: Implementing a multi-sectoral and a cross-disability perspective, CWGHR undertook: 1. An international review of private and public workplace and income support policies and programs to develop progressive solutions for optimal labour force engagement, income and benefit supports for people with episodic disabilities; 2. A cost-benefit analysis of the primary recommendations; 3. A survey/analysis of the knowledge, skills and training needs of human resources professionals about episodic disabilities.

Results: 1. Common themes of effective models include: a) Multi-sector coordination among all relevant private and public sector stakeholders; b) Flexibility in policies and programs to accommodate episodic participation in the labour force; c) Sustainable income and benefit support regardless of employment status. 2. Policy changes that allowed for partial income support when a person with an episodic disability worked part time would result in significant cost savings. 3. There is a need for a core body of knowledge on episodic disabilities for Human Resources professionals.

Conclusions: 1. Current disincentives to employment must be removed from policies and programs. Flexible policies must be implemented to enable people with episodic disabilities to participate effectively in the workforce and promote income security regardless of employment status. 2. Human Resources professionals, disability case workers, employment counselors and employers need education and training about episodic disabilities. 3. Further research is needed to evaluate the recommendations in real-life situations.

Contact Information: Eileen McKee, Tel: 416-513-0440, Email: emckee@hivandrehab.ca