DESCRIPTION DE L'ÉTUDE

1. RATIONNEL

Since 2010, Canada has processed an increasing number of asylum claims made by individuals from HIV-endemic countries.[1] In 2018 alone, Quebec processed 27,965 asylum claims, more than any other province.[1] As a result, Montreal has witnessed a change in the epidemiology of HIV; while people from endemic countries represented only 15-20% of new HIV infections in 2015-2016, they represented 51% of new infections in 2017.[2] A "new" infection/diagnosis is defined as a positive test among someone who has never previously undergone an HIV test or a positive test among someone whose previous HIV tests have always been negative.[3] The McGill University Health Centre (MUHC) and the Jewish General Hospital (JGH) have thus far served as the primary HIV referral centres for >75% of asylum seekers in Montreal.[4]

Dr. Kronfli, a young investigator, recently analyzed a retrospective cohort of 139 asylum seekers linked to the MUHC for HIV care between June 2017 and November 2018.[5] Overall, 43% (60/139) of the cohort was newly diagnosed in Canada; 25% (15/60) of those newly diagnosed presented with high-level viremia (viral load > 100,000 copies/mL) and 17% (10/60) with baseline resistance to at least one antiretroviral agent. The median time from arrival in Canada to mandatory Immigration Medical Examination (IME) screening, during which time a 4th generation HIV screening test is performed, was 39 days among newly diagnosed asylum seekers. The median time from IME to notification of HIV diagnosis was an additional 31 days while the median time to initiation of antiretrovirals following notification of diagnosis was 17 days. *This means that newly-diagnosed asylum seekers were at risk of contributing to forward HIV transmission for a median of 87 days prior to the initiation of antiretrovirals.* This could potentially have important consequences on Quebec's public health and security.

In the context of high-level viremia, these new diagnoses may represent patients presenting in the acute phase of HIV infection, during which time the risk of transmission is highest. In fact, recent European studies have shown that the estimated postmigration HIV acquisition probability is >50% among heterosexual men and women and >70% among men who have sex with men.[6,7] However, this data – i.e. the proportion who may have been infected in the recent past (during their migration trajectory or prior to IME screening) – is currently unknown among asylum seekers in Montreal. Furthermore, determining HIV transmission dynamics and potential transmission clusters among this population – data that is also unknown among asylum seekers in Montreal – is particularly valuable in the context of significant baseline resistance. The data from this pilot would help justify the need for expedited IMEs following arrival, point-of-care HIV testing prior to or at the time of IMEs, and rapid referrals for HIV treatment initiation.

2. HYPOTHÈSE

Asylum seekers who are newly diagnosed with HIV represent a key population for whom there is a paucity of data regarding recency of infection and HIV transmission dynamics after arrival in Canada. We hypothesize that avidity testing and phylogenetic analyses can help determine recency of infection and the existence of transmission clusters, respectively, with the overall goal of improved HIV surveillance among this key sub-population in Montreal. Based on preliminary data, we hypothesize that up to 10% of asylum seekers will be diagnosed in the acute phase of HIV infection, and small clusters (2-4 members) of infections within similar ethnic groups may exist. In the real world, <5% of new HIV infections are diagnosed in the acute phase, therefore our results would be considered clinically significant if this proportion was to double.

3. Objectifs

Primary objectives:

1. To determine recency of HIV infection, we will perform avidity testing on all newly-diagnosed asylum seekers using a multi-assay algorithm.
2. To identify transmission clusters, we will perform phylogenetic analyses on all newly-diagnosed asylum seekers to track linkage of viral variants at a population-level.

Secondary objective:

1. To determine the presence of transmitted or acquired drug resistance from all genotypic analyses among newly-diagnosed asylum seekers.

4. Méthodologie

In order to meet our primary objective (see section 5), we will expand our retrospective cohort to include all newly-diagnosed asylum seekers who have been linked to the JGH (co-candidate Dr. Karl Weiss) between June 2017 and November 2018. This will result in an estimated sample size of 120.[8]

Objective 1: Recency of HIV infection

Avidity testing. Results from avidity tests performed at the Laboratoire de santé publique du Québec (LSPQ) will be obtained on retrospective cross-sectional HIV-1 positive specimens from all newly diagnosed asylum seekers linked to HIV care at the MUHC and the JGH between June 2017 and November 2018. Although the Quebec HIV surveillance program does not differentiate between recent and chronic infections, reflex avidity testing is performed by the LSPQ on all new HIV-1 positive tests (unless the p24 antigen is positive). The LSPQ uses two consecutive tests as part of their Recent Infection Testing Algorithm (RITA); the first is the Centres for Disease Control and Prevention (CDC)-modified Bio-Rad-Avidity assay followed by the Sedia HIV-1 LAg-Avidity assay.[9] The results of the two-assay algorithm can differentiate infections with a recency cut-off of 4.5 months; a weak avidity test indicates infection within the previous 4.5 months while a strong avidity test represents an infection of 4.5 months or greater. Patients' names, medical records numbers (MRNs), and date of births will be provided to Dr. Bouchra Serhir (co-candidate), who will retrieve the results of the two-assay avidity tests on all patients.

Objective 2: Transmission clusters

Genotypic analyses will be retrieved on all newly-diagnosed asylum seekers. These analyses will be used to determine the HIV-1 viral subtypes and the presence of transmitted or acquired drug resistance.[10] We will then perform retrospective (and longitudinal if applicable) phylogenetic and network analyses, which can infer linkages between viral genetic sequences with sufficient similarity to suggest either a recent common source of infection or a putative linked transmission chain (co-candidate Dr. Bluma Brenner). Phylogenetic trees will be reconstructed using Neighbor-joining and Maximum Likelihood analysis. Transmission clustering of linked viral sequences is typically based on strong bootstrap support (>98%) and short genetic distance (0.01–0.05 substitutions/site) or posterior probabilities.[11-14] Transmission cluster analysis using several methodologies, including HIV-1 TRACE, Bayesian and Gap, will be applied to ascertain the trajectories of actively growing transmission clusters among newly-diagnosed asylum seekers in Montreal in near real-time.[11-15]

Feasibility

Dr. Kronfli, the principal applicant and an early career investigator, has already received approval from the Research Institute of the MUHC Research Ethics Board (MUHC 2019-5037) to study a retrospective cohort of asylum seekers linked to care at the MUHC during the study period (June 2017-November 2018). An amendment to the current study would be made to include patients from the JGH and to expand the objectives of the overall study to include those specified within this proposal. Given the retrospective nature of the study, patient consent would be waived. Dr. Kronfli has assembled a new, multidisciplinary team which includes basic scientists, epidemiologists, clinician scientists, and public health professionals to ensure the project's success. Her team consists of Réseau SIDA/MI members (Klein, Cox, Brenner) who have previously worked together, and non-Réseau members (Weiss, Mercure, Narasiah), in attempt to foster new research collaborations and to maximize knowledge translation. No potential barriers or risks that may impede the initiation or completion of the study have been identified. Dr. Brenner has ethics approval to perform phylogenetic analysis on de-identified samples, therefore phylogenetics cannot and will not be used to ascertain who-infected-who or directionality of transmission. This ensures that there are no ethical implications when transmission clusters are detected.

5. ANALYSES ET RÉSULTATS ANTICIPÉS

Patient characteristics will be described for the overall study population. Categorical variables will be reported as frequencies and proportions while continuous variables will be reported as medians and interquartile ranges. Baseline genotypes will be reviewed and mutations will be interpreted using the Stanford University HIV Drug Resistance Database.

The primary outcome is the number and proportion of acute infections (as determined by avidity testing)/total new infections. With a sample size of 120 and a 10% estimated prevalence of acute infections, we would expect 12 individuals to have weak avidity tests [95% confidence interval: 6-19].

Secondary outcome measures will include the proportion of patients will full resistance to at least one drug in each of the antiretroviral drug classes (NRTI, NNRTI, PI, II), as well as the proportion of patients with M184V/I, K103N/S, and K65R mutations.

Expected results, implications and future directions

If our study confirms our hypothesis, the next step will involve partnering with Public Health to pilot a study evaluating the acceptability and feasibility of point-of-care HIV testing at the time of border crossing or at IME screening, with the overall goal of accelerating linkage to care and time to treatment uptake.

6. ÉCHÉANCIER

Milestone	Expected timeframe
Amendment to REB protocol and approval	April – May 2019
Data collection at JGH	June – August 2019
Avidity test result retrieval	September – October 2019
Phylogenetic analyses	September – November 2019
Data analysis	October – December 2019
Manuscript(s) preparation and submission	January – March 2020

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BUDGET ET JUSTIFICATIONS BUDGÉTAIRES

STUDY ITEM	Unit Cost	Total Unit	Sub-Total	Comments
Personnel				
Lab Technician	$ 1,615.00	1	$ 1,615.00	One part time employee (15h/week) for 1 months at $38,000/year + 19% benefits. This individual will retrieve avidity test results and interpret them.
Research Assistant	$ 4,463.00	3	$ 13,388.00	One full time employee for 3 months at $45,000 + 19% benefits. This individual will create and maintain study documents, and will conduct data collection at JGH.
	$ 1,913.00	3	$ 5,738.00	One part time employee (15h/week) for 3 months at $45,000/year + 19% benefits. This individual will conduct data analysis and assist with manuscript preparation.
Master Student	$ 881.00	3	$ 2,643.00	One part time master student (20/h/week) for 3 months, based on a CIHR training stipend of $18,500/year. This individual will perform phylogenetic analysis.
		Sub-Total	**$23,384.00**	
Knowledge Translation				
Publication fees	$ 3,000.00	1	$ 3,000.00	Publication fees for one manuscript in an open access journal.
Poster printer	$ 175.00	1	$ 175.00	Printing costs for one poster.
Conference registration	$ 1,000.00	1	$ 1,000.00	Registration fees for 1 national conference.
Airfare	$ 1,000.00	1	$ 1,000.00	One round-trip national flight.
Hotel	$ 200.00	3	$ 600.00	3 nights per conference ($200 per night).
Meals	$ 150.00	4	$ 600.00	Meals for 4 days per conference ($150/day).
Taxi	$ 60.00	4	$ 240.00	Taxi to/from airport and other transportation costs ($60/day x 4 days).
		Sub-Total	**$ 6,615.00**	
		Proposed Budget	**$29,999.00**	

RÉFÉRENCES

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2. Mercure, Sarah-Amelie. Personal communication. November 28, 2018.
3. Institut National de Santé Publique du Québec (INSPQ). Programme de surveillance de l'infection par le virus de l'immunodéficience humaine (VIH) au Québec. RAPPORT ANNUEL 2016. https://www.inspq.qc.ca/sites/default/files/publications/2322_-programme_surveillance_infection_vih.pdf (Accessed February 14, 2019).
4. Narasiah, Lavanya. Personal communication. January 17, 2019.
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8. Weiss, Karl. Personal communication. January 16, 2019.
9. Serhir B, Hamel D, Doualla-Bell F, et al. Performance of Bio-Rad and Limiting Antigen Avidity Assays in Detecting Recent HIV Infections Using the Quebec Primary HIV-1 Infection Cohort. PLOS One 2016; 11(5):e0156023.
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14. Vrbik I, Brenner BG, Ibanescu RI, Roger M, Stephens DA. A birth-death SIR model reveals varying levels of risk among large cluster outbreaks from the HIV-1 epidemic in Quebec, Canada. Proc Natl Acad Sci USA 2017.
15. Vrbik I, Stephens DA, Roger M, Brenner BG. The Gap Procedure: for the identification of phylogenetic clusters in HIV-1 sequence data. BMC Bioinformatics 2015; 16:355.

Réseau SIDA/MI

RS-009

CRITÈRES DE SÉLECTION

	Impact potentiel	Intervalle	Mérite scientifique
Subventionnable	Extrêmement important	4,5 – 4,9	Exceptionnel
	Très important	4,0 – 4,4	Excellent
	Important	3,5 – 3,9	Excellent, mais peut nécessiter une révision
Non subventionnable	Modéré	3,0 – 3,4	Très bien, mais nécessite une révision pour être subventionnable
	Limité	2,5 – 2,9	Révision importante nécessaire
	Négligeable	0,0 – 2,4	Laisse beaucoup à désirer

Il est proposé aux évaluateurs d'accorder une note (0,0 à 4,9) pour chacun des critères, en vue de les additionner et de les diviser par 5.

1. RATIONNEL *(Mise en contexte et importance de l'étude proposée)*	L'augmentation des découvertes VIH chez des demandeurs d'asile est en train de modifier l'épidémiologie de l'infection VIH au Québec. 4.5
2. HYPOTHÈSE *(Veuillez énoncer clairement l'hypothèse principale du projet et les hypothèses secondaires, le cas échéant).*	La détermination du caractère récent de l'infection VIH chez un demandeur d'asile et l'analyse phylogénétique permettront d'étudier l'influence de ces mouvements migratoires sur l'épidémiologie du VIH 4.5
3. OBJECTIFS *(Veuillez spécifier les objectifs principaux, et les objectifs secondaires, le cas échéant).*	Déterminer le caractère récent de l'infection VIH (test d'avidité) et analyse phylogénétique des virus chez les demandeurs d'asile découverts infectés par le VIH 4.5
4. MÉTHODOLOGIE *(Si des outils ou des méthodologies innovantes seront utilisées pour ce projet, veuillez les spécifier ici. Veuillez préciser la faisabilité, les difficultés potentielles et les mesures d'atténuation, lorsque pertinent)*	Test d'avidité Analyse phylogénétique Recherche de mutations associées à la résistance 4.5
5. ANALYSES ET RÉSULTATS ANTICIPÉS *(Veuillez préciser les méthodes statistiques qui seront utilisées et énoncer les résultats attendus).*	Évaluer le risque de transmission de ces infections nouvellement diagnostiquées 4.5
6. ÉCHÉANCIER *(Veuillez identifier les étapes à suivre pour l'atteinte des objectifs.)*	12 mois 4.5
INSCRIRE LE CODE RS DU PARTICIPANT : 009	**TOTAL** = 4.50

FORCES :

ORIGINALITÉ DE COMBINER TEST D'AVIDITÉ ET PHYLOGÉNIE

IMPORTANCE DE SURVEILLER UNE ÉPIDÉMIOLOGIE CHANGEANTE

Réseau SIDA/MI

RS-009

CRITÈRES DE SÉLECTION

Modèle des Instituts de recherche en santé du Canada / IRSC			
	Impact potentiel	**Intervalle**	**Mérite scientifique**
Subventionnable	Extrêmement important	4,5 – 4,9	Exceptionnel
	Très important	4,0 – 4,4	Excellent X
	Important	3,5 – 3,9	Excellent, mais peut nécessiter une révision
Non subventionnable	Modéré	3,0 – 3,4	Très bien, mais nécessite une révision pour être subventionnable
	Limité	2,5 – 2,9	Révision importante nécessaire
	Négligeable	0,0 – 2,4	Laisse beaucoup à désirer

Il est proposé aux évaluateurs d'accorder une note (0,0 à 4,9) pour chacun des critères, en vue de les additionner et de les diviser par 6

1. RATIONNEL	4,5
2. HYPOTHÈSE	4,4
3. OBJECTIFS	4
4. MÉTHODOLOGIE	4,4
5. ANALYSES ET RÉSULTATS ANTICIPÉS	4
6. ÉCHÉANCIER	4

FORCES : Hypothèse directement applicable à l'épidemiologie actuelle - Méthode des clusters en plein développement scientifique

FAIBLESSES :
Il manque sans doute un volet préventif (mais il y a pilote) = notification des partenaires ? Mais en attendant l'effet TASP ?