Universal HIV Screening and Targeted HCV Screening in Emergency Department

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Dépistage universel du VIH et dépistage ciblé du VHC à l'urgence

Rational:

The cascade of care is a widely used concept in HIV. It is a way of representing a patient's progression from diagnosis to disease management. It is used to assess the quality of care provided, to identify barriers that limit patient progress, to focus research on these barriers, and to develop public health policies.[1,2] The advent of effective treatments for HCV has made it possible to transpose the concept of the cascade to HCV, thus moving away from a research logic focused on optimizing the sustained virological response (SVR) of individuals to a logic of access to this virological response for all.[1] The two steps in the cascade that are most critical for the management of HCV in Quebec, as in other countries, are access to the screening test and linkage to the health care system. Problems with screening, linkage to the health care system and losses to follow-up throughout the cascade are estimated to reduce the effectiveness of treatment by up to 75%.[3]

HCV and HIV screening based on risk factors, according to Quebec and Canadian recommendations, does not allow for the identification of all cases. It is estimated that 44% of Canadians infected with HCV and 21% of Quebecers infected with HIV are unaware of their status.[4,5] In addition, nearly 26% of HCV-positive patients do not obtain their test results and are therefore not managed (loss of follow-up between the test and the results).[3] It is therefore important to evaluate new models of screening adapted to the Quebec healthcare system.

To address the problem of under-testing for HIV and HCV in the United States, the U.S. Preventive Services Task Force recommended universal HIV testing among 15-65 year olds in 2012 and HCV testing among individuals born between 1945 and 1965 in 2013.[6,7] Different approaches to providing expanded testing have been evaluated. With opt-in, the patients are informed of the availability of the test and asked if they want to be tested, whereas with opt-out, the patients are informed that they will be tested unless they decline the test. Several studies have demonstrated the acceptability of the latter approach with a higher rate of testing than the opt-in option.[8,9] One argument cited against the opt-out approach is the need for extensive pre-test counseling before testing for HIV. However, a recent randomized trial evaluated the impact of pre-test counselling on the acquisition of sexually transmitted infections in the six months following counselling and showed no benefit in the group that received counselling.[10] In Quebec, the opt-out approach is currently used for HIV testing of pregnant women.

For HIV, a recent study in an urban setting in Ireland using the opt-out approach identified a proportion of new diagnoses of 0.8 per 1000 patients.[11] In another

opt-out study in an emergency department (ED) in Phoenix, Arizona, 22 468 patients aged 18-64 years were tested for HIV.[12] There were 0.28% of new diagnoses, of which 23% were in the acute phase of infection, the period when the risk of HIV transmission is highest.[12] Universal HIV screening would be cost-effective in clinical settings where the prevalence of undiagnosed HIV infection is ≥ 0.1%.[13] In a study of opt-out HCV screening of baby boomers visiting an emergency department in Alabama, 170 new cases were identified out of 1,529 patients tested (11.1%).[14] However, the results of this American study did not change our approach in Quebec.

Once diagnosed, in order to be treated, patients must see a physician and undergo the various tests and laboratory analyses mentioned above. The patient who engages in this process is considered to be "linked-to-care". However, many patients do not consult or quickly disengage from follow-up. A US study reported that 47% of patients who know their status do not link to the health care system.[3] The often long delays between diagnosis and clinical management contribute to the current loss to follow-up. For example, one Canadian study reported delays of 66.3 months from initial diagnosis to referral to a specialty, an additional 1.5 months to seeing the specialist, and 6.8 months from initial visit to initiation of treatment.[15] Another Canadian study reported loss-to-follow-up rates of 19% during evaluation, while a Scottish study noted that 16% of patients never made it to the first visit and 24% were lost after only one visit.[16,17] It is therefore important to assess whether expediting management would allow more patients to initiate treatment by limiting disengagement from care.

The goal of the first project is to evaluate the feasibility of routine HIV and HCV screening using an opt-out approach in the CHUM emergency department and to determine the rate of new HIV and HCV diagnoses. A sub-analysis will focus more specifically on HCV in the Quebec equivalent of the baby boomers (1945-1975), since this is the group that was targeted in the United States.[18] We also want to evaluate the effectiveness of linkage-to-care for people diagnosed with HIV or HCV and the speed with which these people are taken into care and put on treatment.

Hypothesis:

We believe that it is realistic to observe a proportion of new diagnoses greater than 1/1000 for HIV and 1/100 for HCV in the CHUM emergency department.

Objectives:

Primary objectives

1. To determine the prevalence of new HIV and HCV diagnoses among the patients visiting the CHUM emergency department
2. To determine the overall prevalence of HIV and HCV (new cases and known cases) among the patients visiting the CHUM emergency department

Secondary objectives

1. To determine the prevalence of new and known HCV cases among the "baby boomers" (41-73 years)
2. To determine the proportion of adherence of ED staff to the offer of HIV and HCV testing
3. To determine the proportion of patients "opting out" of routine HIV and HCV testing in the ED
4. To determine the proportion of patients with a newly positive HIV or HCV test in the ED who attended a first appointment at 1 month
5. To determine the proportion who completed certain steps in the HIV and HCV care cascades at 1 or 3 months, namely confirmation of diagnosis (HIV and HCV: 1 month), liver fibrosis assessment (HCV: 3 months), and treatment initiation (HIV: 1 month and HCV: 3 months)
6. To define the organization of services needed to continue screening beyond the research project in terms of costs, nursing time, volume of tests and communication of results.

Design:
Cross-sectional study of ED patients with evaluation of the implementation of the screening program and prospective follow-up for 3 months of the positive cases.

Method:
Implementation: Preparatory meetings will be held with CHUM ED managers, medical leaders, and nurses to discuss issues associated with routine screening and to attempt to find solutions to anticipated barriers in advance. Following these discussions, ED triage staff, including day, evening and night staff, will be met for training on the importance of screening and the procedure that will be followed under this protocol.

Informational Tools:
Patient announcements
Information materials will be prepared to announce to CHUM ED patients that HIV and/or HCV testing will be performed. Posters will be put up in the ED and an information sheet will be given to patients at the time of registration.

Materials for Nurses:
The following items will be added to the triage form already in place in the ED: "Are you infected with HIV? Are you infected with HCV?", "Unless you decline, we will be performing a blood test for HIV (and/or) HCV today." These questions will simultaneously serve as a reminder for staff to offer the test and as a data collection form for investigators.
Pre-printed orders for HIV and HCV testing will also be created with the name and license number of one of the investigators.

Laboratory Tests:
The tests used will be the routine CHUM tests (ARCHITECT HIV Ag/Ab combo and ARCHITECT anti-HCV assay). These were chosen over rapid tests because

they are less expensive and more sensitive, they are more representative of what might be widely available in the event of a provincial rollout of ED screening, and there are no licensed rapid tests for HCV in Canada.

Screening:
At triage, patients will be advised that they will be tested for HIV and/or HCV unless they refuse to be tested or are already known to be infected with HIV and/or HCV. If a patient is known to be infected with HIV or HCV, they may be tested for the virus whose status is unknown. The time required to educate the patient and obtain answers to questions will be measured for a sample of patients after an initial period of staff adjustment. The nurse performing the collection will be the same nurse who performs the patient's regular blood work. She will use the pre-printed orders for this purpose. The physician in charge of receiving the results will be one of the study investigators. Patients who do not have to have their blood drawn for their health problem will still be offered the test.

Results management:
Patients will be notified that they will receive their test results without specifying how. As opposed to having all patients travel or announcing all results over the phone, this strategy is intended to ensure that patients called back for an appointment do not spontaneously understand that they are infected with HIV or hepatitis C when they are home alone, while limiting the number of patients who will have to travel since the vast majority of tests will be negative.

The research nurse will have access to the results of all tests performed via the CHUM computer system. In the event of a positive result (confirmed by the Laboratoire de santé publique du Québec (LSPQ) for HIV and by the CHUM laboratory +/- the LSPQ as needed for HCV), she will notify one of the investigators who will contact the patient in person, if he or she is still present at the hospital, or by giving him or her an appointment, if he or she has left. The research nurse will organize a follow-up with one of the CHUM's specialized clinic coordinators, taking into account the diagnosis, the type of clientele and the person's choice. The time required to reach the patient and plan the liaison with the care team as well as the mode of communication used will be noted. If the result is negative, the physician will delegate the research nurse to contact the patient to give him or her the result, either by telephone or by mail, depending on the method of communication available in the hospital file.

Health system linkage:
The research nurse will check the hospital's computer system to see if the patient has been seen in a specialty clinic within one month of the positive test announcement. If not, the research nurse will follow up with the patient by phone to see if they have been seen outside the hospital for this new diagnosis. If after three attempts to call, the patient is not reached, they will be considered not linked to the health care system. For HIV patients, she will check for confirmatory

serology, viral load, and CD4 count and whether treatment has been initiated. For HCV, she will verify that RNA testing and, if applicable, genotyping have been performed. For chronic HCV patients, she will assess at 3 months whether liver fibrosis has been assessed and whether treatment has been prescribed.

Eligibility criteria for the cross-sectional HIV/HCV screening component of the study:

Inclusion criteria :
Individuals between the ages of 18 and 73 years consulting the CHUM emergency department regardless of the time of consultation.

Exclusion criteria :
Persons unable to refuse the test, notably because of their medical condition leading them to consult the emergency room.
If the person's condition improves during the emergency room visit, they may be offered screening at that time.

Eligibility criteria for the linkage-to-care of HIV/HCV-infected patients component of the study:

Inclusion criteria:
- Patient who has agreed to HIV or HCV test(s) in the UHC emergency department.
- Aged 18 years to 73 years
- Tested positive for HIV and/or HCV
- Able to consent and sign the information and consent form

Outcomes:
Primary outcomes
1. Prevalence of unknown HIV or HCV infections in the CHUM emergency department during the study period: positive tests / tests performed in unknown patients with HIV or HCV
2. Overall prevalence of HCV and HIV during the study period: (positive tests + known positive cases) / (tests performed + known positive cases)

Secondary outcomes
1. For HCV, among baby boomers (1945-1975 or 43-73 years)
    a. Prevalence of new cases (positive tests/tests performed)
    b. Overall prevalence (positive tests + known positive cases) / (tests performed + known positive cases)
2. Staff adherence: (tests performed, refused or known positive) / (eligible patients)
3. Proportion of patient opt-outs: tests refused / (tests performed + tests refused)
4. Linkage of positive cases to a care team 1 month post-test (definition: attended at least one appointment).
5. Progression through the care cascade at 1 and 3 months:

a. HIV and HCV: confirmation of diagnosis and baseline laboratory testing at 1 month (HIV: confirmatory serology, viral load and genotyping; HCV: qualitative RNA measurement and genotyping)
b. HCV: liver fibrosis assessment at 3 months.
c. HIV and HCV: initiation of treatment for HIV at 1 month and HCV at 3 months.

6. Organization of services: nursing time to inform the patient, time for results management, mode of communication used to announce results, number of tests performed per period and associated costs.

Data collection

The number of eligible patients during the study period will be determined via data from the SIURGE system. Completed triage sheets will identify the number of known patients for each virus, the number of refusals, the number of patients not approached for the study and basic patient demographics (age, zip code). The hospital computer system (OACIS) will be used to obtain the results of screening tests (including confirmatory tests performed at the LSPQ as part of an initial screening test) for all screened patients as well as management results for patients included in the cohort of infected patients (2nd confirmatory serology, viral load and genotyping for HIV, qualitative RNA, genotyping and liver fibrosis assessment for HCV). Management and initiation of treatment will be determined in OACIS or by follow-up calls 1 and 3 months after diagnosis depending on whether the patient has decided to be followed at the CHUM or not. The time required to notify patients of results will be recorded in the research nurse's observation sheets, as will the means of communication used to reach the patient. Test costs will be extracted from the Répertoire québécois et système de mesure des procédures de biologie médicale.[19]

Statistical Considerations

Sample size

The sample size was based on the threshold prevalence of newly diagnosed HIV infection that warrants the implementation of a routine HIV testing program (1/1000 according to the CDC). Assuming a prevalence of undiagnosed cases of 1/1000, a study of 4,000 subjects would yield a 95% confidence interval of 0.3/1000 to 2.7/1000. For HCV, assuming a prevalence of undiagnosed cases of 1/100, we will obtain a 95% confidence interval between 0.7 and 1.3%. In 2014-2015, 110 420 consultations took place in the CHUM emergency department.[20] Patients were between 18 and 74 years of age in 85% of cases,[20] which represented 93 857 consultations per year (7821/month). Few studies have reported missed opportunities for screening in emergency department opt-out situations. One study reported 49.9% missed opportunities due to either staff oversight or patient refusal.[11] In other studies, patient refusal rates were in the range of 30-35%.[8,9] Assuming a proportion of patient refusal and staff oversight of 50%, the recruitment period should be a maximum of 2 months.

Analyses

Descriptive statistics with 95% confidence intervals will be used to calculate, separately for HIV and HCV, the prevalences of new and known cases and the proportions of "opt-out" and staff adherence to testing. The prevalences of new and known HCV cases among baby boomers will be calculated in the same way. Medians and their confidence intervals will be calculated for the time required to inform the patient of the screening and for the time required to announce the result. Program costs will be presented in absolute terms and as a cost per newly diagnosed case. Liaison with a specialized team, completion of the initial workup and initiation of treatment at one month (HIV) or three months (HCV) will also be presented as proportions with their confidence intervals.

Ethical and Regulatory Considerations

Research Ethics Board

The protocol, forms and regulatory documents will be submitted to and approved by the CHUM Research Ethics Committee and Scientific Committee.

Information and consent form

In an opt-out evaluation context, consent is an issue. A standard research consent form is definitely an opt-in, not an opt-out. In this context, we will consider the initial tests as part of a screening program and not strictly a research project. It is the program as a whole that must be evaluated. These considerations and the rationale, in agreement with the ethics committee, exempt us from the presentation of a consent form to perform the screening tests. Patients will receive a brochure explaining the introduction of the screening program, the risks and benefits and their right to refuse the test. The triage nurse will validate with them that they have understood the information and ask them if they want to opt out of this screening opportunity.

The second part of the project, linkage-to-care, is more routine. Patients will be met by the research nurse who will present them with the information and consent form and explain the steps in the process and ask for their permission to collect their data. Interested patients will sign the information and consent form approved by the research ethics board.

Subjects will have the opportunity to discuss the project and ask questions before signing the information and consent form. They will also be able to take time to reflect if necessary. They will be free to participate or not or to withdraw at any time. Care will not be compromised. All procedures related to the research project will be initiated following the subject's signature on the information and consent form. A signed and dated copy of the information and consent form will be given to the subject.

Investigator's responsibilities

The principal investigator is responsible for the conduct of this project. She will ensure that the co-investigators, ED personnel and research staff are trained and

competent to perform their duties according to the protocol and objectives of the interventions and then according to their delegation of duties in this study.

Study subjects
Study subjects will receive no monetary compensation for their participation in this research project. The investigator or co-investigator reserves the right to exclude a patient during this project. The reasons for this withdrawal will be noted in the file.

Study changes, follow-up and documentation
Amendments or changes to the protocol will be submitted to the CHUM institutional review board for approval. Deviations will be reported. Compliance rules for clinical studies and GCP will be followed. In the context of this project, which is a cross-sectional and prospective follow-up study, no adverse events are anticipated and will not be noted or reported.

The documents and results of the research will be kept under lock and key in the research premises and at the end of the study, they will be kept at Archivex for 10 years according to CRCHUM procedures.

The information collected from the data collection will be entered on a computerized Window Excel file in a specific confidential secured research file with limited access. Access will be restricted to delegated research personnel according to the signature and task delegation log for this study.

The data may be published in specialized journals or be the subject of scientific discussions while maintaining the confidentiality of the participants and therefore without any reference to the identity of the subjects.

Stopping the project
As this is a cross-cutting and prospective project, the principal investigator reserves the right to discontinue this project at any time due to various considerations and will notify the CHUM institutional review board and the participants of the prospective portion of the project.

Team
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Strengths, limitations, expected contributions
In terms of strengths, the proposed study covers several stages of the care cascade, from diagnosis to initiation of treatment. The target population is easily accessible and is the one in which we believe we have the best chance of identifying new cases. While it is true that the overall prevalence would be higher

if only people who use drugs were to be screened, this would not likely be the case for the prevalence of new cases, as the screening service for people who use drugs in Montreal is already well established. Although similar projects have been carried out in the United States, it is important not to make inferences from the epidemiological data established there. The different context of care in Quebec, including free health care and possibly easier access to screening, may have a major impact on the prevalence of new cases that we will establish. Expanded screening may not be as cost-effective in Quebec as in the United States.

In terms of limitations, it is possible that patients who come to us for reasons that do not warrant blood sampling will refuse the test more often than those who need it. The former group of patients may be healthier, so there may be a bias towards an increase in the observed prevalence. Since the same situation is likely to occur in real practice, our results will still be valid. The night-time clientele may be different from the daytime clientele. It is important that nurses on different shifts adhere to the protocol in the same way to avoid bias. Training will therefore be given to all shifts. Like all serological tests, those used have a window period and may miss acute cases, thus reducing the observed prevalence of new cases. However, the tests used are those with the shortest window period available on the market. Finally, the clientele consulting the emergency room varies greatly depending on the geographic location of a hospital. The results obtained at the CHUM may not be generalizable to other hospitals and a second multicentre project will be necessary if the initial targets are met. This second phase will better establish the prevalence of new cases and the cost-effectiveness of screening in EDs serving populations with fewer traditional risk factors for HIV or HCV than CHUM.

References

1. Yehia BR, Schranz AJ, Umscheid CA, Lo Re V, 3rd. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. PloS one 2014;9:e101554.
2. 90-90-90. An ambitious treatment target to help end the AIDS epidemic. (Accessed 5 septembre 2016, at http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf.)
3. Linas BP, Barter DM, Leff JA, et al. The hepatitis C cascade of care: identifying priorities to improve clinical outcomes. PloS one 2014;9:e97317.
4. Trubnikov M, Yan P, Archibald C. Estimation de la prévalence de l'infection par le virus de l'hépatite C au Canada, 2011. RMTC 2014;40:442-50.
5. Agence de la santé publique du Canada. Actualités en épidémiologie du VIH/sida: Estimations de la prévalence et de l'incidence de l'infection par le VIH au Canada pour 2011. Centre de la lutte contres les maladies transmissibles et les infections 2014.

6. Moyer VA, Force USPST. Screening for hepatitis C virus infection in adults: U.S. Preventive Services Task Force recommendation statement. Annals of internal medicine 2013;159:349-57.
7. Moyer VA, Force* USPST. Screening for HIV: U.S. Preventive Services Task Force Recommendation Statement. Annals of internal medicine 2013;159:51-60.
8. Montoy JC, Dow WH, Kaplan BC. Patient choice in opt-in, active choice, and opt-out HIV screening: randomized clinical trial. Bmj 2016;532:h6895.
9. Prekker ME, Gary BM, Patel R, et al. A comparison of routine, opt-out HIV screening with the expected yield from physician-directed HIV testing in the ED. The American journal of emergency medicine 2015;33:506-11.
10. Metsch LR, Feaster DJ, Gooden L, et al. Effect of risk-reduction counseling with rapid HIV testing on risk of acquiring sexually transmitted infections: the AWARE randomized clinical trial. Jama 2013;310:1701-10.
11. O'Connell S, Lillis D, Cotter A, et al. Opt-Out Panel Testing for HIV, Hepatitis B and Hepatitis C in an Urban Emergency Department: A Pilot Study. PloS one 2016;11:e0150546.
12. Geren KI, Lovecchio F, Knight J, et al. Identification of acute HIV infection using fourth-generation testing in an opt-out emergency department screening program. Annals of emergency medicine 2014;64:537-46.
13. Paltiel AD, Weinstein MC, Kimmel AD, et al. Expanded screening for HIV in the United States--an analysis of cost-effectiveness. The New England journal of medicine 2005;352:586-95.
14. Galbraith JW, Franco RA, Donnelly JP, et al. Unrecognized chronic hepatitis C virus infection among baby boomers in the emergency department. Hepatology 2015;61:776-82.
15. Yau AH, Lee T, Ramji A, Ko HH. Rate, delay and predictors of hepatitis C treatment in British Columbia. Canadian journal of gastroenterology & hepatology 2015;29:315-20.
16. McLaren M, Garber G, Cooper C. Barriers to hepatitis C virus treatment in a Canadian HIV-hepatitis C virus coinfection tertiary care clinic. Canadian journal of gastroenterology = Journal canadien de gastroenterologie 2008;22:133-7.
17. Astell-Burt T, Flowerdew R, Boyle P, Dillon J. Is travel-time to a specialist centre a risk factor for non-referral, non-attendance and loss to follow-up among patients with hepatitis C (HCV) infection? Social science & medicine 2012;75:240-7.
18. Shah HA, Heathcote J, Feld JJ. A Canadian screening program for hepatitis C: is now the time? CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2013;185:1325-8.
19. Répertoire québécois et système de mesure des procédures de biologie médicale. Les annexes. 2016-2017. 2016. (Accessed 26 août 2016, 2016, at http://www.msss.gouv.qc.ca.)
20. Utilisation des urgences - Statistiques interactives. Gouvernement du Québec, 2016. (Accessed 21 juillet 2016, 2016, at http://emis.santemontreal.qc.ca/outils/statistiques-interactives/utilisation-des-services/tableaux-par-services/utilisation-des-urgences/.)