Targeted HIV Screening in Eight Emergency Departments: The DICI-VIH Cluster-Randomized Two-Period Crossover Trial

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THE DICI-VIH CLUSTER-RANDOMIZED TWO-PERIOD CROSSOVER TRIAL

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Abstract

Study objective: This study compares the effectiveness and cost-effectiveness of nurse-driven targeted HIV screening alongside physician-directed diagnostic testing (intervention strategy) with diagnostic testing alone (control strategy) in 8 emergency departments.

Methods: In this cluster-randomized, 2-period, crossover trial, 18- to 64-year-old patients presenting for reasons other than potential exposure to HIV were included. The strategy applied first was randomly assigned. During both periods, diagnostic testing was prescribed by physicians following usual care. During the intervention periods, patients were asked to complete a self-administered questionnaire. According to their answers, the triage nurse suggested performing a rapid test to patients belonging to a high-risk group. The primary outcome was the proportion of new diagnoses among included patients, which further refers to effectiveness. A secondary outcome was the intervention's incremental cost (health care system perspective) per additional diagnosis.

Results: During the intervention periods, 74,161 patients were included, 16,468 completed the questionnaire, 4,341 belonged to high-risk groups, and 2,818 were tested by nurses, yielding 13 new diagnoses. Combined with 9 diagnoses confirmed through 97 diagnostic tests, 22 new diagnoses were established. During the control periods, 74,166 patients were included, 92 were tested, and 6 received a new diagnosis. The proportion of new diagnoses among included patients was higher during the intervention than in the control periods (3.0 per 10,000 versus 0.8 per 10,000; difference 2.2 per 10,000, 95% CI 1.3 to 3.6; relative risk 3.7, 95% CI 1.4 to 9.8). The incremental cost was V1,324 per additional new diagnosis.

Conclusion: The combined strategy of targeted screening and diagnostic testing was effective.

INTRODUCTION

Background

In countries with concentrated HIV epidemics[1], an estimated 10% to 19% of HIV-infected individuals are unaware of their infection status.[2-5] Undiagnosed HIV substantially contributes to on-going transmission.[6,7] Although late diagnosis is associated with increased mortality,[8] early initiation of antiretroviral treatment decreases both morbidity and mortality and reduces secondary transmission.[9-11] HIV screening therefore remains essential in controlling the HIV epidemic.[1]

Since 2006, recommendations have encouraged provider-initiated nontargeted HIV screening in countries with concentrated epidemics, aiming to decrease the number of undiagnosed infections and improve early detection.[12-14] Emergency departments (EDs) have been an important focus in the evaluation of the effect of these recommendations because they treat a large segment of the population, including the economically underprivileged and those with limited access to health care.[15,16] In France, the number of individuals who visit EDs each year represents 30% of the general population.[17]

A previous study evaluating the effectiveness of nontargeted HIV screening in 29 public hospital EDs in the Paris metropolitan area concluded that nontargeted screening was feasible in the ED setting.[18] However, few new HIV diagnoses were identified and most patients with new diagnoses belonged to high-risk groups (either men who have sex with men or migrants from Sub-Saharan Africa). Similarly, studies performed in other countries have shown that non-targeted screening had a modest effectiveness, partly explaining its low implementation in nonspecialist health care settings, particularly in EDs.[19-23]

Importance

By optimizing the use of resources dedicated to HIV screening in overburdened health care settings, targeting a limited number of patients may be an appropriate strategy. Only 2 single-center prospective comparative studies have evaluated the effectiveness of targeted screening in EDs.[24,25] They reported contrasting results, which preclude firm conclusions, and

emphasized the need for a large-scale evaluation. Moreover, in the context of limited financial resources, a cost-effectiveness evaluation appears essential.

In French EDs, only physician-directed diagnostic testing is currently performed for patients with HIV-related symptoms[26] and is not sufficient to detect infections at an early stage. A combination of nurse-driven targeted screening and physician-directed diagnostic testing could increase the proportion of new diagnoses.

Goals of This Investigation

The objective of the *Dépistage infirmier ciblé du VIH* (DICI-VIH [nurse-driven targeted HIV screening]) cluster-randomized trial was to evaluate the effect and cost-effectiveness of targeted HIV screening combined with diagnostic testing on a large scale by comparing it to a control strategy involving diagnostic testing alone, the current practice in EDs.

MATERIALS AND METHODS

Study Design and Setting

In this cluster-randomized, 2-period crossover trial, nurse-driven targeted screening combined with physician-directed diagnostic testing (intervention strategy) was compared to physician-directed diagnostic testing alone (control strategy). Methods, including the choice of study design, have been previously described.[26] Given the number of public hospitals in the Paris metropolitan area (population 12 million[27]), where 42% of France's HIV cases are newly diagnosed annually,[28] 8 EDs were selected according to the proportion of patients belonging to HIV high-risk groups in the populations they serve, based on a previous study.[18] At least 8% of the patient population of the 8 EDs met 1 main targeted screening criterion (eg, men who have sex with men status, Sub-Saharan African origin). The total patient population served by these 8 EDs accounts for approximately 20% of all adult ED patients in the region.[29] All EDs agreed to participate.

Selection of Participants

Patients aged 18 to 64 years who visited the participating EDs during the study periods for reasons other than potential exposure to HIV within less than 48 hours were included. A

poster located in the ED waiting room detailed the study's goals. Information on the study, in particular concerning the completion of the questionnaire and the performance of a rapid test for eligible patients, was provided. After verbal opt-out consent was obtained, the DICI-VIH questionnaire was filled by all included patients and the HIV test was performed for all eligible patients unless they declined.

Interventions

The unit of randomization was the ED. The strategy applied during the first period was assigned using a balanced-block randomization process (block size of 4). The alternative strategy was applied during the second period after a 4-week washout interval. The allocation schedule was computer generated in SAS by an independent statistician who was not otherwise involved in planning or analysis. The participating EDs could not be masked to allocation because of to the nature of the intervention. An equal number of participants was included in each ED during each period, leading to variable period duration.

Before the start of the intervention, ED nurses and auxiliary nurses participated in a 60-minute training session, which included an educational lecture, an explanation of the DICI-VIH questionnaire, a rapid HIV test demonstration, hands-on practice, and guidance on how to disclose test results.

During the intervention periods, targeted HIV screening was performed on a 24-hour basis. The DICI-VIH self-administered paper-based questionnaire was to be distributed at the registration desk before the initial triage assessment to all patients meeting inclusion criteria who could provide consent and who were able to complete the questionnaire (patients with acute life-threatening conditions, altered consciousness, severe neuropsychiatric disorders, or language barriers, and those under arrest were not considered).

Because of the limited number of new HIV infections identified in previous studies,[18,30] it has not been possible to develop a tool predicting the likelihood of undiagnosed HIV infection in French ED patients. The 7-item DICI-VIH risk assessment questionnaire was therefore designed by an expert panel to identify patients belonging to known high-risk groups and was piloted in 2013.[26] The items in the questionnaire are based on variables known to be

associated with HIV infection in mainland France[31,32] and include data on demographics (age, sex, and origin), sexual behavior and drug use.

Patients filled out the questionnaire in the waiting room and returned it to the nurse during triage. HIV infection status was reported by the patient or retrieved from his or her medical records by the triage nurse. Respondents were identified as belonging to a high-risk group if they checked any of the 5 following items: at least 1 male-to-male sexual contact (further referred to as men who have sex with men), Sub-Saharan African origin or partner of person with Sub-Saharan African origin during the past 10 years, more than 5 sexual partners during the past 12 months, or past or current injection drug use.[26] The triage nurse suggested performing a rapid HIV test only to patients who reported belonging to one of these groups. Patients who had recently had a negative HIV test were eligible for testing. A patient who declared having previously completed the questionnaire to the nurse was not eligible to participate.

Once informed verbal consent was obtained following the opt-out process,[33] a finger-stick whole-blood rapid HIV antibody test (VIKIA HIV1/2, bioMérieux, Marcy l'Etoile, France) was performed and interpreted by the triage nurse within 30 minutes. Either the triage nurse or another nurse in the treatment room disclosed negative results and recommended repeating the test if the patient had been at risk of exposure within the past 3 months. Patients were informed of positive or 2 sequentially indeterminate results by the nurse in the treatment room, assisted by an emergency care physician if requested by the nurse. Either the nurse or the physician verified that the patient did not already know his or her HIV-positive status, and blood was drawn for an antigen-antibody combined test and Western blot confirmation. A follow-up visit was scheduled with an on-site infectious disease specialist within 72 hours.

Throughout the intervention, physicians continued to prescribe HIV tests (serology or rapid test) to patients with HIV-related symptoms, following usual practice; nurses then performed the tests and physicians disclosed the results. In each ED, a clinical research nurse or assistant was on site during the intervention periods for 8 hours, 5 days a week, to monitor data collection (ie, data on patient eligibility based on chart review, patient

questionnaires and tests, and data on patients with a positive result). The clinical research nurse or assistant also monitored questionnaire delivery and testing procedures, and ensured that staff adhered to the protocol. In addition, he or she assisted nurses by offering or performing rapid HIV tests when necessary.

During the control periods, usual practice was not influenced in any way. Physicians prescribed HIV tests to patients following usual practice. The clinical research nurse or assistant was never present and data were collected after the periods had ended.

ED flow data, including patient and cluster characteristics, were extracted from the electronic ED databases. All other data relating to patient questionnaires and follow-up visits were collected on a paper-based case report form and subsequently entered into a database (CleanWEB Telemedicine Technologies SAS, Boulogne-Billancourt, France).

Outcome Measures

The primary outcome was the proportion of patients with newly diagnosed HIV among 18- to 64-year-old patients presenting to the participating EDs (excluding those presenting as a result of potential HIV exposure). Secondary outcomes included the following: linkage to follow-up care, assessed as the proportion of patients with a new diagnosis who had a follow-up visit with an infectious disease specialist within 3 months; proportion of patients with a new diagnosis among those tested; proportion of patients with a new diagnosis who had a CD4 count≥350 cells per μl[34] and no HIV-related symptoms, assessed independently by an expert panel of 3 infectious disease specialists (P.de.T., A.-C.C. and an external specialist); implementation of the intervention (proportion of DICI-VIH questionnaires distributed to and completed by eligible patients who were able to provide consent and to complete the questionnaire and were not known to be HIV positive, proportion of patients belonging to high-risk groups among those who filled out the questionnaire, proportion of rapid tests offered by nurses among patients belonging to high-risk groups, proportion of tests accepted among patients who were offered a rapid test, and proportion of patients

screened by nurses among patients belonging to high-risk groups); and costs of the 2 strategies and incremental cost-effectiveness ratio.

Primary Data Analysis

Sample size was calculated under the assumption that the effect of the crossover design, which resulted in matched-pair data within each center, and the effect of the cluster design cancelled each other out.[26,35] We hypothesized that, during the intervention periods, the overall proportion of new HIV diagnoses among included patients would be similar or greater to that found in a previous study evaluating nontargeted screening combined with the usual practice of diagnostic testing in the same EDs.[18] Based on this data, the expected proportion of new HIV diagnoses was 1.04 and 3.38 per 10,000 patients during the control and intervention periods, respectively. Accordingly, a study sample of 140,000 patients (8,750 per center per period) would lead to a statistical power of 80% using a 2-sided Fisher's exact test with a type I error of 5% (Pass,[36] version 11.0.1).

The statistical analysis was based on the intention-to-treat population.

Given the relatively rare occurrence of new HIV diagnoses, a Poisson model for proportions was used for the primary outcome analysis. A generalized linear mixed model with a random center effect was used to account for clustering within EDs.[37] The fixed effects were strategy (intervention or control), period (1 or 2), and strategy-by-period interaction. The logarithm of the number of subjects was included as an offset term in the model. The parameters of the model were estimated with a full maximum likelihood method with adaptive Gaussian quadrature.[38,39] The model was reduced using backward selection adopting an exploratory and hypothesis-generating perspective. The *P* values reported for fixed effects were based on *t* tests using the Kenward-Roger approximation for the denominator degrees of freedom.[39,40] The only missing value was considered as a success (positive test): one patient with a positive rapid test did not have a confirmation test because he left the ED before the medical assessment could be conducted. A sensitivity analysis was performed to verify that considering this missing value as a failure rather than a success did not affect the intervention effect estimate. Additional analyses with Fisher's exact test and the Cochran-

Mantel-Haenszel test were conducted to explore the robustness of the results. For proportions, 95% confidence intervals (CI) were obtained with the Wilson score method, with continuity correction.[41]

The Wilcoxon rank sum test (continuous variables) and Pearson's χ2 or Fisher's exact test (categorical variables) were used to test for differences in secondary outcomes between the 2 strategies. Categorical variables are described as numbers and percentages. Continuous variables are described as medians and interquartile ranges (IQR). Missing values in the questionnaires (1% of records) were not replaced. All analyses were performed with SAS (version 9.4; SAS Institute, Inc., Cary, NC) and R freeware (version 3.3.0)[42] and 2-sided α=5%-level tests.

Refer to Appendix E1 for a full description of the methods and results of the economic analysis.

The study protocol was approved by the Committee for Patient Protection Ile-de-France XI and by the French Data Protection Authorities. A waiver of consent was granted by each committee; as such, included patients did not individually provide written informed consent. This study report follows the cluster extension of Consolidated Standards of Reporting Trials and Consolidated Health Economic Evaluation Reporting Standards statements.[43,44]

RESULTS

Characteristics of Study Subjects

The study was conducted from June 2, 2014 to June 28, 2015. Among the 102,240 patients presenting to the participating EDs during the intervention periods, 74,161 were included. During the control periods, 105,582 patients presented to the EDs and 74,166 were included (Figures 1 and 2). Exclusion criteria included younger than 18 years or older than 64 years (99.0%) and presentation as a result of potential exposure to HIV within less than 48 hours (1.0%) (Table E2). Patient baseline characteristics are shown in Table 1.

Main results

During the intervention periods, 53,612 patients were able to provide consent, to complete the DICI-VIH questionnaire, and were not known to be HIV positive. Among them, 17,727 (33.1%) patients were asked to fill out a questionnaire, which was completed by 16,468 (92.9%) and declined by 1,259 (7.1%) (Figure 2). A total of 4,341 (26.4%) patients belonged to high-risk groups. Of the 3,995 patients (92.0%) to whom nurses suggested performance of a rapid test, 1,177 (29.5%) refused to be tested (Table E1). The main reason for refusal was having had a recent test (n=581).

A total of 2,818 (70.5%) patients were tested. The proportion of patients screened among those belonging to high-risk groups ranged from 59.5% to 70.9% depending on the ED. A clinical research nurse or assistant supported staff nurses with 28.5% (median) of the tests, ranging from 13.8% to 60.7% of tests performed, depending on the ED. Tested patients were mostly men (64.0%) (Table 2). The proportions of patients in the 5 high-risk groups were similar in the tested population and among those refusing to be tested (p=0.60) (Table E1).

During the intervention periods with nurse-driven targeted screening and physician-directed diagnostic testing, of the 2,818 nurse-driven tests performed, 25 (0.9%) were positive, including 13 patients with newly diagnosed HIV, 11 repeated diagnoses and 1 false-positive rapid test result (Figure 2). Combined with the 9 new diagnoses that followed 97 physician-directed diagnostic tests, a total of 22 patients received a new diagnosis (3.0 per 10,000 included patients, 95%CI 1.9 to 4.6) (Figure 2 and Figure E2). During the control periods involving only physician-directed diagnostic testing, 6 patients received a new diagnosis following 92 tests (0.8 per 10,000 included patients, 95%CI 0.3 to 1.9). The proportion of new HIV diagnoses identified during the intervention periods among included patients was significantly higher than during control periods (relative risk 3.7, 95%CI 1.4 to 9.8). Compared with the control periods, 16 additional new HIV diagnoses were identified during the intervention periods, which represents 2.2 additional new HIV diagnoses per 10,000 included patients (95% CI 1.3 to 3.6). No significant period effect or strategy-by-

period interaction was found (Figure E1 and E2). The sensitivity analysis results for the primary outcome were similar to those of the main analysis (Appendix E2).

The characteristics of the patients with newly diagnosed HIV are described in Tables 2 and 3. During the intervention periods, 6 HIV-positive patients were not late presenters (CD4 count≥350 cells per μl, no HIV-related symptoms) and were identified through nurse-driven targeted screening, whereas none of those detected during the control periods had such nonadvanced characteristics of the infection (*NS*). The proportion of new HIV diagnoses identified through targeted screening alone was 2.4% (95% CI 1.0% to 5.3%) in tested men who have sex with men and 0.5% (95% CI 0.2% to 1.0%) in tested Sub-Saharan African heterosexuals. Twenty-one patients (95.5%) received follow-up care during the intervention periods versus six (100%) during the control periods (*NS*).

The mean incremental cost of the intervention strategy was estimated as €2,837 per 10,000 included patients (95% CI €2,298 to €3,445). The incremental cost-effectiveness ratio (ICER) was €1,324 per additional new HIV diagnosis (95% CI dominated to €15,433, "dominated" referring to an intervention resulting in increasing costs with decreased effectiveness) (Appendix E1, Table 2). In the bootstrap analysis, all simulations resulted in additional costs with the intervention compared with the control strategy. In terms of effectiveness, 96.1% of the simulations favored the intervention, ie, resulted in a higher number of new HIV diagnoses in the intervention strategy compared with the control strategy (Appendix E1, Figure 1). In more than 75% of the simulations conducted in the latter set favoring intervention effectiveness, the corresponding incremental cost-effectiveness ratio values ranged between €750 and €3,200 per additional new HIV diagnosis (Appendix E1, Figure 2). Scenario analyses exploring the various costs of rapid test types and the relative involvement of nurses and physicians in the disclosure of positive results resulted in incremental cost-effectiveness ratios ranging from €1,261 to €1,961 (Appendix E1, Table 3).

LIMITATIONS

A limitation of this study was that the paper-based questionnaire was offered to one third of the patient population. However, this reflects the usual time-pressure conditions and constraints of the units. Similar operational limitations preventing the full integration of HIV screening into an ED setting have been reported.[18,24,30,45]

Nevertheless, the proportion of individuals who could be reached through long-term implementation of targeted screening remains to be estimated and could increase with the use of an electronic form completed by nurses during triage. Unlike previous studies conducted in non-French Eds, in which an individualized score was used to identify high-risk patients,[24] the DICI-VIH questionnaire was designed to be administered to the population of metropolitan France.[26] The present study indicates that this tool is applicable to busy health care settings. However, this questionnaire has not been subjected to all the tests required for a strict validation. Generalization issues relate to the adaptation of the questionnaire to local conditions or to the evolution of the epidemic over time. Moreover, the presence of a clinical research nurse or assistant during part of the intervention reminded ED staff of the screening process. Because this clinical research nurse or assistant would not be present in routine conditions, the protocol-driven cost was not included in the cost-effectiveness analysis, whereas it might have increased staff participation and therefore the effectiveness of the intervention. Another limitation of the study is that the DICI-VIH study design did not allow comparisons with targeted screening strategies that used different selection criteria, or with nontargeted screening. However other studies that explore these objectives are under way.[46]

Finally, these results were obtained in EDs that receive a large proportion of high-risk groups. Although they may not be directly applicable or generalizable to all ED settings, they could nonetheless be helpful in improving HIV screening policies tailored to local dynamics and recommendations in countries with concentrated epidemics.

DISCUSSION

Although the targeted HIV screening approach has existed for several years,[47,48] its impact in nonspecialist healthcare settings has seldom been evaluated. Our results indicate that implementing nurse-driven targeted HIV screening in addition to physician-directed diagnostic testing substantially increased the identification of new HIV diagnoses at an average added cost of approximately €3,000 per 10,000 included patients.

Two single-center studies comparing targeted versus nontargeted screening in EDs reported contrasting results.[24,25] The study by Lyons *et al.* found no benefit in the targeted strategy.[25] However, the number of tests performed was not very different in the comparison arms, thus raising questions in regard to the criteria used for targeting. Haukoos *et al.* showed that targeted screening was associated with a greater identification of new HIV diagnoses, compared with non-targeted screening.[24] To date, to our knowledge, no multicenter randomized controlled study had evaluated the effectiveness and cost-effectiveness of targeted HIV screening.

In contrast with these previous studies, we did not compare the targeted strategy with nontargeted practice. Indeed, given both the modest public health impact of the nontargeted screening strategy and the burden of its implementation, nontargeted screening in EDs has been poorly implemented in France (in 2013, none of the 8 participating EDs had adopted the strategy in routine practice)[26]. The literature also points to this screening strategy's being rarely implemented in other countries, such as the United States and the United Kingdom.[20-23] The choice of the control group in this study was therefore a pragmatic decision.

In our study, nurse-driven targeted HIV screening could be implemented in combination with physician-directed diagnostic testing. Almost all patients (93%) who were given the questionnaire agreed to complete it. The few cases of refusal were mostly from patients who declined listening to a description of the questionnaire before being informed of the study's goals. Most patients agreed to answer personal questions, which contradicts a commonly held notion against targeted screening, according to which patients are hesitant to answer

sensitive questions. However, we could not verify the veracity of their answers. Furthermore, only 29% of those offered a rapid test refused to be tested, yielding a refusal rate similar to that reported with nontargeted screening in the same EDs.[18,30] Refusal was mainly motivated by patients' having had a recent test, which has been reported in other studies.[18,25,49-51] Overall, two thirds of the patients identified as belonging to a high-risk group through the questionnaire were tested.

Given that more individuals were screened through the intervention strategy than through the control strategy, a higher proportion of new HIV diagnoses with the intervention was a likely result. However, our hypothesis was that targeted screening could detect at least the same proportion of new HIV diagnoses as nontargeted screening while using fewer resources in high-patient-flow settings. The important finding of the trial was that the proportion of new HIV diagnoses observed with targeted screening reached a threshold equivalent to that previously observed with nontargeted screening: the proportion of new HIV diagnoses observed among eligible patients (13/53,612; 0.024%) was similar to that previously reported in a study evaluating nontargeted screening in EDs in the same region (18/78,411; 0.023%).[18] Targeted screening substantially decreased the rate of tests performed compared with nontargeted screening (13/2,818 tested patients, 0.46%, versus 18/12,754 tested patients, 0.14%, respectively). Thus, targeted screening could be easier to implement than nontargeted screening while detecting similar proportions of unknown HIV infections. Targeted screening alone leads to the detection of approximately 1 new HIV diagnosis for every 200 tested patients, a proportion similar to that reported in voluntary testing centers in the region (0.46% versus 0.55%, respectively) *(unpublished data).*

Furthermore, in the DICI-VIH trial, targeted screening led to new diagnoses only in the 2 main high-risk groups (men who have sex with men and migrants from Sub-Saharan Africa), which is consistent with the characteristics of the HIV epidemic in the Paris metropolitan area.[52] In addition, the majority of patients with a new diagnosis were referred to specialized care (96%), well above the reported 76% average proportion of entry into care after receipt of an HIV-positive result in EDs or urgent care departments in the United States.[53]

Consistent with previous studies,[54-56] our cost-effectiveness results support a nurse-driven targeted screening approach combined with physician-directed diagnostic testing, with an observed incremental cost-effectiveness ratio of €1,324 per additional HIV diagnosis. From the hospital perspective, targeted screening combined with diagnostic testing will result in a cost increase but will detect more undiagnosed HIV-positive individuals than diagnostic testing alone. Previous studies have estimated that a screening strategy would be cost-effective if the proportion of undiagnosed HIV infection exceeded the threshold of 0.1%.[12,57,58] Nurse-driven tests revealed a proportion of undiagnosed infections of 0.46%, which is above this threshold. In addition, the observed incremental cost-effectiveness ratio was well below the average cost per new diagnosis, estimated at €20,400 in voluntary testing centers in the region in 2015.[59] Furthermore, throughout the trial, nurses asked physicians to jointly disclose the positive results. Considering that nurses could gradually take on this responsibility without the support of a physician, the cost-effectiveness of a targeted screening strategy is likely to improve with future implementation.

From these results, we extrapolated that the implementation of targeted screening during the course of 1 full year in the 29 EDs in the Paris metropolitan area – in which the proportion of individuals belonging to risk groups is known -[18] would lead to approximately 300 additional HIV diagnoses, increasing the number of new HIV diagnoses in the region by approximately 10% per year (Appendix E3). This would represent an additional cost of about €400,000 per year.

In a recently published report, French health authorities recommend prioritizing HIV screening to key populations in EDs.[60] The results obtained in the DICI-VIH trial support these recommendations.

In conclusion, this study shows that the intervention strategy involving targeted screening in EDs, using a brief questionnaire and rapid HIV tests performed by nurses, was effective compared with a strategy without targeted screening, with an added hospital cost of approximately 3,000€ per 10,000 included patients. In countries with concentrated HIV epidemics, this strategy may prove to be an interesting approach to the identification of HIV-

positive individuals with undiagnosed disease and could complement other screening programs, allowing timely access to care, reducing ongoing transmission, and thereby contributing to controlling a country's HIV epidemic.

Acknowledgments

APPENDIX

Study investigators

This study was conducted on behalf of the DICI-VIH group, which includes the investigators who led the data collection (listed below in alphabetical order by city name [all in France], emergency department / infectious diseases department / virology department) as well as Pierre Mutuon and Kayigan d'Almeida, who participated to the analysis of the findings; Hélène Fromentin, Maria Martin and Charlotte Cossé, who were involved in the follow-up of the trial; and Espérie Burnet, who reread the article.

Bobigny: Hôpital Avicenne, AP-HP: Gaëlle Duchêne; Carole Jegou; Frédéric Adnet / Olivier Bouchaud / Chakib Alloui.

Gonesse: Centre Hospitalier de Gonesse: Christine Jauneau / Didier Troisvallets / Eric Vandemeulebroucke.

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Tables

Table 1 Characteristics of study participants

Characteristic	Control Strategy (n=74,166), No. (%) or Median (IQR)	Intervention Strategy (n=74,161), No. (%) or Median (IQR)
Age, y[a]	36.6 (27.3–48.7)	36.6 (27.3-48.6)
Missing	84 (0.1)	67 (0.1)
Male sex	41,676 (56.2)	41,595 (56.1)
Missing	6 (0.0)	9 (0.0)
Severity score at ED admission in 7 of 8 centers[b]		
Absolute emergency	62 (0.1)	53 (0.1)
Relative emergency<20 min	7,103 (11.0)	6,971 (10.8)
ED visit<60 min	21,418 (33.1)	21,436 (33.1)
ED visit<120 min	27,500 (42.6)	27,446 (42.4)
ED visit<240 min	6,671 (10.3)	6,828 (10.6)
Missing	1,868 (2.9)	1,970 (3.0)

IQR, Interquartile range.

[a]Age, sex, and severity score were obtained from the ED flow data.

[b]In one center, severity scores were not documented by triage nurses at patient assessment (missing data: control strategy, n=9,544; intervention strategy, n=9,457).

Table 2 Individual-level demographic characteristics of patients who completed the DICI-VIH questionnaire

Characteristic	Completed the DICI-VIH questionnaire (n=16,468), No. (%) or Median (IQR)	Belonged to a high-risk group (n=4,341), No. (%) or Median (IQR)	Were offered nurse-driven targeted HIV screening (n=3,995), No. (%) or Median (IQR)	Tested by nurses (n=2,818), No. (%) or Median (IQR)	Received new diagnosis in the nurse-driven process (n=13)[a], No. (%) or Median (IQR)
Age, y	34.6 (26.3–46.1)	34.3 (26.6–44.7)	34.3 (26.6–44.8)	34.1 (26.4–44.3)	44.4 (35.9–48.8)
Male sex	8,760 (53.2)	2,707 (62.4)	2,515 (63.0)	1,804 (64.0)	12 (92.3)
HIV high-risk group[b]					
Men who have sex with men (MSM)	383 (2.3)[c]	383 (8.8)	350 (8.8)	255 (9.0)	6 (46.2)
Sub-Saharan African (SSA) origin	2,269 (13.8)[d]	2,269 (52.3)	2,081 (52.1)	1,447 (51.3)	7 (53.8)
SSA partner in the past 10 years	613 (3.7)[e]	613 (14.1)	560 (14.0)	395 (14.0)	0 (0.0)
>5 partners in the past 12 months	932 (5.7)[f]	932 (21.5)	869 (21.8)	625 (22.2)	0 (0.0)
Lifetime injection drug use (IDU)	137 (0.8)[g]	137 (3.2)	128 (3.2)	89 (3.2)	0 (0.0)
Missing	7 (0.0)	7 (0.2)	7 (0.2)	7 (0.2)	0 (0.0)

IQR, Interquartile range; *MSM*, Men who have sex with men; *SSA*, Sub-Saharan African; *IDU*, injection drug user

[a]Proportion of patients with a new diagnosis in the nurse-driven process: 0.46 (95% CI 0.26-0.81).
[b]Data on HIV high-risk groups were collected from the DICI-VIH questionnaire and are presented as exclusive items in this order: MSM, SSA origin, SSA partner, greater than 5 partners in the past 12 months, and IDU. A patient included in the first category could not be included in a subsequent category. Overall, 1,166 patients (41.4%) had 2 or more risk factors and 96 (3.4%) had 3 or more. Missing values were not replaced (mean: 1%). They accounted for less than 0.8% of each item, except for the question about having an SSA partner during the past 10 years, which had 3.6% missing values. Missing data correspond to patients for whom none of the 5 risk factors was filled.
[c]MSM: 1.8% in France,[61] data unknown for metropolitan Paris.
[d]SSA origin: 0.8% in France,[27] 2.7% in metropolitan Paris.[27]
[e]SSA partner: data unknown for France or metropolitan Paris.
[f]Greater than five partners in the past 12 months: 1.0% in France,[61] data unknown for metropolitan Paris.
[g]IDU: 0.4% in France among the population aged 15 to 64 years,[62] data unknown for metropolitan Paris.

Table 3 Characteristics of patients with a new HIV diagnosis

Characteristic	Control strategy (n=6), No. (%) or Median (IQR)	Intervention strategy (n=22[a]), No. (%) or Median (IQR)
Age, y	41.5 (34.5 to 54.8)	40.9 (32.7 to 48.7)
Male sex	4 (66.7)	15 (68.2)
HIV high-risk group		
MSM	1 (16.7)	8 (36.4)
SSA origin	3 (50.0)	13 (59.1)
SSA partner in the last 10 y	0 (0.0)	1 (4.5)
Other	2 (33.3)[b]	0 (0.0)
HIV related-symptoms	6 (100)	12 (54.5)[c]
Western-blot confirmatory test performed	6 (100)	21 (95.5)
Disease stage		[d]
CD4 cell count <200 cells per μl or AIDS	3 (50.0)	11 (55.0)[e]
CD4 cell count: 200–349 cells per μl	1 (16.7)	1 (5.0)
CD4 cell count ≥350 cells per μl	2 (33.3)	8 (40.0)
CD4 cell count (cells per μl)	195.5 (102.0 to 404.0)	168.0 (42.0 to 519.5)[d]
Viral load ($\log_{10}$ copies per mL)	6.4 (5.3 to 7.0)[f]	5.1 (4.0 to 5.5)[d]
CD4 count ≥350 cells per μl + no HIV-related symptoms[g]	0 (0.0)	6 (30.0)[h]
Received follow-up care[i]	6 (100)	21 (95.5)
Previous HIV test result	1 (25.0)[j]	5 (23.8)[h]
Contact with a health care provider in the past 12 months	3 (50.0)	13 (70.0)[k]

[a]Thirteen patients received a diagnosis through nurse-driven tests (proportion of new diagnoses among tests performed: 0.46%), and 9 patients received a diagnosis through physician-driven tests (proportion of new diagnoses among tests performed: 9.28%), for a total proportion of new diagnoses among tests performed of 0.75% in the intervention strategy. This proportion was 6.52% in the control strategy

[b]Risk factors were not identified but, in both cases, the partner was documented as an IDU or was highly suspected to be an IDU.

[c]Three patients were diagnosed through nurse-driven tests, and nine patients received a diagnosis through physician-driven tests.

[d]n=20 (2 missing values).

[e]Four patients received a diagnosis through nurse-driven tests, and seven patients received a diagnosis through physician-driven tests.

[f]Three of six patients were in the acute stage of the disease.

[g]For this secondary outcome, groups were compared using Fisher's exact test: $p=.28$.

[h]n=21 (1 missing value). All patients were diagnosed through nurse-driven tests.

[i]For this secondary outcome, groups were compared using Fisher's exact test: $p>.99$. The overall proportion of patients with a new diagnosis and referred to follow-up care in the two groups was 96.4%.

[j]n=4 (2 missing values).

^{k}n=19 (3 missing values).

Figure legends

Fig.1 Study profile following the Consolidated Standards of Reporting Trials statement statement (extension for cluster randomized trials)

Figure Legend:

ªED center characteristics and study period duration are described in Tables E2 and E3.

Fig. 2 Study flow diagram

Figure Legend:

*For the patients who refused nurse-driven tests, no new HIV diagnoses were identified through diagnostic testing. †In addition, 62 nurse-driven tests were performed for patients not belonging to high-risk groups: no new HIV diagnoses were identified in this group.
‡Known positive HIV status was confirmed by the patient, by the ED staff, or by the on-site infectious disease specialist.
§The patient with a false-positive rapid test had a confirmed negative result on the antigen-antibody combined test (Abbott HIV-1:2 Architect; Abbott, Chicago, IL), as well as through the highly sensitive p24 antigen assay (Vidas HIV-1 p24 Ag; bioMérieux).

8 EDs invited to participate in the cluster-randomized, 2-period crossover trial. All consented. **Randomization** assigned **each participating ED** to apply either the **control strategy** (diagnostic testing) or the **intervention strategy** (nurse-driven targeted HIV screening + diagnostic testing) during the first study period, and the alternative strategy during the second period*.

4 EDs allocated to :
Intervention strategy during the 1st period and **control strategy** during the 2nd period.
Among 112,378 patients visiting the EDs, 74,420 were eligible (18-64 y.o., not presenting secondary to potential HIV exposure) and included.

4 EDs allocated to :
Control strategy during the 1st period and **intervention strategy** during the 2nd period.
Among 95,444 patients visiting the EDs, 73,907 were eligible (18-64 y.o., not presenting secondary to potential HIV exposure) and included.

0 clusters lost to follow-up
4 clusters analyzed

0 clusters lost to follow-up
4 clusters analyzed

FIRST STUDY PERIOD

All included patients were analyzed (37,185):
ED1: 9,493
ED2: 9,240
ED3: 9,457
ED4: 8,995

All included patients were analyzed (36,931):
ED5: 9,405
ED6: 9,065
ED7: 9,212
ED8: 9,249

SECOND STUDY PERIOD

(AFTER 4-WEEK WASH-OUT PERIOD)

All included patients were analyzed (37,235):
ED1: 9,452
ED2: 9,219
ED3: 9,544
ED4: 9,020

All included patients were analyzed (36,976):
ED5: 9,344
ED6: 9,163
ED7: 9,247
ED8: 9,222

Randomization assigned each participating ED to apply either the control strategy (diagnostic testing) or the intervention strategy (nurse-driven targeted HIV screening + diagnostic testing) during the first study period, and the alternative strategy during the second period.

Control strategy in the 8 EDs

Intervention strategy in the 8 EDs

20,549 (27.7%) unable to complete the questionnaire: *Unable to give consent (altered consciousness, severe neuropsychiatric disorder, language barrier, under arrest): 73.6%; Who left before questionnaire offer: 9.1%; Life-threatening condition: 7.6%; HIV+: 3.6%; Other: 6.1%*
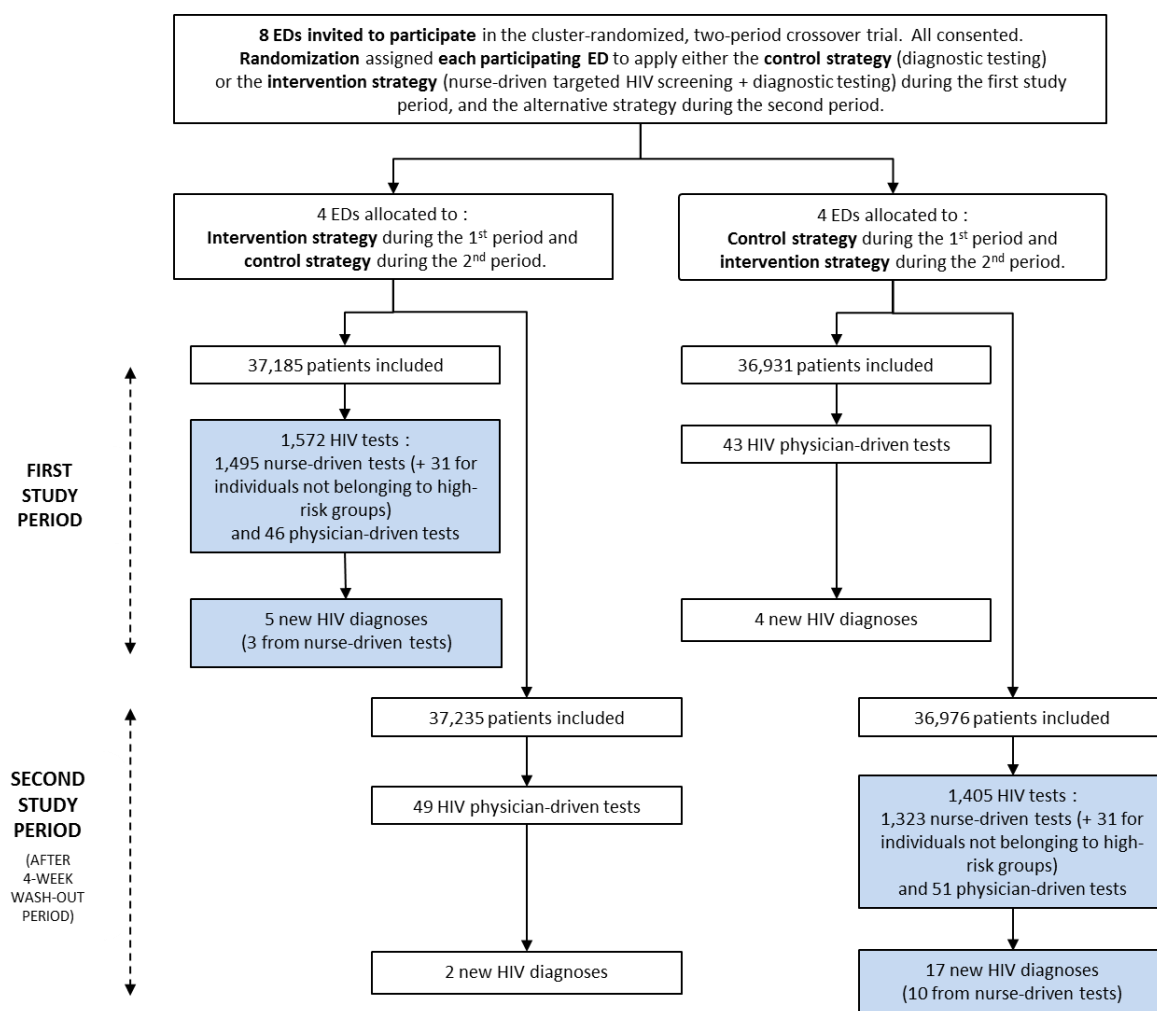
74,166 patients included (18-64 y.o., not presenting secondary to HIV exposure)

74,161 patients included (18-64 y.o., not presenting secondary to HIV exposure)

Among the remaining 53,612 patients (72.3%), the questionnaire was not offered to 35,885 (66.9%)

Questionnaire offered to 17,727 / 53,612 able to complete the questionnaire (33.1%)

1,259 (7.1%) refused to complete the questionnaire

Questionnaire completed by 16,468 (92.9%)

12,127 (73.6%) did not belong to high-risk groups *+ Patients who left:0.3%; HIV+: 0.1%; Other: 0.02%*

4,341 (26.4%) belonged to high-risk groups

346 (8.0%) were not offered a rapid test by nurses: *Unit work overload: 67.6%; Unknown: 32.4%*

3,995 (92.0%) were offered a rapid test by nurses

1,177 (29.5%) refused the rapid test*: *(multiple choice) Recent test: 49.4%; Do not consider self as being at risk for HIV: 15.6%; Other: 30.6%; More than 1 answer checked: 3.0%; Unknown: 1.4%*

92 (0.1%) physician-driven tests

97 (0.1%) physician-driven tests

2,818 (70.5%) nurse-driven tests+

11 (12.0%) positive tests

11 (11.3%) positive tests

25 (0.9%) positive tests

5 (45.5%) known HIV+ status+

2 (18.2%) known HIV+ status

11 (44.0%) known HIV+ status
1 (4.0%) false-positive§

9 new HIV diagnoses

13 new HIV diagnoses

6 new HIV diagnoses / 74,166 patients included (0.8 per 10,000)

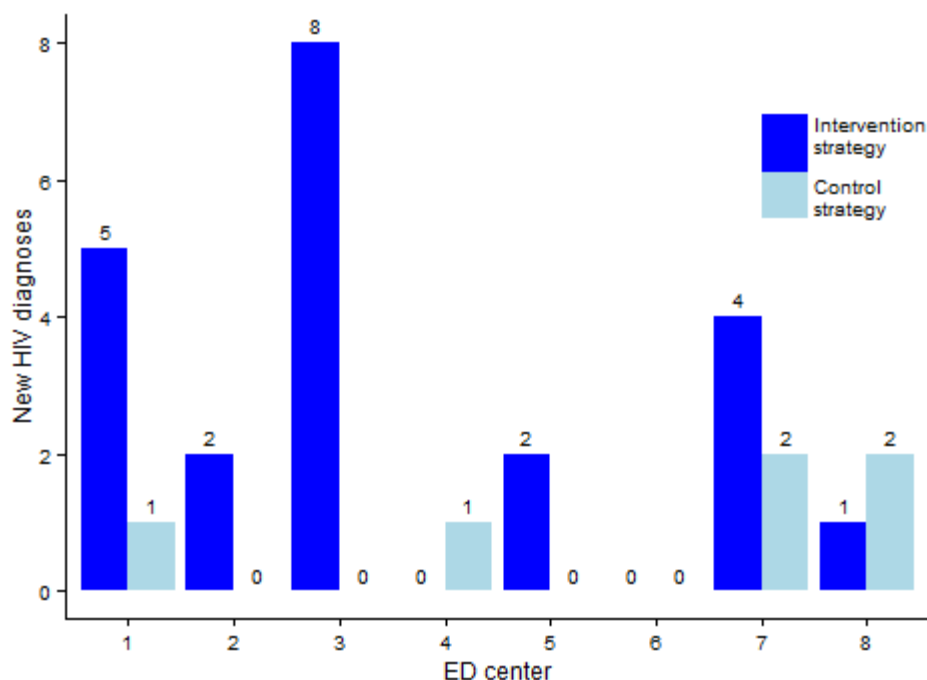22 new HIV diagnoses / 74,161 patients included (3.0 per 10,000)

Additional file

Figure E1: Study flow chart: HIV tests and new HIV diagnoses per period and according to ED randomization

ED, Emergency department.

Figure E2: Absolute number of new HIV diagnoses in each ED in the intervention and control strategies.

Centers 1, 3, 4, and 7 applied the control strategy first followed by the intervention strategy, whereas centers 2, 5, 6, and 8 applied the intervention strategy first followed by the control strategy. In the EDs implementing the intervention first, there were 5 new HIV diagnoses in the first study period (intervention) versus 2 in the second period (control), whereas in the EDs implementing the control strategy first, there were 4 new HIV diagnoses in the first study period (control) versus 17 in the second study period (intervention).

Table E1: Characteristics of patients who accepted the test and of those who refused

HIV high-risk groups[a, b]	Patients tested by nurses[c] n=2,818 No. (%)	Patients who refused nurse-driven tests n=1,177 No. (%)
Men who have sex with men	255 (9.0)	95 (8.1)
Sub-Saharan African (SSA) origin	1,447 (51.3)	634 (53.9)
SSA partner in the past 10 years	395 (14.0)	165 (14.0)
>5 partners in the past 12 months	625 (22.2)	244 (20.7)
Lifetime injection drug use	89 (3.2)	39 (3.3)

[a]Data on HIV high-risk groups are presented as exclusive items.
[b]The distribution is similar between groups (*P*=0.60, Pearson's χ2 test).
[c]Seven patients in the tested group had missing data.

Table E2: ED center characteristics

Characteristic[a]	ED1	ED2	ED3	ED4	ED5	ED6	ED7	ED8
Pediatric care provided	No	Yes[b]	No	Yes[b]	No	Yes[b]	No	No
University hospital	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Inner-Paris ED	Yes	No	Yes	No	Yes	No	No	Yes
Patient examination rooms	13	13	12	15	10	8	8	12
Nurses	63	31	77	48	44	27	41	59
Auxiliary nurses	56	18	46	44	43	20	34	46
Physicians	23	21	22	13	19	16	16	24

Data are presented as numbers.
[a]Structural characteristics of each ED in 2014, median (IQR): patient examination rooms: 12 (10 to 13). Staff (full-time equivalent): nurses: 46 (39 to 60); auxiliary nurses: 44 (31 to 46); physicians: 20 (16 to 22).
[b]ED2 and ED6 include a pediatric emergency unit. The hospital of ED4 also includes a pediatric emergency unit, which is geographically separated from the adult unit in the hospital, and data from children are registered in a separate database.

Table E3: Study period duration

Period[a]	ED1	ED2	ED3	ED4	ED5	ED6	ED7	ED8
Intervention period (day)	76	76	61	84	102	101	111	84
Control period (day)	76	73	57	88	103	105	110	90
Wash-out period(day)	36	66	27	51	32	30	30	30

Data are presented as numbers.
[a]Duration of the intervention, control and wash-out periods (day), respectively, median (IQR): 84 (76 to 101); 89 (75 to 103); 31 (30 to 39).

APPENDIX E1: Cost-effectiveness analysis

Methods

A prospective economic evaluation was conducted concurrently with the DICI-VIH trial. The economic evaluation determined the added cost per additional new HIV diagnosis identified during the intervention periods (compared with control periods). The time horizon was 3 months and included 2 hospital visits (ED visit followed by a follow-up visit with an infectious disease specialist if needed). The perspective taken was that of the health care system and considered hospital resources up to the time of diagnosis, according to staff time and testing equipment. Costs of employing clinical research nurses or assistants were excluded as they would not be present in routine conditions. Treatment costs were also excluded.

Intervention costs were estimated using a bottom-up microcosting approach performed for 2 of the participating EDs. Before the start of the intervention, staff training in each ED consisted of one 2-hour session by a nurse and 1 hour by an infectious disease specialist. The costs of the nurse-driven screening procedure were evaluated during 1 full day in each of the 2 EDs. The 3 main steps of the procedure were directly observed with a stopwatch for at least 15 questionnaires distributed, 5 rapid HIV tests offered, 5 rapid HIV tests performed and 5 results disclosed per center. The cost used for the tests was the manufacturer's price. Staff costs were estimated according to gross salaries. All costs were reported in 2015 Euros (1 US\$=0.84€) and not discounted (Table 1 and Appendix E1).

A cost-effectiveness analysis was conducted: incremental costs (ie, difference between strategies in terms of costs per 10,000 included patients) were estimated and contrasted with the corresponding estimate of incremental effectiveness (ie, difference between strategies in terms of additional new HIV diagnoses per 10,000 included patients), leading to an incremental cost-effectiveness ratio (ICER) expressed as the additional cost of the intervention per additional new HIV diagnosis.

A resampling of all the data from the DICI-VIH trial (n=148,327) was performed 1 million times, and 95% CIs were generated with the nonparametric bootstrap approach. A scenario analysis of the screening strategy's cost-effectiveness was performed, examining the type of rapid test used and the staff involved for the disclosure of positive results. This study report follows the Consolidated Health Economic Evaluation Reporting Standards statement.

Table 1: Unit costs of healthcare resources

Ressource[a]	Unit costs (€)
HIV rapid test (VIKIA HIV1/2, bioMérieux, Marcy l'Etoile, France)	1.65
HIV rapid test (INSTI[TM], HIV-1/2, BioLytical Laboratories, Richmond British Columbia, Canada, Nephrotek France)	5.16
Nurse salary per year[b]	50,010
Nurse hourly wage	31.12
Physician salary per year	119,425
Physician hourly wage	74.32
Antigen-antibody combined test (including related human resource to perform the test)	14.58
Western blot confirmation (including related human resources to perform the test)	43.20
Consultation with an infectious disease specialist	22.00

[a]1US\$=0.84 €.[1]

Table 2: Costs and effectiveness of the study strategies

All relevant cost components of the intervention strategy were identified.

Staff training in each ED consisted of one 2-hour session by a nurse (62.24€) and 1 hour by an infectious disease specialist (74.32€).

The costs of the intervention were obtained using a bottom-up microcosting approach:

a) Questionnaire distribution

The staff in charge of this step varied from one ED to another: nurse, auxiliary nurse or administrative reception staff. The highest salary cost (nurse) was considered for the analysis. This step lasted a mean of 1 minute and was considered to include the questionnaire distribution, its overview as well as the offer of a rapid test for patients who refused it.

b) Rapid HIV test

This step was performed by a triage nurse and included both offering and performing the rapid test. It lasted a mean of 2 minutes.

c) Result disclosure

Negative results were disclosed by a triage nurse or a nurse in the examination room and lasted a mean of 15 seconds.

Positive or 2 sequentially indeterminate results were delivered by a nurse, assisted by an emergency physician if needed. In the analysis, the physician was considered to be systematically present. This step lasted a mean of 30 minutes.

In addition, 10 nurses per center were asked to estimate the duration of each step of the procedure, for both negative and positive rapid test results.

The chosen rapid test was the one used in the DICI-VIH study: the VIKIA HIV1/2, bioMérieux, Marcy l'Etoile, France.

The total costs of a negative HIV rapid test (3.34€) included human resources and equipment for:
1. a nurse distributing the questionnaire (0.52€),
2. a nurse performing the rapid test (1.04€),
3. a nurse disclosing the result (0.13€), and
4. the rapid test (1.65€). Gloves, disinfectant and gauze were not taken into account.

The total costs of a positive HIV rapid test (56.01€) included human resources and equipment for:
1. a nurse distributing the questionnaire (0.52€),
2. a nurse performing the rapid test (1.04€),
3. a nurse (15.60€) and a physician (37.20€) disclosing the result (52.80€ in total), and
4. the rapid test (1.65€).

Resource[a]		Control strategy (n=74,166)	Intervention strategy (n=74,161)
Staff training			
	Cost	NA	€1,092
Questionnaire distribution, not resulting in a rapid test			
	n	NA	14,847
	Cost		€7,720
Negative rapid test result			
	n	NA	2,855
	Cost		€9,536
Positive rapid test result			
	n	NA	25
	Cost		€1,400
Second rapid test following a rapid test with indeterminate result			
	n	NA	33[b]
	Cost		€93
Antigen-antibody combined test + western blot			
	n	92 + 11[c]	118 + 23[d]
	Cost	€1,822	€2,718
Visit with an infectious disease specialist			
	n	6	23[e]
	Cost	€132	€506
Total costs[f]		€1,954	€ 23,066
Mean cost per 10,000 included patients (95% CI)		€260 (€143 to €409)	€3,101 (€2,630 to €3,644)
Mean incremental cost per 10,000 included patients (95% CI)			€2,837 (€2,298 to €3,445)
Mean incremental effectiveness of the intervention strategy (additional new HIV diagnoses per 10,000 included patients) (95% CI)			2.03 (-0.13 to 4.88)
ICER (cost per additional new HIV diagnosis) (95% CI)			€1,324 (dominated to €15,433)

NA, Not applicable. *ICER*, Incremental cost-effectiveness ratio.

[a]All costs are in 2015 Euros, 1US $=0.84€.

[b]The total costs of a second rapid test included: a nurse performing the rapid test (1.04€) and disclosing the result (0.13€), and the rapid test (1.65€).

[c]Included 3 patients with a physician-driven rapid test associated with an antigen-antibody combined test.

[d]In the intervention strategy, there were 118 antigen-antibody combined tests performed after:
- 97 physician-driven tests (including 10 associated with a physician-driven rapid test),
- 21 nurse-driven tests:
    - 14 positive rapid tests (including 1 known HIV+ status and 1 false-positive result to the antigen-antibody combined test),
    - 1 rapid test with an indeterminate result,
    - 6 negative rapid tests.

In addition, there were 23 western blot confirmations performed after:
- 10 physician-driven tests,
- 13 nurse-driven tests (including 1 known positive HIV status).

In both groups, medical costs related to the diagnostic test were considered negligible.

[e]23 visits with the infectious disease specialist included a visit for 1 patient with a known positive HIV status and a visit for 1 patient with a false-positive result to the antigen-antibody combined test. One patient with a positive HIV diagnosis did not attend to the follow-up visit.

[f]Protocol-driven costs were estimated but not included in the ICER calculations. They were related to the clinical research nurses or assistants who spent time in the EDs during the intervention periods to remind the staff of the study protocol and to support them with the screening. Were the screening strategy to be deployed on a routine basis, the research nurses or assistants would not be present. The research nurse's (or assistant's) participation was estimated as equal to a half-time position, representing additional time costs of 54,071€ (or 7,291€ per 10,000 included patients) throughout the 8 centers.

Figure 1: Incremental effectiveness of the intervention according to its incremental cost (N=1 million simulations)
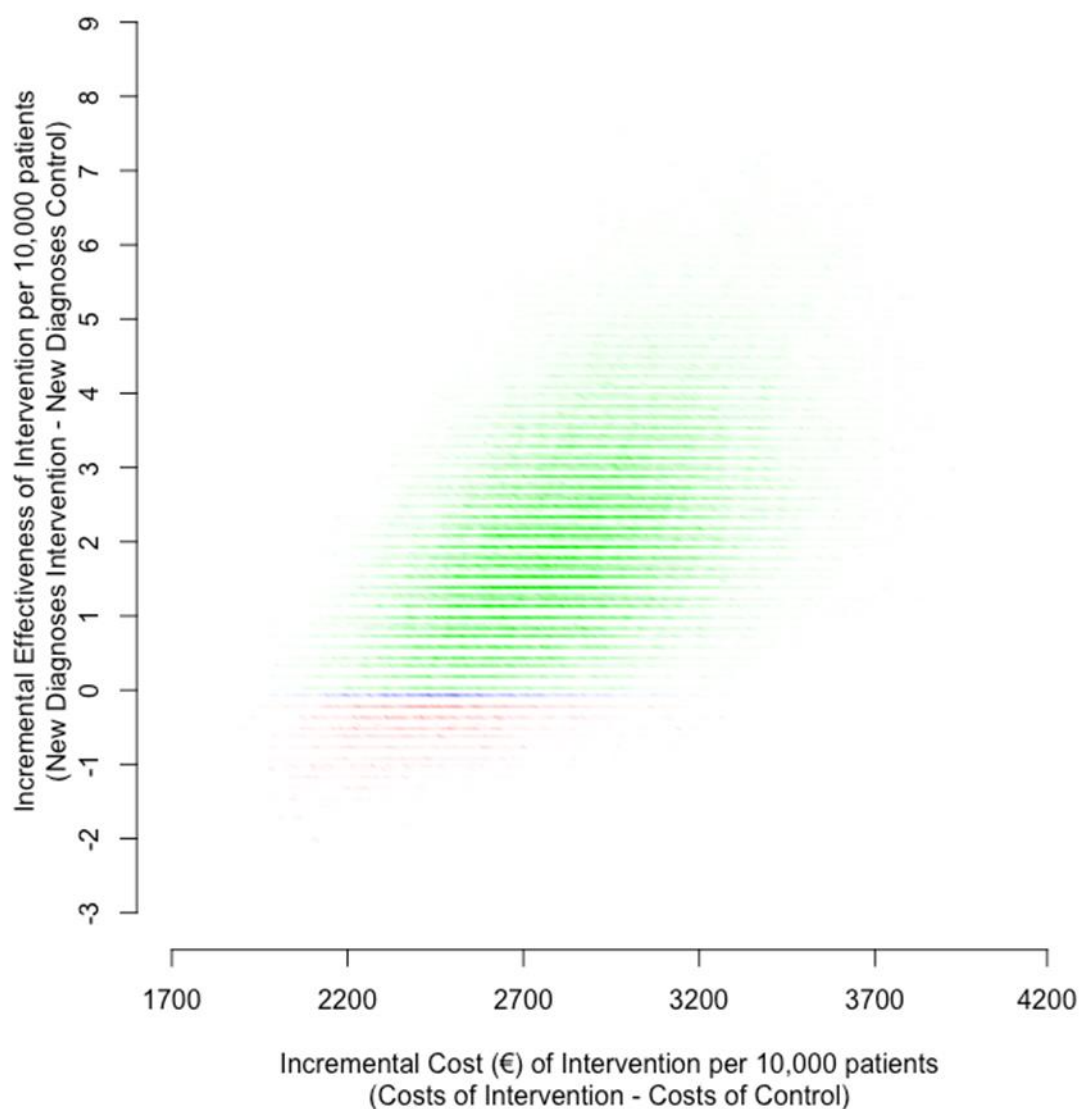
The color intensity increases with the corresponding number of simulations observed:
green, 960,828 simulations (96.1% of the simulations) in favor of the intervention strategy (The central estimation of the incremental cost was €2,845 and the central estimation of the incremental effectiveness was 2.14 new HIV diagnoses); red, 28,143 simulations (2.8% of the simulations) for which the intervention strategy was dominated by the control strategy (cases where the intervention strategy was more expensive while leading to fewer new diagnoses than the control strategy); blue, 11,029 simulations (1.1% of the simulations) for which the simulation led to a strictly equal number of new HIV diagnoses in both strategies.

Figure 2: Willingness to pay for the detection of a new HIV diagnosis (N=1 million simulations)
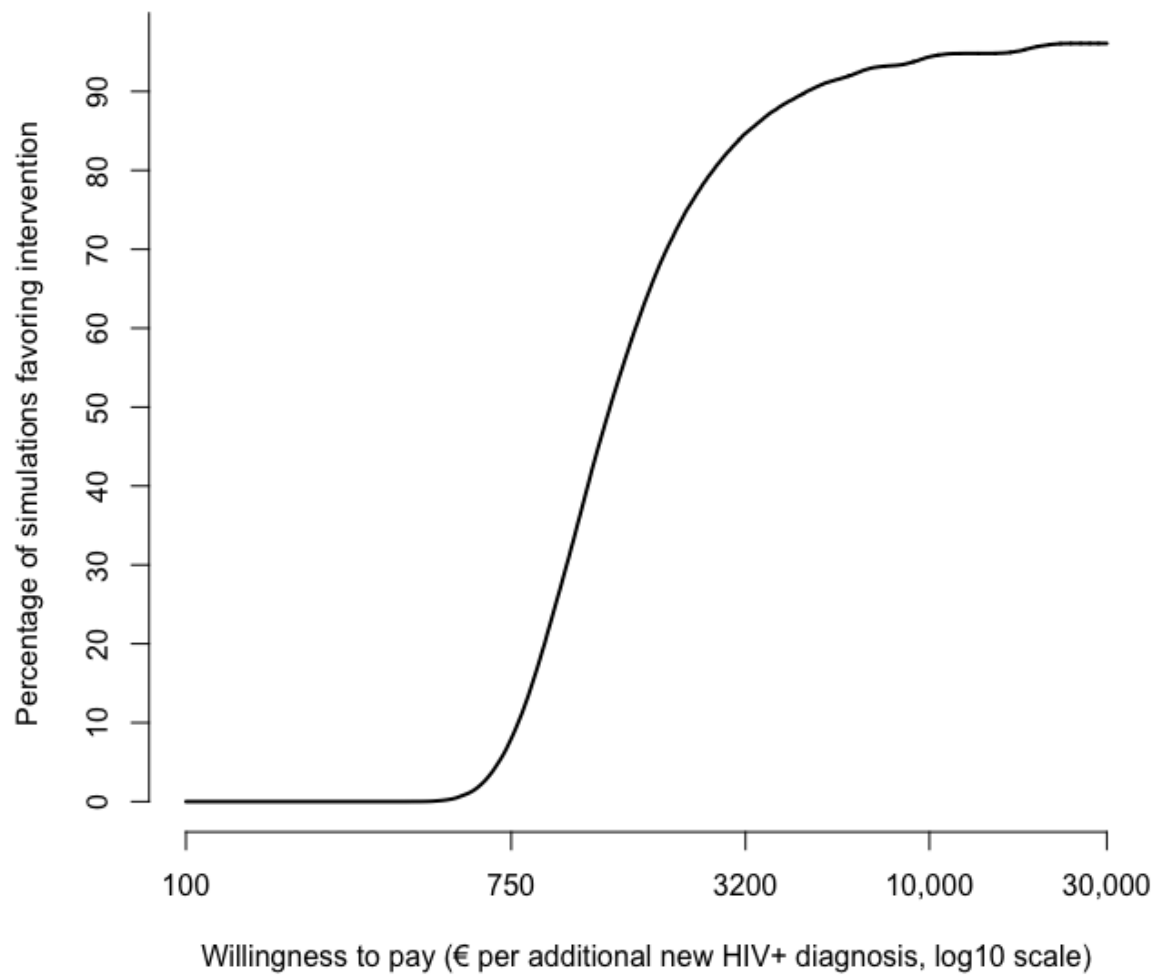
Table 3: Scenario analysis

A scenario analysis of the screening strategy's cost-effectiveness was performed examining the type of rapid test used and the staff involved for the disclosure of positive results:

Cost-effectiveness was calculated according to the use of the rapid test INSTI™, HIV-1/2, BioLytical Laboratories, Richmond, British Columbia, Canada, Nephrotek France, which is available in the participating EDs. It was compared with the use of the rapid test VIKIA HIV1/2, bioMérieux, Marcy l'Etoile, France. The disclosure of a positive test result was undertaken by a nurse alone and was compared to a disclosure performed by a nurse and a physician.

Scenario	Rapid test	Staff involved in the disclosure of positive rapid test results	Incremental cost per 10,000 included patients in the intervention strategy relative to the control strategy (€)	Incremental cost-effectiveness ratio (€ / new HIV diagnosis)
Scenario 1 *(main analysis)*	VIKIA HIV1/2, bioMérieux	Nurse + physician	2,847	1,324
Scenario 2	VIKIA HIV1/2, bioMérieux	Nurse	2721	1,261
Scenario 3	INSTI™, HIV-1/2, BioLytical Laboratories	Nurse + physician	4231	1,961
Scenario 4	INSTI™, HIV-1/2, BioLytical Laboratories	Nurse	4105	1,903

The scenario analysis produced an ICER ranging from €1,261 (with the cheaper rapid test and a nurse alone to disclose a positive result) to €1,961 (with a more expensive rapid test and a nurse with a physician to disclose a positive result).

Results

The mean cost was estimated at €3,101 per 10,000 patients included (95% CI €2,630 to €3,644) in the intervention strategy compared with €260 (95% CI €143 to €409) in the control strategy, for a mean incremental cost of the intervention strategy estimated at €2,837 per 10,000 patients included (95% CI €2,298 to €3,445).
The ICER was estimated as €1,324 per additional new HIV diagnosis (95% CI dominated to €15,433) (Appendix E1, Table 2).

Scenario analyses exploring the costs of the 2 rapid test types and the relative involvement of nurses and physicians in the disclosure of positive results resulted in ICERs ranging from €1,261 to €1,961 per additional new HIV diagnosis (Appendix E1, Table 3).

In all simulations, the total costs in the intervention strategy were greater than those in the control strategy (Appendix E1, Figure 1<) with a mean incremental cost of €2,837 per 10,000 patients included (ranging between €1,758 and €4,111).
In 96.1% of the simulations (960,828 among 1 million simulations), the simulations led to a positive and finite ICER. The values ranged between €375 and €26,065 per additional new HIV diagnosis, with an ICER between €630 and €8,943 per additional new HIV diagnosis in 95% of the 960,828 simulations (lower and upper limits of the interquartile range were respectively €690 and €2,064). A value greater than 20,000 € per additional new HIV diagnosis was found in 4 simulations out of 1,000.

These results indicate that in almost all simulations, the intervention strategy was associated with a very favorable cost-effectiveness ratio, which is also confirmed in Appendix E1, Figure 2, showing the variation in the proportion of simulations in favor of the intervention (green points of Appendix E1, Figure 1) according to the willingness to pay for the detection of a new HIV diagnosis. More than 75% of the simulations in favor of the intervention strategy corresponded to ICERs ranging between €750 and €3,200 per additional new HIV diagnosis.

Moreover, more than half the associated costs of a positive HIV rapid test were attributable to the physician time required for result disclosure. Throughout the study, nurses asked physicians to jointly disclose these positive results. Considering that nurses could gradually take on this responsibility without the assistance of a physician, the cost-effectiveness of a targeted screening strategy is likely to improve with future implementation.

APPENDIX E2

Primary outcome modeling, sensitivity analyses and inter-cluster and intra-cluster correlation coefficients

The following 3 models were compared using likelihood ratio tests:

- Model including a random intercept for center and fixed effect for strategy (intervention or control);
- Model including a random intercept for center and fixed effects for strategy and period (1 or 2);
- Model including a random intercept for center and fixed effects for strategy, period and strategy-by-period interaction.

Backward selection showed that the interaction term (P=0.12) and the period effect (P=0.46) were not statistically significant. The final model is the model with strategy as the only fixed effect.

Table 1: Final model: Coefficient estimate from generalized linear mixed modeling2 with a Poisson model for proportions, including a random center effect and fixed intervention effect (SAS PROC Glimmix[3-5])

Variable	Coefficient	SE	*t* test	*P* value	Relative risk	(95% CI) relative risk
Intervention	1.2985	0.4606	2.82	0.0137	3.6638	(1.3643 to 9.8386)

Covariance	Coefficient	SE
Center	0.4180	0.4061

The variability between centers was estimated as 0.4180, which is small compared to the associated standard error.

Several arguments indicate that data are not over dispersed:
- Ratio of 'Generalized Chi-Square statistic' and its degrees of freedom is 0.86;
- Scaled Pearson statistic for the conditional distribution is 0.93;
- The negative of twice the log likelihood (–2 Log L) for the intercept is 55.4 and for BIC is 61.37.

Sensitivity analysis

Table 2: Analysis considering missing values as failures (1 missing value for the main outcome in the intervention strategy)

Variable	Coefficient	SE	*t* test	*P* value	Relative risk	(95% CI) relative risk
Intervention	1.2523	0.4629	2.71	0.0171	3.4983	(1.2962 to 9.4415)

Table 3: Other tests examining the primary outcome

Method	*P* value	Relative risk	(95% CI) relative risk
Fisher's exact test	0.0023	3.67	(1.44 to 11.06)
Cochran-Mantel-Haenszel test	0.0037	3.66	(1.44 to 11.04)

Inter-cluster and intra-cluster correlation coefficients

Sample size calculation was performed assuming that the crossover design, which resulted in matched-pair data within each center (intercluster or interperiod correlation) and the effect of the cluster study design (intracluster correlation) cancelled each other out[6,7] (a cluster corresponding to one study period per ED).

The intercluster correlation coefficient ρ_{12} and intracluster correlation coefficient ρ were calculated *a posteriori* following the Donner formula.[8]

Very small correlation values were found:

$$\widehat{\rho_{12}} = -0.00009 \quad \text{and} \quad \widehat{\rho} = 0.00014$$

The assumption for the sample size calculation (the effects of crossover design and cluster design cancel each other out) and the basic assumption for the final model (the inter-cluster correlation is zero) are supported by the data.

APPENDIX E3: Extrapolating trial results for potential implementation in the Paris metropolitan area

We estimated the impact of implementing the intervention strategy during the course of 1 full year in 29 EDs of the Paris metropolitan area, taking into account the proportion of MSM visiting each ED. MSM are the most affected group in France and represented 43% of the new HIV diagnoses in 2015.[9]

Considering the proportion of MSM as a proxy, the estimation was based on:
a) the proportion of MSM among the individuals who filled a questionnaire in the 8 emergency departments (EDs) during the DICI-VIH study: 0.52%.
b) the proportion of MSM among the individuals who filled a questionnaire in 21 other EDs in the Paris metropolitan area, using unpublished data gathered in a previous study: 0.37%.[10]

The ratio A of the proportion of MSM in the 21 EDs to that of MSM in the 8 EDs of the DICI-VIH study is 0.73.

Our study was conducted in the 8 EDs during several months (Table E2). The inflation factor for conducting such a study over 1 full year was 4.34.

In 2015, there were 2,555,962 adult visits in the EDs of the Paris metropolitan area, including 457,803 in the 8 EDs of the DICI-VIH study.[11]

Implementing the intervention strategy during 1 full year in the 29 EDs would result in **301** additional HIV diagnoses, representing **12%** of new HIV diagnoses in the region during 1 year.[9]

APPENDIX E4: Protocol summary (as first submitted to French data authorities)

Introduction:
Optimizing HIV screening is a Public Health priority in France, where late stage diagnoses account for one third of positive results despite 5 million tests being administered each year. The 2010-2014 national framework to combat HIV and Sexually Transmitted Infections (*Plan de Lutte VIH-IST*) recommends offering a screening test to all patients presenting to health care facilities, including Emergency Departments (EDs). This non-targeted screening strategy is to complement diagnostic testing prescribed by physicians. A study conducted in 2009-2010 in 29 EDs in *Ile-de-France* (Paris metropolitan area) showed that 1) Nurse-driven screening by rapid test (authorized in France by legal decree) was feasible and well accepted, 2) Despite a large number of tests having been administered, few infections were diagnosed and individuals testing positive belonged to high-risk groups. This paper and other international publications suggest that targeting screening to individuals who are most at risk would be feasible, more effective and less costly. Such a strategy has not been evaluated in France.

Hypothesis: Nurse-driven targeted screening combined with current practice (physician-directed diagnostic testing) carries greater benefits than current practice alone for patients unaware of their positive HIV status presenting to EDs in *Ile-de-France*, where HIV prevalence is high.

Objective and primary outcome:
To determine the effectiveness of nurse-driven targeted screening combined with current practice compared to current practice alone in newly diagnosed HIV patients among those aged 18 to 64 presenting to EDs (not presenting secondary to HIV exposure) during the inclusion periods.

Objectives and secondary outcomes:
- To compare groups in terms of the number of newly diagnosed HIV patients presenting for a specialist consultation within three months, the number of newly diagnosed patients among the total tests performed and how early HIV diagnosis occurs in the course of the disease, expressed as the proportion of newly diagnosed patients with CD4 counts >500, >350 and >200/mm^3, without HIV-related symptoms.
- To evaluate the feasibility of nurse-driven targeted screening in terms of: self-administered questionnaire completion rate, test offering rate, acceptance rate, screening rate.
- To evaluate the acceptability of targeted screening among health care professionals
- To evaluate the implementation costs of the two strategies (targeted screening and diagnostic testing or diagnostic testing alone), their effectiveness, and the incremental cost-effectiveness ratio.

Methodology and study design: multicentre cluster randomized cross-over trial.

Two study periods separated by a one month wash-out period and the order of which is to be randomly assigned will be compared in each centre. One period will consist in current practice (physician-directed diagnostic test). In the other, current practice will be combined with targeted HIV screening performed by rapid test by a nurse to high risk patients identified through a simple self-administered questionnaire (piloted in one of the participating centres in February 2013). The eight EDs in *Ile-de-France* have been selected based on their proportion of high-risk patients

After having trained health-care staff, the self-administered questionnaire will be distributed to every patient aged 18 to 64 during the targeted screening period. It will not be distributed to those presenting for a life-threatening condition or presenting secondary to HIV exposure or who are not able to provide consent. During this period, a rapid test will be offered to patients aged 18 to 64 who have been identified as high risk through the questionnaire (≥ one YES to items on IV drug use, more than five sexual partners in the last 12 months, ≥one male to male intercourse, Sub-Saharan African origin (or partner)) and who are unaware of their positive HIV status. For positive or inconclusive rapid test results, an usual diagnostic test will be performed and the patient will be seen by one of the hospital's referral HIV physicians within 48 hours.

Project's judicial characteristics: Routine-care research (*Recherche en soins courants*).

Study sample: Under the hypothesis of 1.039177 new HIV diagnoses per 10,000 patients with current practice vs. 3.377325 per 10,000 patients with targeted screening, with α=5%, β=20% and a two-tailed Fisher's exact test, 140,000 patients should be included (8750 patients per centre per period).

Inclusion criteria: Patients aged 18 to 64 presenting to the Emergency Departments during the inclusion periods, not presenting secondary to HIV exposure.

Exclusion criteria: Not applicable

Total time of the study: 15 months
Inclusion time per centre: max 8.2 months (2 x 4.1 months separated by a one month wash-out period)
Participation time per patient: Three months (one day + first specialist consultation when applicable)
Number of participating centres: Eight
Average number of patients included per centre per month: 2,130 patients minimum (for the centre with the lowest patient flow), 5,947 patients max (for the centre with the highest patient flow).

APPENDIX E5: Initial statistical analysis plan

A. Description of statistical methods

The statistical analysis will follow an intention-to-treat approach.

Baseline patient characteristics will be described. Qualitative data will be presented in terms of numbers and percentages, and quantitative variables will be described as means and standard deviations, or medians and ranges or interquartile ranges.

Primary outcome measure: The number of newly diagnosed HIV patients among the number of patients aged 18-64 (not presenting secondary to HIV exposure) will be compared between groups (targeted screening + current practice vs. current practice) using a logistic regression model, adjusted for centre and period order.

Secondary outcome measures:

The number of newly diagnosed HIV patients presenting for a specialist consultation within three months, the number of newly diagnosed HIV patients among the number of tests performed, and the proportions of patients with CD4 counts >500, >350 and >200/mm^3, will be compared between groups using a logistic regression model, adjusted for centre and period order.

Self-administered questionnaire completion rate, nurse-driven test offering rate, acceptance rate and screening rate will be described in terms of numbers and percentages.

The interaction between the order of implementation of the two strategies and the difference in the observed outcomes between the two strategies will be tested for.

B. Number of participants to include

Our hypotheses on the two expected proportions of newly diagnosed HIV patients with current practice and with targeted screening + current practice are based on the results of a study conducted in *Ile-de-France* in 2009 – 2010 on non-targeted HIV screening in Emergency Departments (D'Almeida, 2012), in which the eight EDs that participate in this study are included.

Proportion of newly diagnosed HIV patients with current practice (physician-directed diagnostic testing):

During the course of the previous non-targeted screening study, four patients with HIV-related symptoms were newly HIV diagnosed among 38,492 patients aged 18 to 64. Thus, the proportion of newly diagnosed patients with current practice is 1.039177 per 10,000 patients.

Proportion of newly diagnosed HIV patients with targeted screening + current practice:

With non-targeted screening combined with current practice in the previous study, 13 patients were newly HIV diagnosed among the 18,492 patients aged 18 to 64. Therefore the expected proportion of patients newly diagnosed during the targeted screening + current practice period in the present study is 3.377325 per 10,000 patients. We hypothesize that during the targeted screening + current practice period the proportion of newly diagnosed HIV patients is similar to that found with non-targeted screening + current practice.

To calculate the sample size of this study, we considered the crossover effect, resulted in matched-pair data within each centre (increased statistical power of the comparison test), and the effect of clustering (increased between-group variability) (Hejblum, 2009). Sample size calculation is based on the comparison of two proportions. These calculations were conducted using Pass software v11·0·1 (Hintze, 2011).

A study based on 140,000 patients would lead to a power of 0.7983 with α =5% using two-tailed Fisher's exact test. The participation of eight centres leads to a sample of 8,750 patients per centre per period.

The duration of the inclusion period per centre was estimated based on the centre's patient flow and will be adjusted to the patient flow observed during the course of the study.

C. Degree of statistical significance

All statistical tests will be performed at the 5% level.

D. Methods used to account for missing, non-used or non-valid data

Missing data will not be replaced. Only data gathered from patients who were not opposed to participating in the study will be used.

E. Cost-effectiveness analysis

Cost and outcome data will be presented using a disaggregated approach. The costs will be compared using parametric and nonparametric tests.

Costs and outcomes will be compared in a cost-effectiveness analysis. If the strategy with the highest effectiveness also has the highest cost, we will estimate its impact based on the incremental cost-effectiveness ratio (difference in costs over difference in effectiveness): the benefit of one strategy over the alternative would then be expressed in terms of cost per additional newly diagnosed HIV patient.

URC-Eco is responsible for the statistical analysis of the data for the economic evaluation. It will be conducted following an intention to treat approach. The unit of analysis for the evaluation of costs of each strategy is the newly diagnosed HIV patient and for the micro-costing section, it is the intervention. Resources and costs will be described for each strategy using usual methods adapted to the presented data. Categorical variables will be presented in terms of numbers and percentages. Quantitative variables will be presented in terms of means and standard deviations or medians and ranges or inter-quartile ranges depending on their distribution (presumably beta distribution for cost data). Resource spending and resulting costs will be compared using Student's t-tests, Kruskall-Wallis t-test or ANOVA. The Test Uncertainty Ratio will be performed using the bootstrap method.

APPENDIX E6: Final statistical analysis plan (as published in BMC Infect. Dis.)

The statistical analysis will follow the intention-to-treat approach. A statistical analysis report will be written to describe all the findings according to the CONSORT statement recommendations (Campbell, 2012).

The baseline characteristics of centres and patients will be described for each intervention group. Categorical variables will be described as numbers and percentages. Continuous variables will be reported using means and standard deviations or medians and interquartile ranges.

For the primary outcome, we will use generalized linear mixed modelling (Poisson mixed model) to provide statistical estimates controlling for each cluster, with the strategy intervention as a fixed effect and clusters as a random effect. The impact of the implementation order of intervention and control organization in the two periods on this outcome will be assessed. Additional sensitivity analysis could be performed with a permutation test.

Given the low rate of false positive rapid tests, any missing value (reactive rapid test not confirmed) will be considered as a success (positive test) in the analysis. Additional sensitivity analyses will also consider missing values as 1) success in the intervention group (HIV+ diagnosis confirmed) and failure in the control group (HIV-diagnosis confirmed); 2) failure in the intervention group and success in the control group.

The secondary outcomes regarding the presentation of patients newly diagnosed HIV positive for specialist consultation within three months and the rate of positive tests will be compared in the two groups using Pearson's $\chi2$ test or Fisher's exact test when applicable. Any missing value for the rate of positive tests (reactive rapid test not confirmed) will be considered as a success (positive test).

Early diagnosis measured as the proportion of patients with CD4 counts >200/mm^3 with no HIV-related symptoms will be compared between the 2 groups using Pearson's $\chi2$ test or Fisher's exact test when applicable. The two other thresholds (>350/mm^3, >500/mm^3) with no HIV-related symptoms will also be explored. The missing values will not be replaced.

Results of the DICI-VIH questionnaires will be described.

Cost and cost-effectiveness evaluation

The economic evaluation will have three phases: 1) estimation of the intervention strategy costs per patient tested through micro costing, 2) comparison of diagnostic costs with and without targeted screening, 3) estimation of an incremental cost-effectiveness ratio if the strategy with the greatest effectiveness also has the highest cost. In this case, the effectiveness of this strategy, compared to the alternative strategy, will be expressed in terms of extra HIV patient newly diagnosed. If the intervention strategy shows both effectiveness and cost-effectiveness, we will consider modelling the impact on the epidemic's dynamics in Paris metropolitan area.

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