Simultaneous Human Immunodeficiency Virus-Hepatitis B-Hepatitis C Point-of-Care Tests Improve Outcomes in Linkage-to-Care: Results of a Randomized Control Trial in Persons Without Healthcare Coverage

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Background. In Europe and the United States, more than two thirds of individuals infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) and 15%–30% of human immunodeficiency virus (HIV)-positive individuals are unaware of their infection status. Simultaneous HIV-, HBV-, and HCV-rapid tests could help improve infection awareness and linkage-to-care in particularly vulnerable populations.

Methods. The OptiScreen III study was a single-center, randomized, control trial conducted at a free clinic ("Médecins du Monde", Paris, France). Participants were randomized 1:1 to receive 1 of 2 interventions testing for HIV, HBV, and HCV: standard serology-based testing (S-arm) or point-of-care rapid testing (RT-arm). The main study endpoints were the proportion of participants who became aware of their HIV, HBV, and HCV status and who were linked to care when testing positive.

Results. A total of 324 individuals, representing mainly African immigrants, were included. In the S-arm, 115 of 162 (71.0%) participants performed a blood draw and 104 of 162 (64.2%) retrieved their test result. In comparison, 159 of 162 (98.2%) of participants randomized to the RT-arm obtained their results ($P < .001$). Of the 38 (11.7%) participants testing positive (HIV, n = 7; HBV, n = 23; HCV, n = 8), 15 of 18 (83.3%) in the S-arm and 18 of 20 (90.0%) in the RT-arm were linked-to-care ($P = .7$). In post hoc analysis assuming the same disease prevalence in those without obtaining test results, difference in linkage-to-care was more pronounced (S-arm = 60.0% vs RT-arm = 90.0%; $P = .04$).

Conclusions. In a highly at-risk population for chronic viral infections, the simultaneous use of HIV, HBV, and HCV point-of-care tests clearly improves the "cascade of screening" and quite possibly linkage-to-care.

Keywords. HIV; linkage-to-care; point-of-care rapid test; screening; viral hepatitis.

According to recent estimates from the European Union (EU) and the United States (US), 15 million people (EU, 14 million; US, 1 million) are infected with hepatitis B virus (HBV), 12–13 million (EU, 9 million; US, 2.7–3.9 million) are infected with hepatitis C virus (HCV), and 3.3 million (EU, 2.2 million; US, 1.1 million) are infected with human immunodeficiency virus (HIV). In these areas, approximately two thirds of HBV-infected individuals, 50% of HCV-infected

individuals, and 15%–30% of HIV-infected individuals are unaware of their infection status [1–7]. As a result, these persons are at substantial risk of infecting other individuals [8–10] and might not be able to benefit from appropriate care. If ignored and untreated, any one of these infections could lead to more advanced stages of disease, increasing their risk of morbidity and mortality [11–13] and posing, for HCV, a threat to treatment response, even among newer therapeutic regimens [14].

One reason explaining unawareness of infection status is the lack of available testing, especially among populations at high risk of infection. In recent years, a variety of health policy measures have advocated for increased testing and improvement in outcomes related to the cascade of care [2, 15]. Point-of-care (POC) testing could facilitate screening by reducing the material or psychological obstacles of standard testing and provide ease in obtaining results. Several studies have alluded to higher acceptability, more immediate test results, and higher test delivery when using rapid tests [16, 17]. Preliminary evidence has also suggested a beneficial impact for high infection risk groups [18, 19]. However, rarely do these studies extend to immigrants populations, whose often difficult socioeconomic situation prevents them from seeking adequate testing [20, 21].

In France, unawareness of infectious disease status is slightly lower compared with the rest of the EU, yet it remains a widespread problem; with 55% of 280 000 HBV-infected [22], 35% of 230 000 HCV-infected [23] and 15% of 150 000 HIV-positive individuals [24, 25] unaware of their disease status. Compounded with their shared transmission routes and potential health burden among untested and infected individuals, recent French recommendations have highlighted the need to offer simultaneous screening of chronic viral diseases, namely HIV, HBV, and HCV [26]. This testing strategy would be of interest among immigrants, in whom prevalence of any one of these infections or even coinfection can be up to 10% overall [27, 28]. For instance, recent data given by the "Medecins du Monde" (MDM) clinics in France, where mostly immigrants from Sub-Saharan or North Africa, Eastern Europe, and the Middle East seek care, have reported that 2.8% of tested individuals were positive for HIV, 5.4% were positive for HCV, and 8.4% were positive for hepatitis B surface antigen (HBsAg) [29]. These proportions are approximately 6 to 14 times higher than the general population.

We then conducted a randomized control trial evaluating the feasibility of an intervention based on simultaneous HBV, HCV, and HIV POC tests as a means to promote screening and linkage-to-care in a population without healthcare coverage, almost exclusively immigrants, with high risk of viral infection.

METHODS

Study Design and Participants

The Optiscreen III study was a randomized, prospective, pilot intervention trial. Volunteers were recruited from an inner-city clinic for persons without healthcare coverage ("Médecins du Monde", Paris, France). From February 25, 2013 to June 21, 2013, individuals seeking care at the center were asked to participate if they were ≥18 years old and could be available for further medical follow-up testing at Hôpital Saint-Antoine (Paris, France), if necessary. Persons already followed for HIV, HBV, and/or HCV infection or persons whose HIV, HBV, and/or HCV test result from 3 months before inclusion was available were not included. The study was approved by the Hôtel-Dieu Hospital Ethics Committee (Paris, France) in accordance with the Helsinki Declaration.

Study Interventions

Eligible participants were randomized 1:1 to receive 1 of 2 testing interventions for HIV, HBV, and HCV infection: a standard serology-based test (S arm) or a POC rapid test (RT arm). The central data management center (Inserm UMR_S1136, Paris, France) was responsible for randomization. A computerized random number generator was used to select permuted block of size 6. The randomization list was concealed from investigators, who assigned participants to testing groups through a Web site after validating eligibility criteria.

In the S arm, participants received a prescription to perform venipuncture for HIV, HBV, and HCV serology at an outside laboratory. They were then asked to return to the clinic within 8 to 10 days and obtain their results. HIV, HBV, and HCV serostatus were determined using commercially available immunoassays (enzyme immunoassay or enzyme-linked immunosorbent assay) respectively detecting anti-HIV antibodies and HIV p24 antigen (Abbott Architect HIV Ag/Ab combo test), HBV HBsAg, anti-HB core (HBc) and anti-HB surface (HBs) antibodies (Abbott Architect HBsAg, anti-HBc, and anti-HBs Ab assay), and anti-HCV antibodies and HCV core antigen (Bio-Rad Monolisa HCV Ag-Ab ULTRA assay).

In the RT arm, HIV, HBV, and HCV status were determined using rapid tests that detected anti-HIV antibodies (VIKIA HIV, Biomérieux), HBsAg (VIKIA, Biomérieux), and anti-HCV antibodies (Oraquick HCV, Orasure), respectively. Rapid tests were performed by trained clinical research associates according to the manufacturer's specifications. Human immunodeficiency virus, HBsAg and HCV testing required whole blood collected from a finger stick; in case of insufficient blood collection, the HCV test could also be performed on an oral fluid collected via swab. Results were available within 30 minutes and given directly to the participant during a posttest counseling interview.

For both study arms, testing was performed completely free of charge. Any participant presenting with a positive test was given instructions to schedule an appointment at the infectious diseases department of Saint-Antoine Hospital (Paris, France).

Questionnaires

Participants were asked questions on their country of birth, healthcare coverage, history of HIV, HBV, and HCV testing,

and their preferred method of screening (rapid or standard). Reasons for refusal were asked to persons declining participation.

After testing, participants testing positive were asked simple questions on test acceptability and which testing strategy they would have preferred. Physicians were also asked questions on testing feasibility when participants tested positive.

Study Endpoints

The primary outcome was defined as the percentage of persons tested who obtained results for all 3 tests (HIV, HBsAg, HCV). The secondary outcome was linkage-to-care among infected individuals, which was defined as percentage of persons infected with any of the 3 viruses who sought care at Saint-Antoine Hospital within 4 months.

The proportion of individuals accepting to participate in the study and proportion of rapid test failures were also considered as secondary endpoints. We also evaluated the proportion of preferred testing strategies among both participants and study physicians.

Statistical Analysis

At the time this study was conceived, the impact of rapid testing was rarely evaluated on infection awareness and had not yet been evaluated on linkage-to-care, specifically in the context of the French healthcare system. We then approached our analysis as a pilot study with the aim of addressing feasibility. Typically, 70% of patients seen at the MDM clinic obtain a test result with standard serology. Assuming a 20% increase in infection awareness and a type 1 error (α) of 0.05, and a power (1-β) of at least 0.9, a minimum of 82 participants per group would be needed. We decided to recruit all volunteers seen in the clinic during the 4-month time span, which approximately equates to the sample size calculation.

Outcomes were compared using Pearson's χ^2 test. The proportion of patients linked-to-care could be influenced by the potential number of infected persons who did not receive testing, thus we performed a sensitivity analysis accounting for missing data. From estimates obtained in the overall tested population, the expected number of infected patients without testing was added to the denominator and the proportion was recalculated. A range of estimates was calculated based on the 95% confidence interval (CI) of disease prevalence.

Because the number of infected individuals was assumed to be low and only few covariables were to be obtained during the study, no multivariable adjustments were planned. All statistical analysis were performed using STATA (version 13.1; StataCorp, College Station, TX), and significance was determined using $P < .05$. This trial is registered at ClinicalTrials.gov (number NCT01790633).

RESULTS

Study Participants

Figure 1 illustrates participant flow during the study. A total of 551 participants were initially screened for eligibility, 150 did

not meet inclusion criteria, and 16 had a medical condition requiring immediate referral to a specialist. The remaining 327 were randomized to an intervention arm. Three of those participants were later observed to be ineligible (2 were already followed for HIV or viral hepatitis, and 1 was referred to an emergency department) and were further excluded. In total, 324 patients were considered for analysis.

A description of the study population between intervention arms is reported in Table 1. Almost two thirds of participants were male (62.0%) with an average (standard deviation) age of 37.6 (12.1) years. None were registered under a health insurance plan. The vast majority of participants were from Sub-Saharan Africa (n = 244, 75.3%), followed by North Africa (n = 33, 10.2%), Asia (n = 13, 4.0%), Eastern Europe (n = 11, 3.4%), the Indian Subcontinent (n = 9, 2.8%), and South America (n = 7, 2.2%).

One of 5 individuals (n = 65, 20.1%) reported ever having an HIV, HBV, and HCV screening test during their lifetime; with 150 (46.3%) having been previously tested for HIV, 88 (27.2%) for HBsAg, and 71 (21.9%) for HCV. In patients with a previous HIV test, 28% had their most recent test within the last 12 months, 52% 1–5 years ago, and 18% >5 years ago.

### Efficacy of Intervention on Screening

In total, 104 (64.2%) participants randomized to the S arm performed blood tests and returned to clinic to retrieve their test result, compared with 159 (98.2%) of those randomized to the RT arm ($P < .001$) (Figure 2).

Of the 162 participants randomized to the S arm, 47 (29.0%) did not seek testing at an outside laboratory and hence did not complete testing. Among the 115 persons who did have a blood draw, 11 (9.6%) did not return to the clinic to collect their test results.

Of the 162 participants randomized to the RT arm, HBsAg status was unable to be determined in 6 patients due to rapid test failures, which was not the case for HIV and HCV rapid tests. An additional 6 patients were unable to be tested with rapid tests because their blood could not be drawn from finger stick puncture due to over-calloused fingertips. Therefore, infection status was not determined for all 3 viruses in 12 patients, who were prescribed standard serology. Nine of these patients completed serological testing and obtained results.

Efficacy of Intervention on Linkage-to-Care

Among the 274 individuals tested, 38 (13.9%; 95% CI, 10.0%–18.5%) were positive for HIV (n = 7, 2.6%; 95% CI, 1.0%–5.2%), HBV (n = 23, 8.3%; 95% CI, 5.3%–12.2%), or HCV (n = 8, 2.9%; 95% CI, 1.3%–5.6%). No co- or tri-infection was observed. There were no significant differences in the proportion of participants testing positive between S and RT arms (15.7% with 4 HIV, 10 HBV, 4 HCV; vs 12.6% with 3 HIV, 13 HBV,
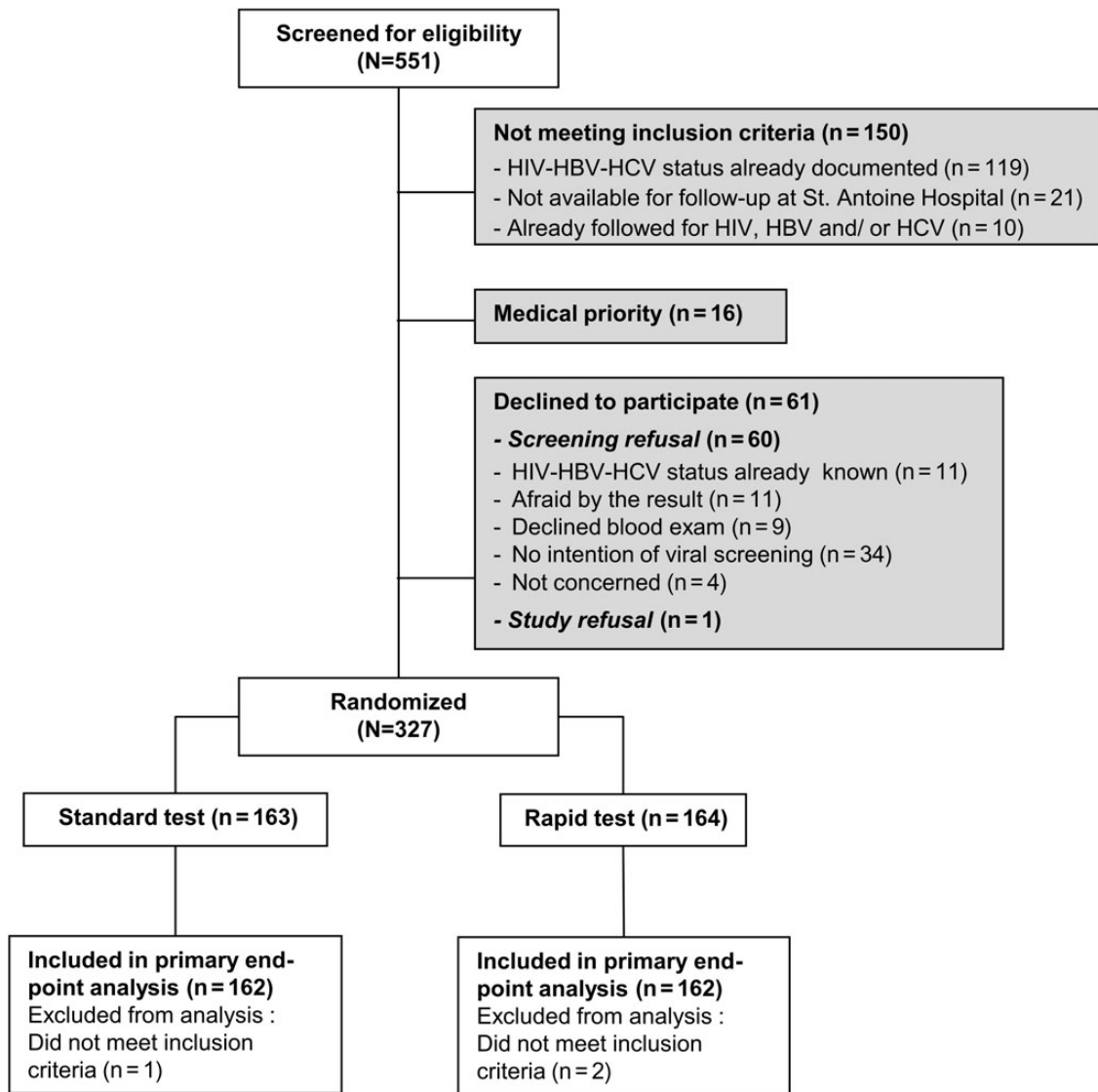
Figure 1. Study flow diagram. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

4 HCV; $P = .5$). Of note, 36 of 38 (94.7%) infected individuals and 227 of 236 (96.2%) noninfected individuals collected their test results ($P = .7$).

In the S arm, 15 of 18 patients (83.3%; 95% CI, 58.6%–96.4%) testing positive for 1 of the viruses were linked to specialized care. In the RT arm, all 20 participants testing positive collected their results and 18 (90.0%) were linked-to-care. No significant differences in linkage-to-care were observed between randomization arms ($P = .7$). In sensitivity analysis, we estimated, from the 50 participants who did not perform testing (47 in the S arm and 3 in the RT arm) and the overall prevalence of 13.9% (95% CI, 10.0%–18.5%), that 7 infected individuals (ranging from 5 to 9) were not tested and linked-to-care in the S arm versus 0 (ranging from 0 to 1) in the RT arm. As a result, an estimated 60.0% of infected participants in the S arm (ranging from 55.6%

to 65.2%) and 90.0% (ranging from 85.7% to 90.0%) in the RT arm were linked to appropriate care.

Perception of Rapid Tests by Participants and Medical Professionals

Among participants, 76% (n = 246) said that they would prefer to undergo HIV, HBV, and HCV testing using rapid rather than standard serological tests, whereas 7% (n = 23) preferred serological tests and 17% (n = 55) had no preference. The most common reasons for preferring rapid tests ($N = 246$) were less stress with same-day results, (n = 171, 52.8%), followed by more practical use (n = 83, 25.6%). In contrast, reasons for preferring serological test ($N = 23$) were being able to perform several tests at the same time (11 of 23) or because participants felt that serological tests were more reliable and accurate (n = 5,
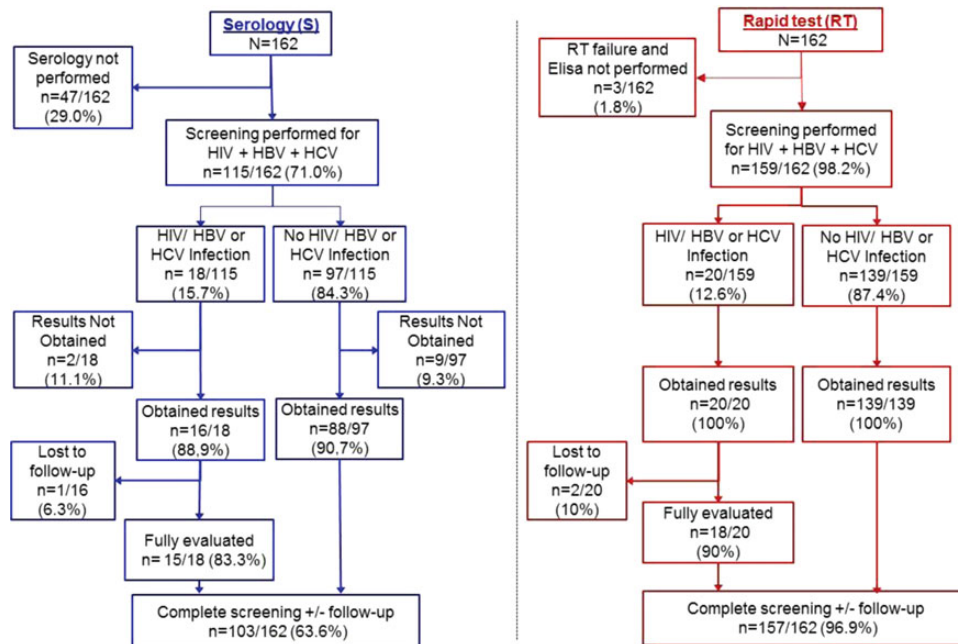
Table 1. Description of the Study Population per Arm[a]

Socio-demographics status	Study Arm		
	Standard Test (n = 162)	Rapid Test (n = 162)	P Value[b]
Male	102 (63.0)	99 (61.1)	.73
Age, years, mean (SD)	39.0 (12.2)	37.0 (12.2)	.08
HBV prevalence of birth country			.33
Low (<2.0%)	2 (1.2)	1 (0.6)	
France	1 (0.6)	0 (0)	
North America	1 (0.6)	1 (0.6)	
Intermediate (2.0%–8.0%)	27 (16.7)	37 (22.8)	
Eastern Europe	2 (1.2)	9 (5.6)	
South Europe	1 (0.6)	0 (0)	
South America	2 (1.2)	5 (3.1)	
North Africa	17 (10.5)	16 (9.9)	
Indian Subcontinent	3 (1.9)	6 (3.7)	
Middle East	2 (1.2)	1 (0.6)	
High (>8.0%)	133 (82.1)	124 (76.5)	
Sub-Saharan Africa	126 (77.8)	118 (72.8)	
Asia	7 (4.3)	6 (3.7)	
Health insurance plan			
None	162 (100)	162 (100)	1

Abbreviations: HBV, hepatitis B virus; SD, standard deviation.

[a] All numbers above represent n (%), except for age where mean (SD) is given.

[b] Statistical comparison between arms was performed using Pearson's χ^2 test for categorical variables and Student's t test for continuous variables.

20.8%) or caused less anxiety (n = 2, 8.3%). In the posttesting questionnaire, 3 of 12 (25%) participants testing positive in the S arm would have preferred to have a rapid test, whereas the remaining 9 (75%) had no testing preference. Of those testing positive in the RT-arm, 1 of 16 (6.3%) patients would have preferred to have a serological test and the remaining 15 (93.7%) had no particular preference. Among the 20 physicians relaying a positive test result, 10 said that rapid testing simplified their consultation, 7 claimed it had no effect, and 3 stated that it became more complicated.

DISCUSSION

In this randomized control trial, the feasibility of an integrated approach based on POC rapid testing for multiple viral infections was evaluated, specifically as it relates to the cascade of screening and linkage-to-care in a targeted population. Among those living in difficult socioeconomic situations, a clear difference was observed between randomization arms in the proportion of participants actively tested for HIV, HBV, and HCV. From this observation alone, the use of POC tests demonstrated clear superiority in promoting screening access within this particular context.

The Médecins du Monde clinic, where this study took place, represents a typical source of healthcare for predominantly immigrant populations. For years, this clinic has been fully invested in HIV and viral hepatitis screening by providing comprehensive information on testing; routinely offering testing
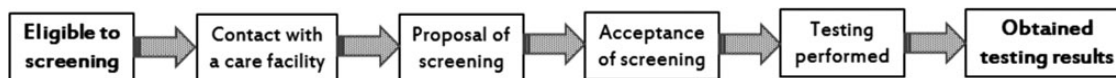

Figure 2. Screening access, human immunodeficiency virus-hepatitis B virus-hepatitis C virus (HIV-HBV-HCV) awareness and linkage to care per testing arm. The proportions of patients from initial screening to linkage-to-care are provided for those randomized to either standard serology (S arm) or rapid testing (RT arm). Patients are stratified by infectious disease status after screening.

Figure 3. Main steps of the cascade of screening. In this figure, the steps needed to appropriately screen individuals for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus are elaborated in detail, as they apply to the French healthcare system.

and personalized medical counseling; and proposing social and administrative support; all of which is free of charge. Yet, before this study, its medical professionals expressed concerns regarding rapid testing, as has been stated by others in the past [30–32], notably the psychosocial stress related to a positive test result and the general unpreparedness of participants receiving such a result. Nevertheless, many of the physicians relaying a positive rapid test result observed that it had in effect facilitated their consultation.

Likewise, participants more readily accepted combined rapid tests than standard serology, which is in line with previous observations evaluating the acceptability of HIV or HCV rapid tests alone [33–36]. This strong preference is supported by the difference in the proportion of participants tested between intervention arms. Furthermore, very few participants who completed a blood draw for serological-based testing at an outside clinic did not return to obtain their test result, which was perhaps slightly lower than another study conducted in French sexually transmitted disease clinics [17]. It would then seem that the major hurdle to screening with standard prescription-issued testing lies in the individual's motivation to seek an appropriate center and not necessarily in obtaining results.

At the end of screening, one third of all participants included in the serology arm remained unaware of their HIV, HBV, and HCV status—which was in total 10 times higher than in the rapid test arm. Other studies have reported the gain in viral-infection awareness when using rapid tests compared with standard serology [37, 38]. One other study conducted in France has shown that only 38% of individuals receiving a prescription for HIV-HBV-HCV testing by their general practitioner completed testing [39].

Oftentimes, previous evaluations of the "cascade of care" have represented screening outcomes in a perhaps too simplistic manner, using a broad definition of whether or not an individual has been screened [40, 41]. As a whole, this one-time outcome is largely insufficient and could render screening programs difficult to evaluate. We based our primary endpoint on what we term the cascade of screening [40, 42], as shown in Figure 3. Within the context of the French healthcare system, we labeled 5 distinct steps: [1] having access to a testing facility or network, [2] being proposed testing, [3] accepting testing, [4] executing a screening test, and [5] receiving test results.

We were able to observe marked improvements in executing a screening test and receiving test results with rapid testing, as reported in a meta-analysis evaluating rapid HIV-tests [34, 43, 44].

Other intervention studies, conducted among specific target populations with few options for testing, have suggested a positive impact of HIV and/or HCV rapid tests. These studies saw improvements in the proportion of individuals with access to a testing facility or network, who were proposed testing, and who accepted testing; especially when these tests are used by community educators and activists [18, 19, 33, 45]. However, in our study, we were only able to evaluate acceptance of screening in our study, which was fairly high for both arms.

It would appear that individuals testing positive for any one of the viral infections studied, be it from rapid or standard serological testing, were likely to pursue further care at a specialized facility. Of course, the fact that specific populations, namely undocumented immigrants, could have access to healthcare in France might have facilitated seeking care. At any rate, this proportion could be highly biased by whether testing was completed in the first place. By assuming that disease prevalence is the same between individuals with and without testing, we observed a stark advantage of rapid testing in the proportion of participants with appropriate care. This analysis demonstrates the close interplay, or rather dependence, between the cascade of screening and proper linkage-to-care.

Some limitations need to be addressed. First, this was a single-center pilot study, which may prevent generalizability to other testing centers or for other at-risk populations. Second, the small number of participants and infected individuals may have decreased power to detect certain differences in linkage-to-care. Third, we attempted to conduct a sensitivity analysis for participants with missing data, assuming that they had the same disease prevalence. This assumption might not be correct; yet nonetheless it would be difficult to evaluate. Finally, not all rapid tests were approved for routine use in France, and testing was conducted in a research setting, within a specific organization, and with staff designated to perform rapid testing.

CONCLUSIONS

In conclusion, a combined approach to HIV and viral hepatitis screening seems to improve the overall cascade of screening and consequently linkage-to-care in a population with high risk of chronic viral infection. As these testing strategies gain acceptance for use in other communities and screening programs, these encouraging results need to be confirmed in other settings. In the future, the development of a single rapid test for

the detection of all 3 chronic viral diseases could ease the burden of multiple testing, allowing a simplified way of identifying infected HIV/HBV/HCV individuals and increasing awareness of disease status.

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