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Routinized Syphilis Screening Among Men Living With Human Immunodeficiency Virus: A Stepped Wedge Cluster Randomized Controlled Trial

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Background. We implemented an opt-out clinic-based intervention pairing syphilis tests with routine human immunodeficiency virus (HIV) viral load testing. The primary objective was to determine the degree to which this intervention increased the detection of early syphilis.

Methods. The Enhanced Syphilis Screening Among HIV-Positive Men (ESSAHM) Trial was a stepped wedge cluster-randomized controlled trial involving 4 urban HIV clinics in Ontario, Canada, from 2015 to 2017. The population was HIV-positive adult males. The intervention was standing orders for syphilis serological testing with viral loads, and control was usual practice. We obtained test results via linkage with the centralized provincial laboratory and defined cases using a standardized clinical worksheet and medical record review. We employed a generalized linear mixed model with a logit link to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of the intervention.

Results. A total of 3895 men were followed over 7471 person-years. The mean number of syphilis tests increased from 0.53 to 2.02 tests per person per year. There were 217 new diagnoses of syphilis (control, 81; intervention, 136), for which 147 (68%) were cases of early syphilis (control, 61 [75%]; intervention, 86 [63%]). The annualized proportion with newly detected early syphilis increased from 0.009 to 0.032 with implementation of the intervention; the corresponding time-adjusted OR was 1.25 (95% CI, .71–2.20).

Conclusions. The implementation of standing orders for syphilis testing with HIV viral loads was feasible and increased testing, yet produced less-than-expected increases in case detection compared to past uncontrolled pre–post trials.

Clinical Trials Registration. NCT02019043.

Keywords. HIV; syphilis; men; screening; outpatient clinics; intervention; cluster-randomized controlled trial.

Sexual transmission of syphilis, caused by the bacterium *Treponema pallidum*, has increased substantially in many communities of men who have sex with men (MSM) throughout the world including men living with human immunodeficiency virus (HIV) [1–7]. In Ontario, Canada, reported cases of infectious syphilis occur predominantly among males, increasing from 6 per 100 000 person-years in 2005 to 21 per 100 000 as of 2017. Also in Ontario, lifetime syphilis prevalence among MSM in HIV care was 23% as of 2009, and in 2010, incidence of a new syphilis diagnosis was 4.3 per 100 person-years [8]. These rates underestimate true infection because they reflect cases detected by routine practice rather than by active surveillance.

Frequent syphilis screening has the potential to detect cases at earlier stages, leading to earlier treatment and decreased morbidity, and could help to reduce onward transmission [9, 10]. Canadian sexually transmitted infection (STI) guidelines recommend syphilis testing at 3-month intervals even in the absence of symptoms for individuals at ongoing risk for STIs, including MSM with multiple partners [11]. International guidelines recommend syphilis screening

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among people with HIV at least once per year, with some experts advising more frequent testing at 3- to 6-month intervals [11–13]. Mathematical model projections suggest that testing every 3 months at high coverage could reduce syphilis transmission at the population level [10, 14, 15]. However, if screening is dependent on risk assessments, there may be practice barriers due to difficulties obtaining sexual histories and time constraints [16].

In HIV care there are practical and efficient opportunities to conduct syphilis screening when patients undergo routine blood tests [17, 18]. The introduction of this practice has generally resulted in 3-fold increases in syphilis case detection according to uncontrolled pre–post trials [19–22]. To our knowledge, it has not been evaluated using a randomized controlled design. We conducted the Enhanced Syphilis Screening Among HIV-Positive Men (ESSAHM) Trial, which implemented an opt-out clinic-based intervention to routinize syphilis testing with HIV viral loads [23]. Specific objectives were to determine the degree to which the intervention (1) increased the detection of early syphilis; (2) increased the proportion of men who undergo syphilis screening at least annually; and (3) increased screening frequency. We hypothesized that the intervention would increase case detection by 75%, annual screening to 85%, and screening frequency to 3 tests per person per year. When the trial was designed, it was standard practice in our setting for persons in HIV care to undergo viral load testing every 3 to 6 months, at the discretion of the treating physician [17].

METHODS

Design and Setting

The trial took place from 1 February 2015 to 31 July 2017 in Toronto and Ottawa, the 2 largest cities in Ontario with the highest rates of reported syphilis cases since the mid-2000s [24–26]. The participating HIV outpatient clinics were St Michael's Hospital Positive Care Clinic, Toronto; Sunnybrook Health Sciences Centre Medical Outpatient Clinic, Toronto; Toronto General Hospital Immunodeficiency Clinic; and The Ottawa Hospital Immunodeficiency Clinic. Previous research suggests that approximately 73% of male patients attending these clinics report a history of sex with men [23].

We used a pragmatic, cluster-randomized controlled trial with a stepped wedge design (SW-CRCT) [27–29] that introduced stepwise across clinics a practice change to pair syphilis testing with routine HIV viral load testing. Each clinic represented a "cluster." Full details of the trial protocol were published previously [23] and the trial was registered with ClinicalTrials.gov (NCT02019043).

Randomization and Masking

The 30-month trial was divided into 5 "steps," each lasting 6 months (Figure 1). All clinics were in the control condition in step 1. They were then randomized to 1 of 4 roll-out schedules. The sequence was assigned in a random allocation fashion at month 5 by a biostatistician who was not a member of the project team and who was blinded to clinic names. Once randomized, allocation was unblinded to the study team. We report clinic-specific findings in the order of implementation: clinics A, B, C, and D implemented the intervention at steps 2, 3, 4, and 5, respectively.

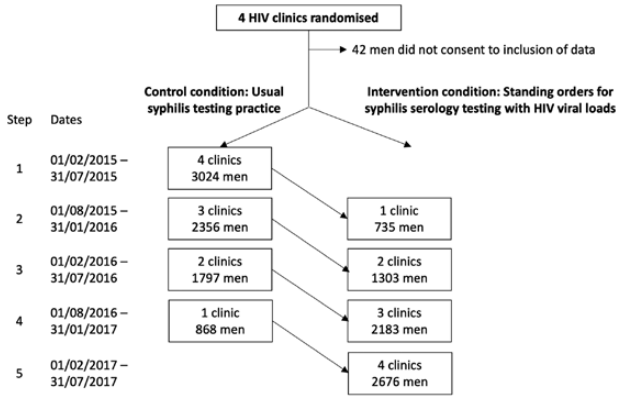

Figure 1. Study flowchart. Dates are shown as day/month/year. Abbreviation: HIV, human immunodeficiency virus.

Study Population and Eligibility Criteria

The study population was all men in HIV care whose viral load monitoring was ordered at the participating clinics and submitted to the centralized provincial laboratory. The cohort was open, that is, patients could enter at any step. We did not restrict to sexually active MSM, eliminating the need to document sexual histories [22]. Women were excluded because we had neither observed new cases of syphilis among women attending these HIV clinics [30] nor found reports of such cases in provincial surveillance data from 2002 to 2014 [31].

Intervention and Control Conditions

The intervention involved opt-out standing orders for syphilis serology whenever men underwent routine HIV viral load tests (Supplementary Materials). The control condition was the usual syphilis testing practices prompted by signs or symptoms, exposure to active cases, patient disclosure of sexual risk behavior, patient request, and physicians' experience-based knowledge of syphilis risk.

Primary Outcome: Detection of New Untreated Cases of Early Syphilis

We accessed syphilis test records through the centralized provincial laboratory, the repository of all syphilis tests in Ontario. The laboratory used a reverse algorithm: (1) screen with chemiluminescent immunoassay (CLIA); (2) if CLIA was reactive or indeterminate, additional testing was performed with the rapid plasma reagin (RPR) test as well as the *Treponema pallidum* particle agglutination (TPPA) test for confirmation of CLIA screening results; (3) if RPR and TPPA were nonreactive or indeterminate, the laboratory may have also included the fluorescent treponemal antibody absorbance test [32].

We defined a new case of early syphilis as any of the following: (1) seroconversion with prior negative syphilis serology within the previous 12 months; (2) in men previously diagnosed with syphilis, a ≥4-fold rise in RPR titer from the last titer within the prior 12 months, indicative of reinfection; or (3) clinical evidence of primary or secondary syphilis together with laboratory confirmation [23].

All reactive syphilis serologies were considered possible cases. We applied the above criteria in hierarchical fashion, such that if a possible case met the first or second criteria, we considered it a case whether or not a clinical diagnosis of early syphilis was noted in the patient record. Discrepancies were reviewed by authors V. G. A., D. H. S. T., A. N. B., and R. G., and resolved by consensus.

Case detection was modeled as a binomial proportion for each 6-month step, defined as the number of men with early syphilis divided by the total number of men under observation in that step. For ease of interpretation, we annualized this proportion using the following equation: Proportion with early syphilis 1 or more times in 12 months = 1 – exp{-[(proportion with early syphilis 1 or more times in 6 months) / 6] × 12}.

Secondary Outcomes: Screening Coverage and Frequency

Coverage was modeled as the proportion of men tested at least once during a 6-month step; for reporting, we annualized this proportion as described above. Similarly, frequency was modeled as the number of times men underwent syphilis serologic testing per 6-month step, which we transformed into the annualized rate by expressing as the mean count of tests per 1 person-year.

Sample Size and Power

When designing the trial, we used the method recommended by Hussey and Hughes [29] and additionally conducted simulations to estimate the sample sizes required [23]. Under varying assumptions, a minimum sample size of 2278 men would provide at least 80% power to detect a ≥75% increase in case detection, with >90% power to detect changes in screening coverage from 55% to 85% tested at least annually, and an increase in screening frequency from 1 to 3 tests per year.

Data Collection

At the centralized provincial laboratory, syphilis and viral load testing data were linked using provincial health insurance numbers, or, when unavailable, the patient's name and date of birth. Syphilis tests included those with and without a corresponding viral load test. At the clinics, a standardized clinical worksheet aided clinicians throughout the trial in determining which reactive syphilis tests required further information to be collected from the patient [23]. At the end of the trial, we performed records review for all patients with reactive syphilis serologies to collect data regarding symptoms, clinical diagnosis, and staging.

Preplanned Analyses

Analyses used intention-to-treat principles and methods according to our published protocol [23]. We used descriptive statistics to characterize the study population at baseline in terms of age, number of viral load tests, whether viral load tests were undetectable, and whether there was a known past history of syphilis. Case characteristics were compared between control and intervention periods.

We used a generalized linear mixed model (GLMM) for the primary analysis of case detection [33, 34]. Recurrent diagnoses were included. The model employed a logit link with intervention status as a fixed effect and random effects for participant and clinic. The first model estimated the treatment effect without adjustment for time and the second model adjusted for time (steps 1 to 5), as per the SW-CRCT design. Treatment effects are expressed as odds ratios (OR), which approximate the rate ratio given the uncommon nature of the outcome [35].

For secondary outcomes, we similarly used GLMM to estimate the OR using a logit link for screening coverage and the rate ratio using a log link for screening frequency associated with the intervention with sequential adjustment for time. Because a syphilis diagnosis is typically followed by additional testing for follow-up management, we censored men who had a new syphilis diagnosis at the beginning of the 6-month period in which they were diagnosed.

Post Hoc Analyses

In a sensitivity analysis, we excluded cases that met our first or second case definition, but in which the clinical worksheet had a recorded clinical judgment that it was not a new active case. We also estimated the intervention effect excluding the clinic with the lowest intervention fidelity. Finally, we compared the rate of diagnosis of any new case (ie, including late latent cases and latent cases of unknown duration) between the intervention and control periods.

Ethical Considerations

The trial protocol was approved by the research ethics boards at all participating institutions. We used multiple strategies to inform patients that the clinic was participating in the ESSAHM Trial using an "opt-out" model (Supplementary Materials).

RESULTS

From 1 February 2015 to 31 July 2017, 3895 men were followed over 7471 person-years of observation (Figure 1). An additional 42 men asked that their data not be included in the study; their data are excluded from all analyses. Among the 3024 men who attended the clinic at baseline, when all clinics were in the control setting, the mean age was 49.1 years and 82.3% had at least 1 viral load that was undetectable (Table 1).

The number of HIV viral loads per 6-month step ranged from 3245 to 3421 tests and summed to 16 721 over 30 months.

Men had a mean of 1.1 viral load tests per step, equivalent to 2.2 viral load tests per person per year. The frequency of viral load testing did not vary over the 30-month trial (data not shown).

Syphilis Case Detection

There were 217 new syphilis cases in total (control: 81; intervention: 136), of which 147 (68%) met our case definitions for early syphilis (control: 61 [75%]; intervention: 86 [63%]) (Table 2). There were no substantial differences in recorded symptoms nor stage between control and intervention periods (Table 2). These 147 cases were detected among 128 men; most (114/128) had only 1 diagnosis of early syphilis and 11% (14) had 2 or more (maximum 3).

The annualized proportion of men with newly detected early syphilis increased from 0.009 in step 1, when all sites were in the control condition, to 0.032 in step 5, when all sites had implemented the intervention, with a corresponding unadjusted OR of 2.10 comparing intervention to control periods (95% confidence interval [CI], 1.46–3.02) (Table 3). With time-adjustment to account for the SW-CRCT design, the OR was considerably attenuated at 1.25 (95% CI, .71–2.20).

We carried out post hoc sensitivity analyses. We excluded the 24 cases that met one of the serology-based case definitions, but for which a diagnosis of early syphilis was absent from the medical chart, and calculated a time-adjusted OR of 1.35 (95% CI, .74–2.46). Excluding clinic A, which had the lowest intervention fidelity (Supplementary Figure 1), the time-adjusted OR was 1.44 (95% CI, .76–2.74). We also examined changes in the detection of any new syphilis case regardless of stage (Table 3). The annualized proportion of men with a new syphilis diagnosis increased from 0.013 to 0.054 (unadjusted OR comparing intervention to control periods: 2.66 [95% CI, 1.96–3.60]); the time-adjusted OR was 1.44 (95% CI, .90–2.31).

Syphilis Testing Coverage and Frequency

From step 1 to step 5, the proportion of men with at least 1 test per year increased from 0.364 to 0.794, an improvement that persisted with time adjustment (OR, 3.73 [95% CI, 3.21–4.32]) (Table 3). Similarly, the mean number of tests per person per year increased from 0.53 to 2.02 (time-adjusted rate ratio, 2.03 [95% CI, 1.85–2.22]) (Table 3); during the final 6-month step, 19.9% of men had zero syphilis tests, 59.9% had 1, 17.5% had 2, and 2.7% had 3 or more tests. From step 1 to step 5, the proportion of viral load tests that had a corresponding syphilis test increased from 19.5% to 74.3% with variation between clinics (Supplementary Figure 1).

DISCUSSION

At hospital-based HIV clinics in Ontario, Canada, the implementation of standing orders for syphilis serological testing with HIV viral loads resulted in a 25% increase in early syphilis case detection, although the degree of benefit was inconclusive given the 95% CI of .71–2.20 and statistical nonsignificance. The odds of annual screening increased nearly 4-fold and the mean number of tests per year increased 2-fold. Once all sites had implemented routine syphilis screening, annual coverage was 79.4% and men were tested on average twice per year.

Strengths of the study were its inclusion of multiple clinics and the SW-CRCT design, which allowed for adjustment for underlying time trends [28]. Without time adjustment, we would have overestimated the increase in case detection attributable to the intervention because, in our setting, syphilis case reporting

Table 1. Baseline Characteristics of 3024 Participants in the Enhanced Syphilis Screening Among HIV-Positive Men (ESSAHM) Trial—Toronto and Ottawa, Canada, 2015

Characteristic[a]	All Clinics	Clinic A	Clinic B	Clinic C	Clinic D
No. of men	3024	717	551	896	860
Age, y					
Mean (SD)	49.1 (11.73)	50.5 (11.37)	51.2 (11.0)	46.1 (12.3)	49.6 (11.3)
<30	199 (6.6)	37 (5.2)	23 (4.2)	93 (10.4)	46 (5.3)
30–39	424 (14.0)	72 (10.0)	57 (10.4)	180 (20.1)	115 (13.4)
40–49	822 (27.2)	198 (27.6)	139 (25.3)	253 (28.2)	232 (27.0)
50–59	1058 (35.0)	258 (36.0)	221 (40.1)	253 (28.2)	326 (37.9)
≥60	521 (17.2)	152 (21.2)	111 (20.2)	117 (13.0)	141 (16.4)
No. of viral loads per person in 6-mo period					
Mean (SD)	1.13 (0.74)	0.93 (0.69)	1.21 (0.87)	1.09 (0.63)	1.30 (0.76)
Result of (first) HIV viral load					
Undetectable (<40 copies/mL)	2488 (82.3)	610 (85.1)	461 (83.7)	693 (77.3)	724 (84.2)
Known history of syphilis at baseline[b]	599 (19.8)	104 (14.5)	119 (21.6)	168 (18.7)	208 (24.2)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation.

[a]Baseline characteristics are shown for male patients under study during the first 6-month step of the cluster-randomized controlled trial with a stepped wedge design, when all clinics were in the "control" setting. The 871 men who entered the study in subsequent steps are not shown.

[b]History of syphilis as determined by (1) reactive syphilis serology in the year preceding the trial start; or (2) clinical notation that the patient was a past case.

Table 2. Characteristics of 147 New Early Syphilis Cases, by Control Versus Intervention Period in the Enhanced Syphilis Screening Among HIV-Positive Men (ESSAHM) Trial—Toronto and Ottawa, Canada, 2015–2017

	All Periods (n = 147)		Control Periods (n = 61)		Intervention Periods (n = 86)		Control vs Intervention
Characteristic	No.	(%)	No.	(%)	No.	(%)	*P* Value
Case definition classification							.76
1: Seroconversion with prior negative syphilis serology within past 12 mo	35	(23.8)	15	(24.6)	20	(23.3)	
2: ≥4-fold rise in RPR titer from the last titer within past 12 mo	71	(48.3)	31	(50.8)	40	(46.5)	
3: Clinical evidence of primary or secondary syphilis and laboratory confirmation	41	(27.9)	15	(24.6)	26	(30.2)	
Syphilis stage[a]							.41
Primary	36	(24.5)	12	(19.7)	24	(27.9)	
Secondary	63	(42.9)	24	(39.3)	39	(45.4)	
Early latent	17	(11.6)	8	(13.1)	9	(10.5)	
Late latent/latent of unknown duration	4	(2.7)	2	(3.3)	2	(2.3)	
Missing	27	(18.4)	15	(24.6)	12	(14.0)	
Symptomatic							.028
At least 1 symptom recorded	82	(55.8)	30	(49.2)	52	(60.5)	(c)
No symptoms recorded	37	(25.2)	13	(21.3)	24	(27.9)	
Unknown[b]	28	(19.1)	18	(29.5)	10	(11.6)	

All *P* values estimated by Fisher exact test.

Abbreviation: RPR, rapid plasma reagin.

[a]Among the 147 early syphilis cases, 4 cases met the criteria for early syphilis based on definition 1 (n = 1) or definition 2 (n = 3) but were classified as "late latent/latent of unknown duration" by the attending physician in the medical record. A further 27 cases with missing syphilis stage met the criteria for early syphilis based on definition 1 (n = 4) or definition 2 (n = 23) but were not classified as such by the attending physician in the medical record. Among the 70 non-early cases not included in the table, there were 29 late latent, 23 latent of unknown duration, and 3 tertiary cases; there were also cases staged as "primary" (n = 1) or "early latent" (n = 14) in the medical chart, but none met the laboratory criteria to confirm early syphilis.

[b]Classified as "unknown" if case report form reported "don't know" or if symptom data were not recorded; the latter occurred for cases that met serologic definitions 1 and 2 but did not have a recorded clinical diagnosis of early syphilis.

[c]*P* value when unknown category is reclassified as "no" was 0.18.

increased over the course of the trial [26]. In Toronto, reported cases of early syphilis rose from 50.5 per 100 000 males in 2015 to 67.8 per 100 000 males in 2017. In Ottawa, rates per 100 000 males fluctuated between 20.9 in 2015, 26.7 in 2016, and 19.7 in 2017. This underlines the critical need to consider population trends in ongoing syphilis epidemics when carrying out such interventions using trial designs without a concurrent control.

Our finding of a 25% increase in syphilis case detection is at odds with published observations from uncontrolled pre–post designs. For example, Cohen et al added syphilis serology to computerized routine blood order sets for asymptomatic patients at an outpatient HIV clinic in London, United Kingdom [21]; they reported a 160% increase in asymptomatic early syphilis case detection. Bissessor and colleagues implemented automatic stamping of syphilis serology orders on all HIV laboratory request forms at the Melbourne Sexual Health Centre in Australia, which increased the median number of syphilis tests per patient per year from 1 to 2 [22], also with a 160% increase in early syphilis diagnosis. An Australian national recommendation for opt-out routinized serological screening for syphilis in HIV-infected MSM was introduced in 2009; from 2007 to 2014, there was a 150% increase in annual rates of early syphilis diagnosis [19, 36]. Because these pre–post designs did not incorporate time controls, it is possible that the observed changes could have been affected by secular changes in syphilis incidence.

Our trial achieved high intervention fidelity at 3 of the 4 participating clinics (Supplementary Materials) and was well received by providers and patients. In qualitative process evaluation interviews, most expressed support for routinized syphilis testing as part of standard HIV care. Among providers, most, but not all, believed that the intervention led to increased syphilis awareness, improved case detection, and was likely to be sustainable [37]. Among patients, many perceived benefits including convenience, reducing STI stigma, and ensuring that such testing is not missed [38]. However, some men felt that, based on personal circumstances, being routinely tested themselves may not be necessary [38].

Mathematical models predict that testing every 3 months at high coverage could reduce syphilis transmission, but that suboptimal coverage and frequency may paradoxically increase transmission [10, 14, 15]. In our trial, syphilis screening increased substantially and resulted in testing every 6 months but not every 3 months. Testing every 3 months is unlikely to be achieved by coupling syphilis and viral load testing because the latter now occurs less often once patients are virally suppressed [17]. When we designed the ESSAHM Trial in 2013, viral load testing every 3 months was commonplace, but by the

Table 3. Syphilis Case Detection and Testing Rates by Intervention Status and Time, Enhanced Syphilis Screening Among HIV-Positive Men (ESSAHM) Trial—Toronto and Ottawa, Canada, 2015–2017

Status	Step/Study Period					Unadjusted OR (95% CI)	Time-Adjusted OR (95% CI)
	Step 1: Months 1–6	Step 2: Months 7–12	Step 3: Months 13–18	Step 4: Months 19–24	Step 5: Months 25–30		
Annualized proportion of men with newly detected early syphilis[a]							
Intervention	…	0.016	0.017	0.021	0.032	2.10 (1.46–3.02)	1.25 (.71–2.20)
Control	0.009	0.016	0.020	0.021	…	Referent	Referent
Annualized proportion of men with newly detected syphilis, any stage[a,b]							
Intervention	…	0.027	0.024	0.031	0.054	2.66 (1.96–3.60)	1.44 (.90–2.31)
Control	0.013	0.018	0.029	0.030	…	Referent	Referent
Annualized proportion of men with ≥1 syphilis tests[a]							
Intervention	…	0.311	0.614	0.570	0.794	8.70 (7.89–9.61)	3.73 (3.21–4.32)
Control	0.364	0.422	0.361	0.513	…	Referent	Referent
Annualized count of syphilis tests per 1 PY[c]							
Intervention	…	0.43	1.21	1.06	2.02	3.06 (2.90–3.23)	2.03 (1.85–2.22)
Control	0.53	0.65	0.55	0.91	…	Referent	Referent

Abbreviations: CI, confidence interval; OR, odds ratio; PY, person-year.

[a]Odds ratio estimated by general linear mixed model using a logit link.

[b]Includes new cases of early syphilis as well as new late latent cases and cases of unknown duration.

[c]Rate ratio estimated by general linear mixed model using a log link.

time the trial began in 2015, testing every 6 months had become the norm. An important public health question is whether routine testing among men living with HIV could slow syphilis transmission at a population level. In Australia, where syphilis testing is routine in HIV care, with an estimated 77% of men tested at least once per year [36], infectious syphilis reports continue to rise [7]. Population control must also consider HIV-negative individuals. Although HIV coinfection is commonly reported among new cases of infectious syphilis, in Toronto it declined from 57% of syphilis cases in 2007 to 34% in 2017 [39].

Among cases of early syphilis, we did not observe substantial changes in symptoms or stage. Our observations are contrary to those by Bissessor et al, who noted a rise in asymptomatic cases (from 21% to 85%) following implementation of routinized syphilis testing [22]. Similarly, Chow et al observed an increase from 23% to 45% in the proportion of cases that had early latent syphilis and a drop from 45% to 26% having secondary syphilis [36]. Greater detection of asymptomatic cases was interpreted as a benefit of screening [22, 36]. An alternative hypothesis is that repeat infections are increasing over time and these are more likely to be asymptomatic, particularly among men living with HIV [40, 41].

There were limitations. The trial was powered to detect a 75% improvement in early syphilis detection; thus, we were underpowered to measure precisely the 25% improvement that we observed. We were limited by unmeasured data. Fundamentally, the ability of the intervention to exert an effect depends on men's sexual activity and possible exposure to syphilis; however, sexual histories were not collected by design. Reasons for noncompliance were also unmeasured. When viral loads did not have a corresponding syphilis test, we could not determine whether this was because a syphilis test requisition was not provided to men, or whether men chose not to have the syphilis test done. In general, the proportion of viral load tests with a corresponding syphilis test was less than expected, which highlights the importance of using quality improvement approaches to monitor practice-based changes [42].

Our findings have implications for clinical practice. Syphilis testing and treatment remain critical for improving patient care and preventing transmission. Most people living with HIV who are diagnosed with syphilis will have a satisfactory treatment response [6]. Risk- and symptom-based testing alone will miss some cases due to the growing proportion of repeat syphilis infections and the greater likelihood of asymptomatic cases in these instances. By the time all clinics implemented routinized testing in this trial, 3.2% of men per year were newly diagnosed with early syphilis, underlining the need for screening in this population. Early detection may also result in cost savings; we are carrying out costing analyses to estimate economic benefits resulting from a 25% improvement in case detection as observed in this trial. In 2016, the United States Preventive Services Task Force recommended screening for syphilis every 3 months in

at-risk populations, including MSM and people living with HIV, due to evidence that screening provides substantial benefit by "curing syphilis infection, preventing manifestations of late-stage disease, and preventing sexual transmission to others" [43]. We have demonstrated that routine syphilis screening in conjunction with HIV viral load monitoring is one way to implement this recommendation to achieve testing every 6 months. To reach a target of testing every 3 months, additional strategies will be needed, such as improved diagnostics that allow for self-testing, virtual and express testing, and patient reminders, among others [44].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author Contributions. A. N. B. was the principal investigator responsible for overall direction and management of project tasks. A. N. B. conceived the study along with co–principal investigators V. G. A. and D. H. S. T.; V. G. A. leads the syphilis test program at the centralized provincial laboratory in Ontario (Public Health Ontario Laboratories) and facilitated collaboration with the laboratory. R. G. was the trial coordinator. D. H. S. T., P. A. M., A. R., N. A., and S. W. were site principal investigators. Statistical analysis was conducted by R. G., guided by S. L. G., J. R., and A. N. B. Clinical investigators D. H. S. T., P. A. M., C. C., K. G., A. R., I. E. S., and S. W. provided clinical expertise on HIV and syphilis. R. R. and J. M. provided community expertise and were members of the Trial Steering Committee. All authors contributed to the study design, provided substantive feedback on earlier versions of the manuscript, and read and approved the final manuscript.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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