Title: Impact of point-of-care testing on the management of sexually transmitted infections in South Africa: Evidence from the HVTN702 HIV vaccine trial

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ABSTRACT

Background: Alternative approaches to syndromic management are needed to reduce high rates of sexually transmitted infections (STI) in resource-limited sub-Saharan African settings. We aimed to determine the impact of point-of-care (POC) versus central laboratory-based testing on early treatment initiations and adverse event (AE) reporting of STIs.

Methods: We used Kaplan-Meier and Cox regression models to compare time-to-STI treatment initiation and STI-AE reporting at three research clinics participating in the HVTN702 HIV vaccine trial in South Africa. *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) were diagnosed with POC assays at eThekwini clinic and with laboratory-based assays at Verulam and Isipingo clinics, while all clinics used POC assays for *Trichomonas vaginalis* (TV) testing.

Results: Among 959 women (median age 23 years, IQR 21-26), median days (95%CI) to NG/CT treatment initiation and AE reporting were 0.20 (0.16-0.25) and 0.24 (0.19-0.27) at eThekwini versus 14.22 (14.12-15.09) and 15.12 (13.22-21.24) at Verulam/Isipingo clinics (all $p<0.001$). Median days (95%CI) to TV treatment initiation and AE reporting were 0.17 (0.12-0.27) and 0.25 (0.20-0.99) at eThekwini versus 0.18 (0.15-0.2) and 0.24 (0.15-0.99) at Verulam/Isipingo clinics (all $p>0.05$). Cox regression analysis revealed that NG/CT treatment initiation (aHR=39.09, 95%CI 14.82-103.10) and AE reporting (aHR=3.50, 95%CI 2.30-5.32) occurred faster at eThekwini compared to Verulam/Isipingo clinics, while times to TV treatment initiation (aHR=0.99, 95%CI 0.59-1.68) and AE reporting (aHR=1.58, 95%CI 0.97-2.59) were similar between clinics.

Conclusions: POC testing led to prompt STI management with potential therapeutic and prevention benefits, highlighting the utility as a diagnostic tool in resource-limited healthcare settings.

INTRODUCTION

Sexually transmitted infections (STIs) continue to affect large populations and challenge health care systems globally, despite the availability of effective treatment [1-4]. The World Health Organization (WHO) estimates that 374 million new infections of curable *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), *Trichomonas vaginalis* (TV) and *Treponema pallidum* occur annually among adults aged 15-49 years worldwide, of which 63 million (16%) are recorded in the WHO-Africa region [5]. These curable STIs are known to be associated with pelvic inflammatory disease [6,7], ectopic pregnancy [8,9], infertility [6], genital ulcerations [10,11], foetal and neonatal complications including deaths [2-4], and HIV transmission risk [12].

Many years after the introduction of the syndromic management approach for STI care [13], the population-level burden of STIs remains high in sub-Saharan Africa (SSA) [5]. Syndromic management entails the identification of STI syndromes (e.g., vaginal, and urethral discharge syndromes) and providing treatment to deal with the common pathogens [1]. This approach has a low implementation cost and allows promptness in STI syndrome treatment, leading to its recommendation for resource-limited settings by the WHO in the 1990s. However, due to the asymptomatic state of many STIs [1,14,15], particularly among women [16], and the low diagnostic accuracy of syndromic case finding [15,17-19], high rates of untreated STIs have been recorded in most SSA settings [15,17]. Furthermore, the low diagnostic specificity of the syndromic management approach results in the overuse of antibiotics [16], which can fuel antimicrobial resistance, with negative implications for the efficacy of STI treatment [20].

Diagnostic STI testing is arguably the best approach to management [21], but the gold standard laboratory-based polymerase chain reaction (PCR) testing usually has substantial operational

costs and is hence less sustainable for resource-limited settings [1]. Moreover, central laboratory-based assays can cause delays in STI treatment initiation [22] due to long turnaround times for result availability [21,23,24]. Thus, a diagnostic method that possesses the strengths of diagnostic accuracy, prompt result turnaround, early treatment initiation or management, and cheaper operational costs would be ideal for clinical STI care in resource-limited settings.

Recent developments in diagnostic technologies have enabled an influx of potentially cheaper and more sensitive point-of-care (POC) assays for clinical care [13,25,26]. In South Africa, POC assays such as the Xpert CT/NG (Cepheid, Sunnydale, California, USA) and OSOM TV (Sekisui Diagnostics, Lexington, Massachusetts, USA) have demonstrated high diagnostic accuracy when compared to standard laboratory-based PCR assays [27]. Similar findings have been recorded with different POC assays in other SSA settings [28,29]. However, it is still unclear whether POC assays' real-time diagnosis and accuracy practically translate into earlier STI management in resource-limited settings. To our knowledge, no studies in SSA have yet compared POC and laboratory-based diagnostic approaches to determine their relative impact on early STI treatment initiation or management outcomes. Thus, the recent calls for healthcare systems in resource-limited settings to consider POC testing as an alternative diagnostic care solution for STI management [13-15,30] lack scientific evidence.

This study tested the hypothesis that "*POC testing leads to early STI management compared to central laboratory-based testing"*. The objective was to determine the relative effects of POC versus central laboratory-based testing on time to STI treatment initiation and time to adverse event (AE) reporting in a cohort of women followed prospectively for up to 3 years in a phase 2b/3 HIV vaccine clinical trial in South Africa.

METHODS

Study design, population and setting

The randomised, double-blind, placebo-controlled HVTN702 trial was conducted between 2017 and 2020 to assess the efficacy of an ALVAC and bivalent subtype C gp120 HIV vaccine regimen adjuvanted with MF59 in South Africa. Briefly, the trial enrolled 5400 HIV-negative adults aged 18 to 35 years. Of these, 2700 were assigned to vaccine and 2700 to placebo at 14 clinical research sites (CRSs). The HVTN702 vaccine regimen did not prevent HIV-1 acquisition [31].

This sub-study included HVTN702 female vaccine and placebo recipients enrolled at three CRSs in eThekwini, Isipingo and Verulam in the KwaZulu-Natal province. Testing, treatment, and AE reporting of NG, CT and TV were performed at enrollment and every six months after until study exit. The eThekwini CRS used POC assays, and the Isipingo and Verulam CRSs used a central laboratory-based system for NG and CT testing, but all three CRSs used POC assays for TV diagnosis. The HVTN702 trial was approved by the ethics committees of the University of the Witwatersrand, University of Cape Town, University of KwaZulu-Natal, Sefako Makgatho University and the South African Medical Research Council [31]. The Biomedical Research Ethics Committee of the University of KwaZulu-Natal, Durban, South Africa approved this study (BREC/00003808/2022).

Study measures and assessments: STI testing, treatment initiation and AE reporting

Experienced clinical research staff at the eThekwini CRS collected vaginal and cervical swabs or urine samples for CT and NG testing with the Xpert CT/NG POC assay on the GeneXpert System. Clinical staff at the Isipingo and Verulam CRSs collected vaginal and cervical swabs or urine samples for CT and NG testing with laboratory-based assays at a central laboratory.

The OSOM TV assay was used for POC diagnosis of TV on collected vaginal and cervical swab samples. Women diagnosed with STIs were appropriately treated based on the diagnostic test results. Treatments were initiated depending on the availability of the results, either on the same day of sample collection or later at scheduled or unscheduled study visits.

All HVTN702 trial participants were monitored for AEs, including AEs of STIs (STI-AEs). A STI-AE was defined as any AE of a confirmed diagnosis of NG, CT, or TV using a validated assay. STI-AE reporting time was the time the laboratory result was received. The CRSs reported all collected AEs to the statistical and data management centre (SDMC) of the HVTN702 trial on appropriate Case Report Forms. All study events and timings for sample collection, treatment initiation, and AE reporting were recorded based on quality assurance guidelines as part of the HVTN702 trial.

Statistical analyses

We performed all data analyses with STATA statistical package version 17 (StataCorp LLC, Texas, USA) [32]. We compared eThekwini CRS to Verulam/Isipingo CRSs on the study outcomes in all analyses. First, we summarised and compared the demographic profiles of enrolled women using Chi-squared (for proportion) and rank-sum (for median) tests to ascertain baseline comparability. We used Chi-squared tests to compare the study variables and outcomes, including the percentage of STI cases, treatment initiation and timing, STI-AE reporting and timing. We then evaluated the impact of POC versus central laboratory-based testing on prompt STI treatment initiation and STI-AE reporting with time-to-event analysis models.

The analysis time for all time-to-event models started at the time of sample collection and ended with study event occurrence (treatment initiation or AE reporting) or censoring (study exit or the next sample collection observation during follow-up). We used the Kaplan-Meier survival function estimate and compared the cumulative probabilities of NG/CT treatment initiation and AE reporting with log-rank tests. We used Cox proportional hazard regression to determine the relative effects of POC compared to laboratory-based testing on time to NG/CT treatment initiation and AE reporting. We repeated the Kaplan-Meier and Cox regression analyses to compare time to TV treatment initiation and AE reporting to confirm the consistency of the impact of POC testing on STI management since all CRSs used POC assays for TV testing.

Due to the longitudinal design of HVTN702, STI tests conducted at different follow-up visits yielded repeated observations of interest for each participant. We adjusted for repeated observations with a robust estimation of standard errors and used Breslow's method to account for tied survival times in all Cox regression models [33]. We evaluated the goodness-of-fit of the Cox regression models with proportional hazard tests using Schoenfeld's residuals and adjusted models with time-varying covariate specifications when required [34,35]. All multivariable Cox models were adjusted for demographic characteristics and study visit type (scheduled or unscheduled) at which events occurred. All Cox regression analyses included censored survival time. We used a 5% level of significance in all hypothesis tests.

RESULTS

Baseline profile of study population

A total of 959 women were enrolled and tested for STIs (NG, CT, or TV) over a median of 4 visits (IQR 3-5) between March 2017 and June 2020 (median follow-up 2.3 years, IQR 1.7-

2.9). For NG and CT diagnosis, 699 women were tested with central laboratory-based assays at the Isipingo and Verulam CRSs and 260 with POC assays at the eThekwini CRS. Nine hundred and fifty-eight women were tested for TV with POC assays at all three CRSs. The baseline demographic details and STI prevalence stratified by CRS are presented in Table 1. The median age was 23 years (IQR 21-26), and 60.3% were <25 years old. Most women (96.4%) indicated being married or having a stable sexual partner. At enrolment into the trial, the prevalence of NG, CT, and TV were 3.3%, 19.8%, and 4.7% respectively, and 21.4% had either NG or CT. Baseline characteristics of women across clinics were similar according to age categories, educational status, race/ethnicity and STI (NG, CT, and TV) prevalence (all $p>0.05$).

Overall STI testing, prevalence, treatment initiation and AE reporting

The total number of STI tests performed during the trial, the percentage of positive cases, the corresponding percentage of treatment initiation and STI-AE reporting and their timing are shown in Table 2. The overall percentage of NG, CT, and TV cases were 3.7%, 13.5%, and 3.1%, respectively, and 16.0% had either NG or CT. Of those diagnosed with NG, CT, and TV, 76.9%, 94.2%, and 89.7% initiated appropriate treatment, respectively. Furthermore, 72.0%, 65.4%, and 58.1% of NG, CT, and TV diagnoses were STI-AEs. The number of STI cases, the corresponding treatment initiations and STI-AE reports were similar across CRSs (all $p>0.05$).

NG/CT treatment initiation and AE reporting were faster at eThekwini than Verulam/Isipingo CRSs (all $p<0.05$). Most NG/CT cases (92.4%) at eThekwini CRS received appropriate treatment on the day of sample collection compared to 1.2% at Verulam/Isipingo CRSs ($p<0.001$). At Verulam/Isipingo CRSs, NG/CT treatment initiations occurred within seven days (8.2%), between 8 and 14 days (36.6%) and after 14 days (55.2%) of sample collection.

Furthermore, 98.5% of NG/CT AEs were reported at eThekwini compared to 4.8% at Verulam/Isipingo CRSs on the same day of sample collection (p<0.001). At Verulam/Isipingo CRSs, NG/CT AE reporting occurred within seven days (35.7%), between 8 to 14 days (37.1%), and after 14 days (27.2%) of sample collection. The timing of TV treatment initiation and AE reporting were similar at all CRSs. Overall, 99.1% of TV treatment initiations (eThekwini 100% versus Verulam/Isipingo 98.7%, p=0.554) and 100% of TV AE reporting (eThekwini 100% versus Verulam/Isipingo 100%) occurred on the same day as POC testing. In addition, more NG/CT treatments were initiated during scheduled visits at eThekwini CRS (91.8%) compared to Verulam/Isipingo CRSs (62.2%), p<0.001. However, the percentage of TV treatment initiations at scheduled visits was similar across CRSs (eThekwini=100%, Verulam/Isipingo=93.6%, p= 0.178).

Impact of POC versus central laboratory-based testing on time to STI treatment initiation

The impact of POC testing compared to central laboratory-based testing on the cumulative probability trend of STI treatment initiation is shown in Figures 1A and 1C. Over 9781.0 person-days (PDs) of observation, 572 NG/CT treatments were initiated out of the 612 NG/CT cases (40 cases were not treated). Figure 1A illustrates that NG/CT treatment initiation occurred faster at eThekwini (median days 0.20, 95%CI 0.16-0.25) compared to Verulam/Isipingo CRSs (median days 14.22, 95%CI 14.12-15.09) (p<0.001). In contrast, Figure 1C displays a near perfect overlap in TV treatment initiation timing with 0.17 (95%CI 0.12-0.27) median days at eThekwini CRS versus 0.18 (95%CI 0.15-0.20) at Verulam/Isipingo CRSs (p=0.704).

Table 3 presents the Cox proportional hazard regression results showing the relative probability of time to treatment initiation of NG/CT (model A) and TV (model B) with estimated hazard

ratios. After adjusting for demographic variables and study visit type, the time to NG/CT treatment initiation was 39 times faster with POC testing at eThekwini CRS compared to laboratory-based testing at Verulam/Isipingo CRSs (aHR=39.09, 95%CI 14.82-103.10, p<0.001), while there was no difference in the time to TV treatment initiation across the CRSs (aHR=0.99, 95%CI 0.59-1.68, p=0.983). Older women (>=35 years) compared to younger women (18-24 years) were more likely to receive NG/CT treatment (aHR=1.50, 95%CI 1.10-2.04, p=0.010).

Impact of POC versus central laboratory-based testing on time to STI-AE reporting

The impact of POC compared to central laboratory-based testing on STI-AE reporting trends among women is illustrated in Figures 1B and 1D. Of the 612 NG/CT cases, 404 NG/CT AEs were reported over 28487.7 PDs of observation (208 cases were not NG/CT AEs). Figure 1B shows that the trend in NG/CT AE reporting was faster at eThekwini CRS (median days 0.24, 95%CI 0.19-0.27) compared to Verulam/Isipingo CRSs (median days 15.12, 95%CI 13.22-21.24) (p<0.001). In contrast, Figure 1D shows that there was no difference in the timing of TV AE reporting between eThekwini CRS (median days 0.25, 95%CI 0.20-0.99) and Verulam/Isipingo CRSs (median days 0.24, 95%CI 0.15-0.99), p=0.388.

The Cox proportional hazard regression (Table 4, Models C and D) shows the effects of POC testing on the hazard of STI-AE reporting. After adjusting for demographic variables and study visit type, the probability of reporting NG/CT AEs was 3.5 times faster with POC testing at eThekwini CRS compared to laboratory-based testing at Verulam/Isipingo CRSs (aHR 3.50, 95%CI 2.30-5.32, p<0.001), while again there was no significant difference in the time to TV AE reporting (aHR 1.58, 95%CI 0.97-2.59, p=0.066) with POC testing between CRSs.

DISCUSSION

This study tested the hypothesis that POC testing leads to prompt STI management compared to centralised laboratory-based testing among a cohort of women from higher-risk communities for STIs in KwaZulu-Natal, South Africa. The indicators for early STI management were time to STI treatment initiation and STI-AE reporting after sample collection. We found that most participants with NG/CT initiated treatment and had AEs reported on the day of sample collection when POC testing was used at the clinics. In contrast, these often occurred more than 14 days later when specimens were sent to a central laboratory. We also showed that NG/CT treatment was initiated 39 times faster, and AEs were reported 3.5 times faster when POC testing was used. When we compared TV management, the POC testing effects extended to the research clinics that used central laboratory testing for NG/CT but POC testing for TV, indicating that the findings were due to the testing modalities such as result turnaround times rather than other procedures or processes at the clinics. Our results highlight the strengths of POC testing as a clinically sustainable, suitable, and effective STI diagnostic care solution for resource-limited settings.

To the best of our knowledge, we found no study in SSA that prospectively determined the relative effects of POC testing against a gold standard PCR central laboratory-based algorithm on prompt STI management. Some studies in SSA [36,37] and globally [23,24] have evaluated the effects of individual testing approaches (POC or central laboratory-based) on prompt STI treatment initiation without reference to a gold standard. Consistent with our findings, a study in South Africa that enrolled and tested women with POC assays recorded 91.9% same-day STI (CT, NG, TV) treatment initiations after sample collection [36]. In another study from South Africa that did not specify the STI testing approach, despite 63.9% of CT positive results being available within 72 hours after sample collection, the treatment prevalence (cumulative)

was 1.7% within 48 hours, 56% within seven days, 92.2% within 14 days and 97.5% within 28 days after result availability [23].

Our study has added evidence by determining the effects of the two current aetiological testing approaches on prompt STI management. Grounded in the argument that the effectiveness of a diagnostic test depends on the likelihood of leading to early and accurate treatment [38], our findings suggest that POC testing is a clinically superior and more effective approach to central laboratory-based testing. We posit that POC testing is potentially more effective than syndromic or clinical diagnosis for STI care based on these findings.

Our results also underscore additional practical and potential cost implications for STI/HIV research institutions and health system stakeholders that could lead to a re-think of STI testing approaches. Same-day STI management reduced the number of unscheduled visits by 91.8%, simplified trial conduct, reduced costs, and, more importantly, benefited trial participants by preventing unnecessary trips to the clinic. Extrapolated to a health care system, the POC testing intervention could potentially reduce the burden on primary health care and STI clinics, and result in healthcare savings while at the same time improving STI care [27,39,40]. Compared to the syndromic management approach, POC testing could lead to more accurate diagnosis and treatment, resulting in a reduction in STI complications, reinfections, drug resistance and reduced risk of HIV transmission.

The study had some limitations. First, the HVTN702 trial population included a large proportion of women (70%) [31], and we, therefore, restricted this analysis to female participants, thereby reducing generalizability to men. However, current POC assays are available for males and females and are likely to have similar diagnostic and management

311 outcomes. Second, our study did not retain the randomised design of the HVTN702 trial, as
312 participants were randomised to receive a vaccine and not an STI testing approach. While
313 baseline characteristics were broadly similar, we cannot rule out the effects of unmeasured
314 confounding variables. Furthermore, the almost identical results of the early TV management
315 at all CRSs, where all sites used POC testing, further strengthen the validity of our findings.
316
317 In conclusion, we found POC testing led to prompt STI management in a clinical setting in
318 South Africa, where such evidence is most needed for decision making. Our study provides
319 strong evidence to consider POC testing when strengthening STI care systems in resource-
320 limited settings. These assays could support a shift from the current syndromic management
321 approach to a diagnosis-based approach satisfying WHO's ASSURED (affordable, sensitive,
322 specific, user-friendly, rapid, equipment-free, delivered) criteria [30]. This paradigm shift
323 could improve STI care outcomes and reduce the associated disease burden, including HIV
324 transmission. Further evidence is needed on the feasibility of a POC testing model for STI care
325 in under-resourced settings, as the three clinics in this study were well-resourced trial sites in
326 central areas and conducive to the effortless implementation of POC testing.

NOTES

Author contributions

KA, TA, AT, and NG designed the study and are responsible for the overall content of the manuscript. KA performed the statistical analyses and wrote the draft manuscript. All authors critically reviewed and approved the final submitted version.

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Potential conflicts of interest

The authors have no potential conflicts of interest to disclose. Conflicts that the editors consider relevant to the manuscript's content have been disclosed.

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463 **Tables**

Table 1 Baseline demographic characteristics of enrolled women stratified by clinical research site (CRS)

Variable	Category	Total (N=959) % (n)	Verulam/Isipingo [a] CRSs (N=699) % (n)	eThekwini [b] CRS (N=260) % (n)	P value
Age in years	Median	23 (21-26)	23 (21-27)	23 (21-26)	0.040
Age group in years	18-24	60.3 (578/959)	58.7 (410/699)	64.6 (168/260)	0.083
	25-34	31.6 (303/959)	33.6 (235/699)	26.2 (68/260)	
	35+	8.1 (78/959)	7.7 (54/699)	9.2 (24/260)	
School level completed	High school	61.8 (592/958)	61.7 (431/698)	61.9 (161/260)	0.994
	Primary School	37.8 (362/958)	37.8 (264/698)	37.7 (98/260)	
	No schooling	0.4 (4/958)	0.4 (3/698)	0.4 (1/260)	
Married/stable partner	Yes	96.4 (889/922)	97.3 (651/669)	94.1 (238/253)	0.018
Race/Ethnicity	Black	99.6 (955/959)	99.4 (695/699)	100.0 (260/260)	0.474
	White	0.3 (3/959)	0.4 (3/699)	0.0 (0/260)	
	Indian	0.1 (1/959)	0.1 (1/699)	0.0 (0/260)	
Neisseria gonorrhoeae (NG)	Prevalence	3.3 (31/954)	3.5 (24/694)	2.7 (7/260)	0.552
Chlamydia trachomatis (CT)	Prevalence	19.8 (189/956)	20.6 (143/696)	17.7 (46/260)	0.324
NG/CT	Prevalence	21.4 (205/958)	22.4 (156/698)	18.9 (49/260)	0.240
Trichomonas vaginalis [c] (TV)	Prevalence	4.7 (44/946)	5.1 (35/691)	3.5 (9/255)	0.320

464 [a] Central laboratory-based testing for NG and CT was conducted at the Isipingo and Verulam clinical research sites (CRSs). [b] POC testing for
465 NG and CT was conducted at the eThekwini CRS. [c]All CRSs used POC assays for TV testing. STI=Sexually Transmitted Infection.
466 Denominators that do not equal sample sizes are due to missing data. Percentages may not total 100 because of rounding.

Variable	Category	% (n)	% (n)	% (n)	
Neisseria gonorrhoeae (NG)	Positive	3.7 (143/3830)	3.4 (91/2692)	4.6 (52/1138)	0.076
Chlamydia trachomatis (CT)	Positive	13.5 (518/3828)	13.8 (371/2692)	12.9 (147/1136)	0.487
NG/CT	Positive	16.0 (612/3838)	16.0 (432/2700)	15.8 (180/1138)	0.888
Trichomonas vaginalis [c] (TV)	Positive	3.1 (117/3784)	3.3 (87/2,656)	2.7 (30/1128)	0.317
NG	Treatments initiated	76.9 (110/143)	80.2 (73/91)	71.2 (37/52)	0. 216
CT	Treatments initiated	94.2 (488/518)	93.3 (346/371)	96.6 (142/147)	0.143
NG/CT	Treatments initiated	93.5 (572/612)	93.1 (402/432)	94.4 (170/180)	0.526
TV	Treatments initiated	89.7 (105/117)	89.7 (78/87)	90.0 (27/30)	0.957
Time to NG/CT treatment initiation after sample collection	Same day	28.3 (162/572)	1.2 (5/402)	92.4 (157/170)	<0.001
	2-7 days	6.6 (38/572)	7.0 (28/402)	5.9 (10/170)	
	8-14 days	25.9 (148/572)	36.6 (147/402)	0.6 (1/170)	
	After 14 days	39.2 (224/572)	55.2 (222/402)	1.2 (2/170)	
Type of study visit at which NG/CT treatment was initiated	Scheduled	71.0 (406/572)	62.2 (250/402)	91.8 (156/170)	<0.001
	Unscheduled	29.0 (166/572)	37.8 (152/402)	8.2 (14/170)	
Time to TV treatment initiation after sample collection	Same day	99.1 (104/105)	98.7 (77/78)	100.0 (27/27)	0.554
	2-7 days	0.0 (0/0)	0.0 (0/0)	0.0 (0/0)	
	8-14 days	1.0 (1/105)	1.3 (1/78)	0.0 (0/27)	
	After 14 days	0.0 (0/0)	0.0 (0/0)	0.0 (0/0)	
Type of study visit at which TV treatment was initiated	Scheduled	95.2 (100/105)	93.6 (73/78)	100.0 (27/27)	0.178
	Unscheduled	4.8 (5/105)	6.4 (5/78)	0.0 (0/27)	
NG AE reported	Yes	72.0 (103/143)	67.0 (61/91)	80.8 (42/52)	0.078
CT AE reported	Yes	65.4 (339/518)	63.3 (235/371)	70.8 (104/147)	0.110
NG/CT AE reported	Yes	66.0 (404/612)	63.0 (272/432)	73.3 (132/180)	0.014
TV AE reported	Yes	58.1 (68/117)	56.3 (49/87)	63.3 (19/30)	0.502
Time to NG/CT AE reporting after sample collection	Same day	35.4 (143/404)	4.8 (13/272)	98.5 (130/132)	<0.001
	2-7 days	21.0 (85/404)	30.9 (84/272)	0.8 (1/132)	
	8-14 days	25.0 (101/404)	37.1 (101/272)	0.0 (0/132)	
	After 14 days	18.6 (75/404)	27.2 (74/272)	0.8 (1/132)	
Type of study visit at which NG/CT AE was reported	Scheduled	97.5 (394/404)	97.1 (264/272)	98.5 (130/132)	0.387
	Unscheduled	2.5 (10/404)	2.9 (8/272)	1.5 (2/132)	
Time to TV AE reporting after sample collection	Same day	100.0 (68/68)	100.0 (49/49)	100.0 (19/19)	-
	2-7 days	-	-	-	
	8-14 days				
		-	-	-	
	After 14 days	-	-	-	
Type of study visit at which TV AE was reported	Scheduled	98.5 (67/68)	98 (48/49)	100 (19/19)	0.530
	Unscheduled	1.5 (1/68)	2 (1/49)	0.0 (0/19)	

[a] Central laboratory-based testing for NG and CT was conducted at the Isipingo and Verulam clinical research sites (CRSs). [b] POC testing for NG and CT was conducted at the eThekwini CRS. [c] All CRSs used POC assays for TV testing. STI=Sexually Transmitted Infection, AE=adverse event, POC=Point-of-Care. Denominators that do not equal sample sizes are due to missing data. Percentages may not total 100 because of rounding.

Table 3 Cox proportional hazard regression for the impact of POC versus central laboratory-based testing on time to STI treatment initiation among women

		Model A NG/CT outcome			**Model B** TV [c] outcome		
Variable	Category	Treatments/ Person Days	aHR (95% CI)	P-value	Treatments/ Person Days	aHR (95% CI)	P-value
Age group in years	18-24	413/8913.7	1	-	55/1312.2	1	-
	25-34	138/3080.6	1.02 (0.83-1.25)	0.865	37/174.9	1.50 (0.94-2.38)	0.088
	35+	21/230.4	1.50 (1.10-2.04)	0.010	13/4.4	1.04 (0.62-1.74)	0.884
School level completed	High school	354/7786.9	1.17 (0.45-3.01)	0.746	59/1208.1	1.04 (0.68-1.58)	0.859
	Primary school	216/4341.4	1.21 (0.47-3.14)	0.688	44/460.3	1.04 (0.64-1.67)	0.878
	No school	2/96.4	1	-	2/0.3	1	-
Married/stable partner	No	22/510.3	1	-	2/0.4	1	-
	Yes	541/11583.4	1.23 (0.96-1.59)	0.101	99/1667.2	1.26 (0.70-2.25)	0.440
CRS [d]	Verulam/Isipingo [a]	402/11396.3	1	-	78/1124.0	1	-
	eThekwini [b]	170/828.3	39.09 (14.82-103.10)	<0.001	27/534.8	0.99 (0.59-1.68)	0.983
Study visit type at which STI treatment was initiated [d]	Scheduled	406/9430.6	1	-	100/1634.9	1	-
	Unscheduled	166/2794.1	0.77 (0.52-1.13)	0.182	5/33.9	0.68 (0.36-1.28)	0.228

[a] Central laboratory-based testing for NG and CT was conducted at the Isipingo and Verulam clinical research sites (CRSs). [b] POC testing for NG and CT was conducted at the eThekwini CRS. [c]All CRSs used POC assays for TV testing. STI=Sexually Transmitted Infection, CT=*Chlamydia trachomatis*, NG=*Neisseria gonorrhoeae*, TV=*Trichomonas vaginalis*, CRS=Clinical research Site, POC=Point-of-Care, aHR=adjusted Hazard Ratio, CI=Confidence Interval. Denominators that do not equal sample sizes are due to missing data. [d] STI treatment initiation trend between CRSs violated the proportional hazard assumption in Model A and the related variables adjusted accordingly as time-varying covariates. Model B satisfied the proportional hazard assumption (Schoenfeld test p= 0.211). Denominators that do not equal the sample sizes are due to missing data.

Table 4 Cox proportional hazard regression for the impact of POC versus central laboratory-based testing on time to STI-AE reporting among women

		Model C NG/CT outcome			**Model D** TV [c] outcome		
Variable	Category	AEs reported/ Person Days	aHR (95%CI)	P-value	AEs reported / Person Days	aHR (95%CI)	P-value
Age group in years	18-24	302/19938.0	1	-	34/3567.4	1	-
	25-34	94/7049.9	0.94 (0.75-1.17)	0.579	26/1453.8	1.63 (1.02-2.61)	0.041
	35+	8/1499.9	0.44 (0.21-0.91)	0.027	8/820.9	1 (0.58-1.74)	0.998
School level completed	High school	249/17610.0	1.86 (0.43-8.02)	0.406	37/3705.0	1.93 (1.21-3.07)	0.006
	Primary school	154/10730.4	1.95 (0.45-8.41)	0.371	30/2096.3	2.16 (1.48-3.16)	<0.001
	No school	1/147.4	1	-	1/113.3	1	-
Married/stable partner	No	12/1520.6	1	-	1/98.4	1	-
	Yes	389/25759.1	1.65 (0.97-2.78)	0.062	67/5254.1	2.33 (1.31-4.15)	0.004
CRS [d]	Verulam/Isipingo [a]	272/22453.2	1	-	49/4384.0		
	eThekwini [b]	132/6034.6	3.5 (2.30-5.32)	<0.001	19/1461.8	1.58 (0.97-2.59)	0.066
Study visit type at which STI-AE was reported	Scheduled	394/28346.2	1	-	67/5914.4		
	Unscheduled	10/141.6	1.71 (1.18-2.49)	0.005	1/0.3	0.91 (0.62-1.34)	0.647

[a] Central laboratory-based testing for NG and CT was conducted at the Isipingo and Verulam clinical research sites (CRSs). [b] POC testing for NG and CT was conducted at the eThekwini CRS. [c] All CRSs used POC assays for TV testing. STI=Sexually Transmitted Infection, CT=*Chlamydia trachomatis*, NG=*Neisseria gonorrhoeae*, TV=*Trichomonas vaginalis*, CRS=Clinical research Site, POC=Point-of-Care, AE=adverse event, aHR=Adjusted Hazard Ratio, CI=Confidence Interval. Denominators that do not equal sample sizes are due to missing data. [d] STI AE reporting trend between CRSs violated proportional hazard assumption in Model C and adjusted accordingly as a time-varying covariate. Model D satisfied the proportional hazard assumption (Schoenfeld test p= 0.8507). Denominators that do not equal the sample sizes are due to missing data.

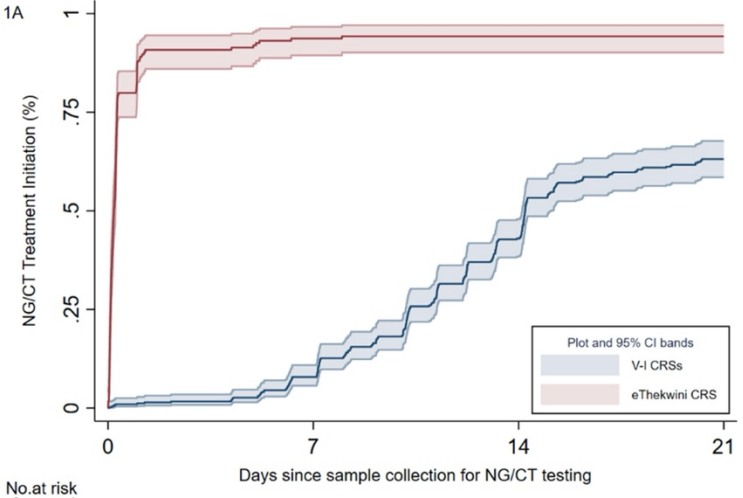
Figure legends

Figure 1 Kaplan-Meier cumulative probability graphs displaying the effects of POC versus central laboratory-based testing on STI treatment initiation and AE reporting after sample collection for testing among women. V-I CRS= Verulam and Isipingo Clinical Research Sites. NG=*Neisseria gonorrhoeae,* CT= *Chlamydia trachomatis*, TV=*Trichomonas vaginalis*, AE=adverse event, POC=Point-of-Care. Figures 1A and 1C compare the time to NG/CT treatment initiation and NG/CT AE reporting between CRSs that used either POC (eThekwini) or central laboratory-based testing (Verulam and Isipingo). Figures 1B and 1D compare the same groups of CRSs in A and B on the time to TV treatment initiation and TV AE reporting tested with POC assays at all CRSs.

Median time in days (95% CI), log-rank test p-value:

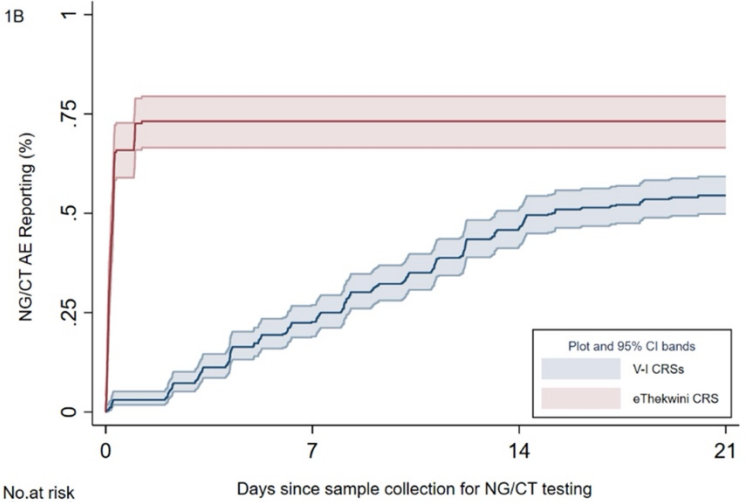
Figure 1A (Verulam/Isipingo CRSs=14.22 (14.12-15.09), eThekwini CRS NG/CT CRS= 0.20 (0.16-0.25), <0.001). **Figure 1C** (Verulam/Isipingo CRS=0.18 (0.15-0.2), eThekwini CRS=0.17 (0.12-0.27), 0.704). **Figure 1B** (Verulam/Isipingo CRSs=15.12 (13.22-21.24), eThekwini CRS=0.24 (0.19-0.27), <0.001). **Figure 1D** (Verulam/Isipingo CRSs=0.24 (0.15-0.99), eThekwini CRS=0.25 (0.20-0.99), 0.388).

Figure 1A



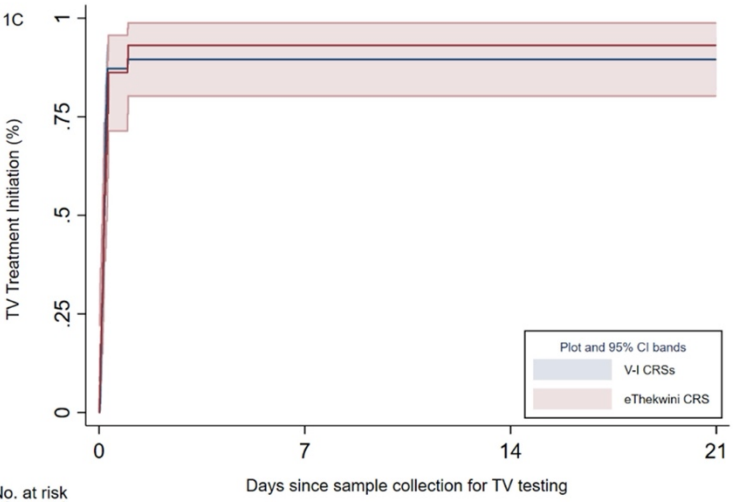
No.at risk (No. of events)							
V-I CRSs	432	(33)	386	(147)	238	(84)	154
eThekwini CRS	180	(167)	11	(1)	8	(0)	8

Figure 1B



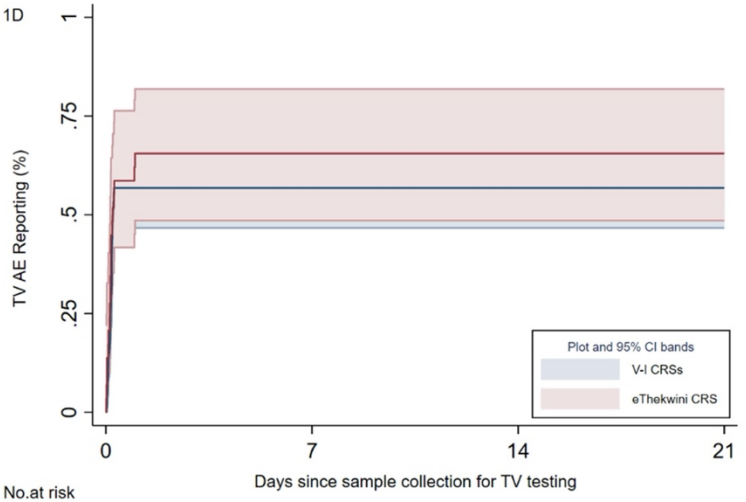
No.at risk (No. of events)							
V-I CRSs	432	(97)	331	(101)	230	(35)	194
eThekwini CRS	180	(131)	48	(0)	48	(0)	48

Figure 1C



No. at risk (No. of events)							
V-I CRSs	86	(77)	9	(0)	9	(0)	9
eThekwini CRS	29	(27)	2	(0)	2	(0)	2

Figure 1D



No.at risk (No. of events)							
V-I CRSs	87	(49)	37	(0)	37	(0)	37
eThekwini CRS	29	(19)	10	(0)	10	(0)	10