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MAJOR ARTICLE

Comparison of QuantiFERON Gold In-Tube Versus Tuberculin Skin Tests on the Initiation of Tuberculosis Preventive Therapy Among Patients Newly Diagnosed With HIV in the North West Province of South Africa (the Teko Study): A Cluster Randomized Trial

Brooke A. Jarrett,[1] Kate Shearer,[2] Katlego Motlhaoleng,[3] Sandy Chon,[2] Gaolaolwe Gabriel Letuba,[3] Cokiswa Qomfo,[3] Lawrence H. Moulton,[2,4] Silvia Cohn,[2] Limakatso Lebina,[3] Richard E. Chaisson,[2,4] Ebrahim Variava,[5] Neil A. Martinson,[2,3,a] and Jonathan E. Golub[1,2,4,a]

[1]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA; [2]Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore Maryland, USA; [3]Perinatal HIV Research Unit, The University of the Witwatersrand, Soweto, South Africa; [4]Department of International Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA; and [5]Department of Internal Medicine, Klerksdorp–Tshepong Hospital Complex, Klerksdorp, South Africa

Background. Tuberculosis (TB) preventive therapy (TPT) reduces the risk of TB disease in people with human immunodeficiency virus (HIV), yet uptake has been suboptimal in many countries. We assessed whether QuantiFERON Gold In-Tube (QGIT) during routine HIV care increased TB infection (TBI) testing and TPT prescriptions.

Methods. This parallel-arm, 1:1 cluster-randomized controlled trial compared the standard-of-care tuberculin skin test to QGIT in South Africa. We enrolled consenting, TPT-eligible adults diagnosed with HIV ≤30 days prior and used intention-to-treat analyses for the outcomes: proportion of patients with documented TBI results, proportion with documented TPT, and time from enrollment to outcomes.

Findings. We enrolled 2232 patients across 14 clinics from November 2014 to May 2017 (58% in intervention clinics). At 24 months of follow-up, more participants in intervention clinics had TBI results (69% vs 2%, $P < .001$) and TPT prescriptions (45% vs 30%, $P = .13$) than control clinics. Controlling for baseline covariates, intervention clinics had 60% (95% confidence interval, 51–68; $P < .001$) more participants with TBI results and 12% (95% confidence interval, −6 to 31; $P = .18$) more with TPT prescriptions. Among participants with results, those in intervention clinics received results and TPT faster (intervention: median of 6 and 29 days after enrollment vs control: 21 and 54 days, respectively).

Interpretation. In this setting, QGIT in routine HIV care resulted in more patients with TBI results. Clinicians also initiated more people with HIV on TPT in QGIT intervention clinics, and did so more quickly, than the control arm.

Clinical Trials Registration. NCT02119130.

Keywords. latent tuberculosis; prevention and control; interferon-gamma release tests; tuberculin test; HIV.

More than 7.8 million people with human immunodeficiency virus (PHIV) were living in South Africa in 2020, of whom an estimated 35%–60% had tuberculosis (TB) infections (TBI) [1–3]. TB disease remains the leading cause of death for PHIV in South Africa, despite free-of-charge TB preventive therapy (TPT) and antiretroviral therapy (ART). Both substantially reduce TB disease incidence and mortality [4–6]. TPT is critical for the End TB Strategy and the South African national strategic health plan [7,8]

Provision of TPT to PHIV to prevent TB disease is a multistep care cascade. Between 2015 and 2018, South Africa's TPT guidelines for PHIV required symptom screening, assessing for contraindications, administering a tuberculin skin test (TST), and using a clinical algorithm (Figure 1). The World Health Organization reported that 63% of newly diagnosed PHIV in South Africa received TPT in 2021; however, this may be overestimated [9–11]. Thus, despite recent research demonstrating that shorter TPT regimens improve adherence, many newly HIV-diagnosed South Africans never initiate TPT.

PHIV who test positive for TBI have an 11-fold higher annual risk of developing TB disease (vs TBI-negative PHIV) [12]. Yet healthcare providers in South Africa and elsewhere

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[a]N. A. M. and J. E. G. contributed equally to this work.

Correspondence: B. A. Jarrett, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St., Baltimore, MD 21205 (brooke@jhmi.edu); J. E. Golub, Johns Hopkins School of Medicine Medicine, 733 N. Broadway, Baltimore, MD 21205 (jgolub@jhmi.edu).

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	Pregnant	Pre-ART	ART
TB immunoreactivity status			
Reactive	36 months	36 months	36 months
Non-reactive	12 months	—	12 months
Unavailable	12 months	6 months	12 months

* If tuberculin skin test is not initially available at initiation of TPT, it must be done within ONE month of initiating TPT. If patients is not TB immunoreactive, re-assess annually until it becomes positive.
ART = antiretroviral therapy. TB = tuberculosis. TPT = tuberculosis preventive therapy.

Figure 1. Clinical algorithm for tuberculosis preventive therapy per 2015 South African National Guidelines.

frequently cite TBI testing, especially TSTs, as a barrier to TPT [13]. TST has frequent global stockouts, requires training to correctly administer, and depends on patients to return within 2–3 days for test interpretation. The difficulties of TST are compounded by staff workloads and shortages [14].

Interferon-gamma release assays (IGRAs), such as QuantiFERON Gold In-Tube (QGIT), detect immunoreactivity to *Mycobacterium tuberculosis* antigens via blood samples. QGIT tests require a simple blood draw, patients need not return to complete the test, results do not rely on readers' subjectivity, and, for PHIV, it is modestly more sensitive than TST including those with previous Bacille Calmette-Guérin vaccination [15, 16]. However, there are limitations to widespread adoption of IGRAs in resource-limited settings including the need for laboratory processing and transportation of samples and a higher per-unit cost than TST.

In this trial, we sought to evaluate whether integrating QGIT into HIV care would increase the number of patients with documented TBI results and TPT prescriptions, compared to educating clinicians on the then standard of care (TST). After the trial started, a new QGIT (QFT-Plus) was released; however, we continued using the original for consistency and its similar diagnostic performance [17]. Moreover, though guidelines in South Africa have recently changed to not require TBI testing before prescribing TPT to PHIV, this study provides valuable alternative evidence for this setting and new evidence for regions that still require TBI testing before TPT provision.

METHODS

Study Design and Clusters

Teko Study was a parallel-arm, 1:1 cluster-randomized controlled trial, with clinics as clusters, conducted in the Matlosana and JB Marks (then known as Tlokwe) municipalities of South Africa. The Johns Hopkins School of Medicine institutional review board (00085133), University of Witwatersrand Human Research Ethics Committee (130609), and North West Province Department of Health's research committee provided ethical approval. This publication is consistent with the Stop TB Partnership Guidelines for Tuberculosis Communications, CONSORT, and TIDieR [18–20]. The trial did not require a data safety monitoring board; a study protocol is included (Supplementary material).

Study Population

Fifteen public sector clinics and community health centers (of 26 total) met the inclusion criteria of diagnosing a monthly average of ≥25 patients with HIV between August 2013 and January 2014. All clinics consented to participate.

Adult patients (aged 18+ years) were eligible if diagnosed with HIV ≤30 days ago; self-reported the clinic as their usual; were not currently diagnosed with, receiving treatment for, nor had symptoms of active TB per the World Health Organization 4-symptom screen; and were eligible for TPT (ie, no acute/chronic liver disease, history of adverse reactions to TPT, peripheral neuropathy, nor excessive alcohol use). We did not enroll patients who refused or were incapable of consenting in languages common to the region (Setswana, Sesotho, Xhosa, English). National guidelines recommended TPT for patients with previous TB disease and evidence of bacteriologic cure. However, few could produce documentation, so patients with previous TB were excluded from our analyses. HIV was confirmed with ≥1 positive, double-rapid HIV tests, enzyme-linked immunosorbent assay HIV assay, or detectable plasma HIV viral load (≥400 copies/mL). All participants provided written informed consent.

Randomization and Masking

An independent statistician randomized clinics to intervention or control using highly constrained randomization [21]. The

statistician identified and randomly selected from 182 possible treatment assignments that achieved balance between arms on geographical quadrants and the monthly number of people screened/diagnosed for HIV and started on ART. All clinics had a non-zero probability of being in the same arm as all others, except 2 in a quadrant that were restricted from being randomized to the same arm because of their proximity. The study team, clinics, and participants were not masked to clinic allocations.

Intervention and Procedures

The control condition included trainings on placing/interpreting TSTs and then-current guidelines for prescribing TPT. Intervention clinics received the control condition plus QGIT supplies, trainings on collecting blood into QGIT-specific tubes, processing samples, delivery of printed QGIT results, and training on interpreting QGIT results. A study-appointed doctor trained clinicians (ie, doctors and nurses) already employed at clinics twice—once before enrollment and again midway through. Participants with indeterminate results were tested again, though these did not count toward our analysis. We did not provide any TST or TPT supplies, which periodically experienced stockouts during the trial. We designed the intervention and solicited input on its implementation alongside local clinicians and PHIV [22].

We staffed each clinic with 1 study-appointed fieldworker to enroll patients and abstract data from medical records. All fieldworkers had ≥12 grade schooling, previous HIV counseling experience, and Good Clinical Practice certification. Fieldworkers were trained once before the study started and approximately every 6 months thereafter, with additional training when national medical records changed formats.

In both arms, clinicians completed an initial consultation with patients newly diagnosed with HIV, per routine care, and then referred them as potential participants to study fieldworkers. Fieldworkers explained the study's purpose and procedures, screened interested patients, obtained consent from eligible patients, and interviewed enrolled participants in a private room to ascertain baseline data. There was no further contact between fieldworkers and participants. Participants then returned to clinicians for the standard-of-care blood draw via peripheral venipuncture (to attain a CD4 count before ART initiation). At this time, in intervention clinics, clinicians also collected 1 mL of blood into three, 5-mL, high-altitude QGIT tubes.

Study-appointed drivers collected blood samples daily and transported them to a private laboratory in Johannesburg. We incubated, processed, stored, and batch-analyzed samples according to manufacturer instructions. As QGIT results became available, drivers delivered paper copies to clinics. Clinic staff and fieldworkers inserted results into participants' clinic-maintained medical records.

Approximately every 6 months after enrollment for 2 years, fieldworkers abstracted data from participants' paper medical records onto paper study documents. These records were supplemented with 3 electronic databases: (1) Tier.net for TPT data; (2) the electronic TB disease register for prior TB diagnoses; and (3) the National Health Laboratory Services TrakCare Webview database for CD4 counts. TBI testing and results were unavailable in these databases. Separate study staff entered data from paper study documents into REDCap [23].

Primary Outcomes

There were 2 primary outcomes: (1) documentation of a TBI result (QGIT, TST, or both) and (2) documentation a postenrollment TPT prescription. Proof of documentation was recorded if a QGIT result from the laboratory, a TST result, or TPT prescription was found in a participant's medical record. TST and TPT were often handwritten in standard existing fields, clinicians' notes, and elsewhere. The secondary outcome was median time from enrollment to first-occurring primary outcomes.

Statistical Analyses

We estimated that 14 clinics would provide 80% power to detect a ≥ 25% absolute improvement in primary outcomes between arms of equal cluster sizes, with an average of 40% of participants having the outcome in control clinics (significance of 0.05). We anticipated 700 participants per arm would be sufficient, assuming 20% attrition and a coefficient of variation (CV) of 0.25 [24]

The first primary analysis used an intention-to-treat approach to calculate cluster-summarized proportions. We compared arms using unpaired *t*-tests, per our a priori plan and compared those *P* values qualitatively with nonparametric Wilcoxon rank-sum tests to confirm robustness to actual underlying data distributions. We described cluster- and arm-specific intervention fidelity using the proportion of participants with each outcome stratified by 6-month intervals, categorizing fidelity as low (<40%), moderate (40%–79%), and high (≥80%) [14].

To attain risk differences and ratios adjusted for imbalances in baseline covariates (defined in Table 2), we implemented a 2-stage procedure recommended for trials of <15 clusters per arm [24]. We accounted for clustering while computing all confidence intervals (CIs). We present the empirical CVs in the control arm, based on a random effects model, for comparison to our original sample size calculations assumption. Statistical significance was determined according to a 2-tailed *P* value of .05.

For the second primary analysis, we calculated the median time from enrollment to primary outcomes but only among participants with each outcome. Because this procedure breaks randomization, we did not provide CIs.

We also described the distribution of TBI tests initiated, TBI results, TPT prescriptions stratified by TBI result, and TPT prescriptions according to South African national guidelines at the

time. Finally, we conducted a post hoc analysis among participants deemed "retained in early HIV care" to evaluate the intervention without loss to follow-up. We conducted all analyses in STATAv14.2.

Role of the Funding Source

Funders had no role in study design, data collection, analysis, interpretation, or reporting. The corresponding author had access to all data and final responsibility for publication submission.

RESULTS

Recruitment

Of 15 eligible clinics, 1 was randomly deselected and 14 were randomized (7 clinics per arm; Figure 2). Of 4680 patients screened, 3515 were enrolled between 11 November 2014 and

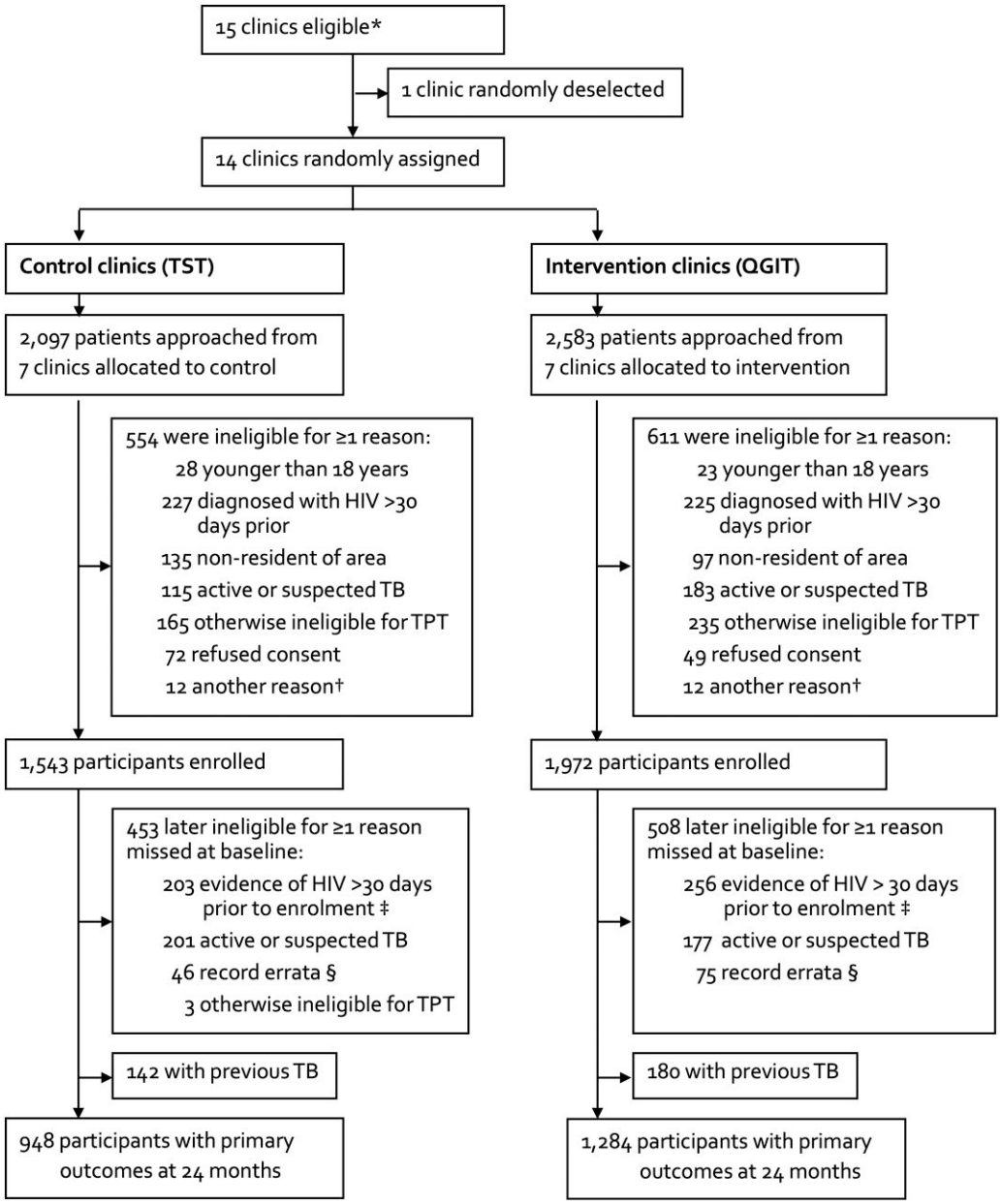

Figure 2. CONSORT diagram of the Teko cluster randomized trial among people newly HIV-diagnosed between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa. HIV, human immunodeficiency virus; QGIT, QuantiFERON Gold in-Tube; TB, tuberculosis; TPT, tuberculosis preventive therapy; TST, tuberculin skin tetst. *Of 26 clinics in Tlokwe and Matlosana municipalities, 15 were eligible per the cluster inclusion criteria (monthly average of ≥25 people diagnosed with HIV). † Being physically incapable (eg, critically ill), being mentally unstable, not speaking/reading the available languages on study forms, being in shock because of one's HIV result, not having an address, or an unlisted reason. ‡ According to dates of HIV diagnosis, antiretroviral treatment, CD4 count, and viral loads > 30 d before enrollment. People with a viral load within 30 d of enrollment were also excluded. § Errata included mistaken participant reenrollments, duplications resulting from paper record mismanagement, etc.

31 May 2017. Data collection continued until May 2019. Of the 3515 enrolled, 322 (9.2%) had a history of TB and 961 (27.3%) were ineligible based on disqualifying information in their medical records; both groups were excluded. The final analytic population was 2232 (47.7%) participants with 1284 (57.5%) in intervention clinics. Baseline characteristics were balanced between groups (Table 1).

Primary Analyses

For the first primary outcome, 880 (68.8%) of 1284 participants in intervention clinics and 15 (1.4%) of 948 participants in control clinics had a documented TBI result using crude cluster-summarized proportions (Table 2; Supplementary Figure 1). Control clinics only had TST results recorded; intervention clinics had a mixture of QGIT and TST. After adjusting

Table 1. Baseline Demographics From the Teko Cluster Randomized Trial Among People Newly HIV-diagnosed Between November 2014 and May 2017 in the Dr. Kenneth Kaunda District of South Africa

Clinic level	Total N = 14	Control n = 7	Intervention n = 7
Clinics per geographic quadrant			
Klerksdorp East	3	1	2
Klerksdorp West	5	3	2
Orkney	2	1	1
Potchefstroom	4	2	2
Monthly mean (SD)[a] number of			
New HIV diagnoses	39.8 (15.2)	24 (10.7)	21 (5.9)
Tuberculosis screenings for PHIV	52.3 (22.3)	50.4 (21.5)	54.1 (24.5)
Antiretroviral initiations for PHIV	22.5 (8.4)	41.8 (16.7)	37.7 (14.6)
Median (min, max) participants per clinic	149 (59, 289)	154 (59, 196)	144 (99, 289)
Individual level	**Total N = 2232**	**Control n = 948**	**Intervention n = 1284**
Age (y)			
<20	78 (3.5%)	26 (2.7%)	52 (4.0%)
20–29	907 (40.6%)	399 (42.1%)	508 (39.6%)
30–39	715 (32.0%)	293 (30.9%)	422 (32.9%)
40–49	339 (15.2%)	138 (14.6%)	201 (15.7%)
50–59	153 (6.9%)	77 (8.1%)	76 (5.9%)
60+	40 (1.8%)	15 (1.6%)	25 (1.9%)
Sex at birth (pregnancy status)			
Male	671 (30.1%)	494 (52.1%)	646 (50.3%)
Female (not pregnant)	1058 (47.4%)	268 (28.3%)	403 (31.4%)
Female (pregnant)	421 (18.9%)	186 (19.6%)	235 (18.3%)
Female (missing pregnancy status)	82 (3.7%)	44 (4.6%)	38 (3.0%)
Median (IQR) baseline CD4[b]	337 (194, 520)	338 (199, 520)	337 (190, 521)
Missing	153 (6.8%)	112 (11.8%)	41 (3.2%)
Education			
None	63 (2.8%)	25 (2.6%)	38 (3.0%)
Grades 0–5	204 (9.1%)	95 (10.0%)	109 (8.5%)
Grades 6–11	1352 (60.6%)	543 (57.3%)	809 (63.0%)
Grade 12	561 (25.1%)	254 (26.8%)	307 (23.9%)
Degree/diploma	50 (2.2%)	30 (3.2%)	20 (1.6%)
Missing	2 (0.1%)	1 (0.1%)	1 (0.1%)
Employment status			
Unemployed	1209 (54.2%)	463 (48.8%)	746 (58.1%)
Employed, student, or retired	1020 (45.7%)	484 (51.1%)	536 (41.7%)
Missing	3 (0.1%)	1 (0.1%)	2 (0.2%)
Monthly income (Rand)			
0	1294 (58.0%)	500 (52.7%)	794 (61.8%)
1–999	186 (8.3%)	77 (8.1%)	109 (8.5%)
1000–4999	665 (29.8%)	318 (33.5%)	347 (27.0%)
5000–9999	64 (2.9%)	38 (4.0%)	26 (2.0%)
≥10 000	6 (0.3%)	3 (0.3%)	3 (0.2%)
Missing	17 (0.8%)	12 (1.3%)	5 (0.4%)

Table 1. Continued

Individual level	Total N = 2232	Control n = 948	Intervention n = 1284
Lives in house, flat, or shack	2186 (98.1%)	912 (96.2%)	1274 (99.5%)
Cohabitates with ≥ 1 other person	2032 (91.2%)	857 (90.5%)	1175 (91.7%)
Mode of transport to clinic			
On foot (≤35 min)	1106 (49.6%)	397 (41.9%)	709 (55.2%)
On foot (36–240 min)	320 (14.3%)	101 (10.7%)	219 (17.1%)
Communal (bus, taxi)	631 (28.3%)	351 (37.0%)	280 (21.8%)
Private vehicle	114 (5.1%)	56 (5.9%)	58 (4.5%)
Bicycle	20 (0.9%)	9 (0.9%)	11 (0.9%)
Missing	41 (1.8%)	34 (3.6%)	7 (0.5%)
Median (IQR) cost of transport to the clinic in Rand	0 (0, 10)	0 (0, 10)	0 (0, 0)
Weekly alcohol intake [c]			
None	1493 (66.9%)	631 (66.6%)	862 (67.1%)
Moderate	652 (29.2%)	269 (28.4%)	383 (29.8%)
Heavy	78 (3.5%)	43 (4.5%)	35 (2.7%)
Missing	9 (0.4%)	5 (0.5%)	4 (0.3%)
≥1 comorbidity [d]	290 (13.0%)	135 (14.2%)	155 (12.1%)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; PHIV, people with HIV; SD, standard deviation.

[a]Each clinic's statistics were averaged from August 2013 to January 2014.

[b]Assay completed closest to enrollment, within ± 30 days

[c]For people assigned male at birth, 1–13 weekly drinks is moderate and ≥14 is heavy. For people assigned female at birth, 1–6 weekly drinks is moderate and ≥ 7 is heavy.

[d]Diabetes, cardiovascular disease, high blood pressure, epilepsy, asthma, cancer, or depression.

for imbalances in baseline covariates between arms, there was a cluster-summarized difference of 59.6% (95% CI, 50.9–68.3) more participants with documented TBI results in intervention than control clinics. The cluster-summarized, adjusted relative risk was 40.0 (95% CI, 15.8–101.1) times higher in intervention clinics than control clinics. Fidelity to the intervention is reported in Supplementary Figure 2a. In intervention clinics, 1253 (97.6%) of 1284 participants gave blood for QGIT at enrollment, and results were documented within a median of 6 days (interquartile range [IQR]: 3–8) later. In comparison, TSTs in control clinics were applied a median of 19 (IQR: 12–55) days after enrollment, and results occurred within the standard 48- to 72-hour postapplication timeframe.

Among 1007 patients with evidence of initiating a TBI test, 369 (38.4%) were positive, 478 (47.5%) were negative, 48 (4.8%) were indeterminate, and 112 (11.1%) were missing documentation of a result (Table 3). The empirical CV for a documented TBI result in control clinics could not be reliably calculated because of the small number of outcomes.

For the second primary outcome, 516 (45.5%) of 1284 participants in intervention clinics and 271 (30.2%) of 948 in control clinics had a documented TPT prescription, based on crude cluster-summarized proportions. After adjusting for imbalances in covariates between arms, this was a cluster-summarized difference of 12.1% (95% CI, −6.4 to 30.6) more participants having a documented TPT prescription in intervention than control clinics. The proportion of participants with a documented TPT prescription remained relatively consistent over time in each arm, with little within-clinic variation (Supplementary Figure 2b). Among participants prescribed TPT, the median time from enrollment to prescription was shorter in intervention clinics (29 days; IQR: 6–89) than control clinics (54 days; IQR: 16–155). The CV for documented TPT prescriptions was 0.431 in the control arm. *P* values from rank-sum tests were consistent with the unpaired *t*-tests for both primary outcomes (Supplementary Table 1).

Within-arm TPT prescriptions were similar between participants with positive and negative TBI results. TPT was more commonly prescribed to participants with either a positive or negative TBI result (vs participants with a missing result, indeterminate result, or no TBI test documented). For example, in intervention clinics, 145 (39.8%) of 364 TBI-positive and 206 (44.0%) of 468 TBI-negative participants had TPT documented versus 165 (36.5%) of 452 participants with a missing result, indeterminate result, or no TBI test. Among 421 pregnant women, 206 (48.9%) had a documented TPT prescription (Supplementary Table 2), with the proportion being greater in intervention than control clinics (142 of 235 [60.4%] vs 64 of 186 [34.0%]). Based on the 2015 national guidelines, 67 participants would have been ineligible to receive TPT because of their CD4 count, ART status, and being TBI negative; yet 16 (23.9%) were still prescribed TPT. Post hoc analytical results are in the supplementary materials (Supplementary Tables 3 and 4).

DISCUSSION

In this trial among people newly diagnosed with HIV, the addition of QGIT to routine CD4 bloodwork resulted in 59.6% more TBI results and 12.1% more TPT prescriptions, compared

Table 2. Crude and Adjusted Cluster-level Estimates of the Proportion of Participants With a Documented TBI Test Result and a TPT Prescription From the Teko Cluster Randomized Trial Among People Newly HIV-diagnosed Between November 2014 and May 2017 in the Dr. Kenneth Kaunda District of South Africa (N = 2232)

Arm And Clinic ID	Cluster Size (N)	Outcomes (n)	%[a]	Unadjusted Cluster-Level Summaries (95% CI)	Adjusted[b] Cluster-Level Summaries (95% CI)
TBI test result documented					
TST (control)					
C	59	0	0.00	…	…
E	104	3	2.88	…	…
F	170	6	3.53	…	…
G	100	0	0.00	…	…
K	196	0	0.00	…	…
M	165	4	2.42	…	…
N	154	2	1.30	…	…
Total	948	15	…	1.45%	…
Median time to event (IQR)	…	…	…	21 d (14–61)	…
QGIT (intervention)					
A	142	95	66.90	…	…
B	139	106	76.26	…	…
D	265	162	61.13	…	…
H	144	80	55.56	…	…
I	99	73	73.74	…	…
J	206	156	75.73	…	…
L	289	208	71.97	…	…
Total	1284	880	…	68.76%	…
Median time to event (IQR)	…	…	…	6 d (3–8)	…
…	…		Risk Difference	67.3 (60.7–73.9)	59.6 (50.9–68.3)
…	…	…	Risk Ratio	47.4 (20.8–108.0)	40.0 (15.8–101.1)
TPT prescription documented					
TST (control)					
C	59	22	37.29	…	…
E	104	40	38.46	…	…
F	170	65	38.24	…	…
G	100	21	21.00	…	…
K	196	18	9.18	…	…
M	165	29	17.58	…	…
N	154	76	49.3%	…	…
Total	948	271	…	30.16%	…
Median time to event (IQR)	…	…	…	54 d (16–155)	…
QGIT (intervention)					
A	142	82	57.75	…	…
B	139	68	48.92	…	…
D	265	49	18.49	…	…
H	144	71	49.31	…	…
I	99	78	78.79	…	…
J	206	50	24.27	…	…
L	289	118	40.83	…	…
Total	1284	516	…	45.48%	…
Median time to event (IQR)	…	…	…	29 d (6–89)	…
…	…		Risk Difference	15.3 (−5.2 to 35.8)	12.1 (−6.4 to 30.6)
…	…	…	Risk Ratio	1.5 (0.9–2.6)	1.4 (0.8–2.2)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; ID, identification; IQR, interquartile range; TBI, tuberculosis infection; TPT, tuberculin preventive therapy; TST, tuberculin skin test; QGIT, QuantiFERON Gold in-Tube.

[a]For a cluster-level summary, also known as a cluster-summarized proportion, each cluster calculates their cluster-specific proportion with the outcome (eg, in clinic A, there were 95 [66.9%] of 142 participants with a documented TBI test). Then, the average of those cluster-level proportions is calculated by summing and dividing by the number of clinics.

[b]Adjusted for the following self-reported variables measured at baseline: age, sex assigned at birth, pregnancy status, CD4 count, highest education attained, employment status, income, homelessness, cohabitation with others, mode of transport to clinic, cost of transport to clinic, weekly alcohol intake, and presence of comorbidities (ie, diabetes, cardiovascular disease, high blood pressure, epilepsy, asthma, cancer, or depression).

Table 3. The TPT Cascade of Care Includes Initiation of a TBI Test, Documentation of Test Results, and Prescription of TPT[a]

	Overall	Control	Intervention
TBI Tests Initiated (not necessarily finished)			
Any Test (TST or QGIT)	1007 (45.1%)	58 (6.1%)	949 (73.9%)[b]
Positive	369 (36.6%)	5 (8.6%)	364 (38.4%)
Negative	478 (47.5%)	10 (17.2%)	468 (49.3%)
Indeterminate	48 (4.8%)	0 (0%)	48 (5.1%)
Missing result[c]	112 (11.1%)	43 (74.1%)	69 (7.3%)
TST	138 (6.2%)	58 (6.1%)	80 (6.2%)
Positive	14 (10.1%)	5 (8.6%)	9 (11.2%)
Negative	35 (25.4%)	10 (17.2%)	25 (31.2%)
Missing result	89 (64.5%)	43 (74.1%)	46 (57.5)
QGIT	921 (41.3%)	0 (0%)	921 (71.7%)
Positive	—	—	362 (39.3%)
Negative	—	—	462 (50.2%)
Indeterminate	—	—	48 (5.2%)
Missing result	—	—	49 (5.3%)
Proportion with Documented TPT Prescription			
Among the TBI Positive	150 (40.6%)	5 (100.0%)	145 (39.8%)
Among the TBI Negative	214 (44.8%)	8 (80.0%)	206 (44.0%)
Among those with a TBI test not done, missing, or indeterminate	423 (30.5%)	258 (27.6%)	165 (36.5%)

Data from the Teko cluster randomized trial among people newly HIV-diagnosed between November 2014 and May 2017 in the Dr. Kenneth Kaunda District of South Africa (N = 2232).

Abbreviations: HIV, human immunodeficiency virus; TBI, tuberculosis infection; TST, tuberculin skin test; QGIT, QuantiFERON Gold in-Tube.

[a]Reported numbers are crude proportions without cluster adjustment.

[b]Of 880 participants with TBI results in intervention clinics, 846 (96.1%) had QGIT only, 8 (0.9%) had TST only, and 26 (3.0%) had both TST and QGIT results.

[c]Patients with documentation that a TST was placed or a blood draw occurred for QGIT testing, but there was no documentation of a result.

to control clinics. Intervention clinics implemented QGIT with moderate fidelity (68.8% with TBI results), whereas TBI results were rare (1.5%) in control clinics. TPT prescriptions occurred more quickly in intervention clinics (29 vs 54 days after enrollment). The timeframe of 29 days in intervention clinics suggests that clinicians prescribed TPT at patients' first regular monthly HIV visit. These results provide evidence that clinicians could feasibly incorporate QGIT into routine HIV care. This study, from a middle-income country, both extends the generalizability of and supports a previous systematic review, which found that QGIT (vs TST) promoted TBI testing in a high-income setting [25]. Our data go beyond this by also demonstrating a trend toward increased TPT prescribing in intervention clinics.

In addition to QGIT results themselves, the *presence* of QGIT testing in intervention clinics may have motivated clinicians to prescribe TPT. This is partially demonstrated by the mismatch between QGIT fidelity and TPT prescriptions over time. TPT generally peaked mid-trial, whereas QGIT peaked at the start and end. The latter pattern may reflect a "fresh start" effect (ie, higher motivation at landmark times). Additionally, for patients without documented TBI results, TPT prescriptions were more common in intervention than control clinics (36.5% vs 27.6%). We did not conduct formal interviews with clinicians, but posit that, alongside feeling more confident prescribing TPT to patients with QGIT results, the presence of QGIT tubes or results in the medical records generally may have cued clinicians to prescribe TPT [26].

Although these are promising results, South Africa has since updated its clinical guidelines and an updated version of QGIT (QFT-Plus) was released. Since April 2018, the National Department of Health recommends "universal TPT" for all PHIV—eliminating the need for TBI testing before TPT initiation. This change aimed to overcome country-specific hurdles to TPT [14, 27, 28] and was supported by a systematic review showing TPT benefits for all PHIV on ART regardless of TBI status in high TB-burden settings [5]. Further research is needed to understand whether TPT with documentation of TBI leads to greater acceptance of TPT among patients and clinicians compared to a universal TPT approach supplemented by targeted universal TB testing [28, 29].

For countries still requiring TST before TPT, however, our study provides valuable evidence that integrating IGRAs into routine HIV care is a feasible, effective alternative. At least 1 study suggests that, in high-burden settings, the majority (~70%) of new TB cases stem from people infected in the prior 2 years [30]. Routine IGRAs (eg, linking QFT-Plus to annual viral load testing) may enable more targeted, and potentially more efficient, TPT programming in regions with TBI testing requirements. Although IGRA-directed TPT may be more costly than universal TPT, especially in high-burden settings, recent trends would likely improve its cost-effectiveness [31]. These trends include the evidence provided by this study that IGRAs can encourage TPT, the declining cost–benefit of universal TPT resulting from decreases in TB incidence among PHIV on ART, and higher costs of newer, shorter TPT regimens.

This trial has several limitations. First, our sample size calculations assumed a between-clinic CV of 0.25, but the observed post hoc CV for the TPT outcome was higher. Second, because of the limited pharmaceutical records available to us, we could not control our estimates for TST and TPT stockouts. However, such stockouts were a reality and a key motivator to exploring an alternative TBI test. Additionally, the observed substandard implementation of TST may have been due to clinicians not placing TSTs and that two-thirds of TSTs placed never had results recorded. Fourth, our trial was designed to reflect how clinicians might interact with IGRAs during HIV care (ie, blood draw and result interpretation) but also provided supplies, transport, and laboratory processing of QGIT samples. Although South Africa has substantial existing capacity to process biological samples, our results may not be generalizable to regions without similar infrastructure or financial resources. Last, the reporting of these results was substantially delayed because of the severe acute respiratory syndrome coronavirus 2 pandemic and subsequent repercussions on professional and personal lives.

In summary, integrating QGIT into routine HIV care increased the number and speed of TBI tests performed and TPT prescriptions made in a trial among 14 clinics in South Africa. Though the country has since moved to "universal TPT," these findings apply to settings still using TST before TPT where, our results suggest, integrating QGIT into scheduled blood draws for PHIV may help prevent TB.

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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Data availability. The deidentified dataset and data dictionary pertinent to the results reported in this article will be available upon reasonable request. Additional documents (ie, informed consent form and analytic code) may also be shared. The study protocol is included in this article as supplemental material. Data will be available beginning 3 months and ending 5 years following article publication. Researchers may request access via a proposal that outlines their motivation, scope of use, and a sound analytical methodology. Acceptable scopes of purpose include meta-analyses and verification of the analyses presented in this paper. Proposals will be reviewed and approved by an independent review committee identified by the authorship team. Researchers whose proposals have been approved will need to sign a data access agreement and other relevant paperwork, after which a transfer will occur via a secured link. Proposals can be directed to jgolub@jhmi.edu.

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