Point-of-care HIV viral load testing combined with task shifting to improve treatment outcomes: an open-label non-inferiority randomized controlled trial to Simplify HIV TREAtment and Monitoring (STREAM Study)

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Summary

Background Monitoring HIV treatment with laboratory testing introduces delays for providing appropriate care in resource-limited settings. The study aim was to determine whether point-of-care HIV viral load testing with task shifting changed treatment and care outcomes for adults on antiretroviral therapy (ART).

Methods We enrolled HIV-positive adults six months after ART initiation and randomized them to receive either point-of-care viral load testing (Xpert® HIV-1 viral load, Cepheid) with task shifting to enrolled nurses (intervention arm) or laboratory viral load testing (standard-of-care arm) at a public clinic in Durban, South Africa from February 2017 to October 2018 (NCT03066128). HIV care followed South African guidelines and HIV viral load testing was conducted at enrollment and after six months. In the intervention arm, clinically stable participants with a suppressed viral load were seen and had ART issued by an enrolled nurse rather than the standard professional nurse. The primary outcome combined viral suppression (<200 copies per mL) and retention at 12 months post-enrollment. We also evaluated switching to second-line ART and referral into community-based ART delivery programs.

Findings Among 390 people enrolled (195 per arm), 175 (89·7%) intervention and 148 (75·9%) standard-of-care participants achieved the primary outcome of retention with viral suppression, a difference of +13·9% (95% CI: 6·4-21·2; p<0·0040). Examining components of the primary outcome, in the intervention arm viral suppression was 10·3% higher (93·3% vs 83·1%; p=0·0025), and retention in care was 7·7% higher (92·3% vs 84·6%; p=0·026). During the study, 99·8% of intervention participants received their viral load result, 99·0% on the same day, while 81·5% of standard-of-care participants received viral load results a median of 28 [IQR 28-53] days after blood draw. In the intervention arm, time to second-line ART initiation for treatment failure (sustained viral load >1,000 copies per mL) was 76 days shorter. There were no adverse events related to point-of-care HIV viral load testing or task shifting care.

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Interpretation Point-of-care viral load testing combined with task shifting significantly improved viral suppression and retention in HIV care. Point-of-care testing can simplify treatment and improve outcomes for HIV-positive adults receiving ART in resource-limited settings.

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Research in context

Evidence before this study

On May 30, 2019, we searched PubMed for studies assessing the outcomes of point-of-care HIV viral load testing in people living with HIV receiving antiretroviral therapy. We used the search terms "point-of-care," "viral load," and "HIV," without language restrictions, and did not find any randomized controlled trials or implementation science studies. Therefore, we are not aware of any published data to evaluate the clinical effectiveness or impact of point-of-care HIV viral load testing, as compared to standard laboratory viral load testing, for improving treatment monitoring for HIV-positive adults on antiretroviral therapy.

Added value of this study

To our knowledge, this is the first randomized controlled trial to evaluate the impact of point-of-care HIV viral load monitoring for people living with HIV receiving antiretroviral therapy. Overall, implementation of point-of-care HIV viral load testing, following the recommended schedule for testing in South Africa, significantly increased the outcome of retained in care with viral suppression by 13.9%, from 75.9% to 89.7%. In addition, the intervention significantly accelerated switching to second-line ART for those with treatment failure (sustained viral load >1,000 copies per mL), as well as referral into a community-based ART delivery program.

Implications of all the available evidence

Our results suggest that ensuring rapid receipt of viral load results to patients and their providers can improve HIV viral suppression and retention in care, lead to a faster switch to second-line ART for those with viral failure, and improve referral into community ART delivery programs in resource-limited settings.

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Introduction

Over half of the 37 million people living with HIV are accessing antiretroviral therapy (ART), which has significantly reduced AIDS-related deaths worldwide.[1] The goal of ART is to maintain viral suppression, which restores immunological function, reduces transmission, and improves patient-centered outcomes. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has set an ambitious target for 90% of people receiving ART to achieve viral suppression by 2020.[2] Globally, less than half of all HIV-positive people have achieved viral suppression, and ART coverage and HIV treatment outcomes have large regional disparities, particularly in low- and middle-income countries.[1]

The World Health Organization (WHO) recommends monitoring ART with routine HIV viral load testing.[3] Patients with HIV viremia should receive prompt adherence counselling and potential switching to second-line ART, while those with viral suppression may be candidates for differentiated care through task shifting to other healthcare workers or community-based ART delivery programs. These programs aim to increase health system efficiencies and improve patient-centered care, and are facilitated by availability of viral load monitoring.[4] The WHO estimates the annual demand for viral load tests will increase from 10·7 million in 2016 to 28·5 million in 2021,[5] but scaling up viral load testing has been limited by infrastructure and human resources.[6-8] Even where laboratory viral load testing is available, such as in South Africa, some patients do not receive their results in a timely manner, which can lead to emergence of drug resistance, risk of ongoing transmission, and excess morbidity and mortality.[9]

Diagnostic point-of-care tests have rapidly emerged worldwide.[10] The Xpert® HIV-1 viral load assay (Cepheid, Sunnyvale, CA, US) requires one milliliter of plasma to provide a quantitative result (40-10 million copies per mL) in less than two hours and has received both European and WHO regulatory approvals.[11,12] The assay is performed on an automated molecular GeneXpert® platform, which is widely used for diagnosing tuberculosis.[12] We demonstrated good accuracy of Xpert® HIV-1 viral load when performed in a South African clinic,[13] but there have been no studies demonstrating the effectiveness of point-of-care viral load testing to improve treatment outcomes. Furthermore, while ART is mainly provided by professional nurses in primary care clinics, there may be a role for 'task shifting' of ART provision to less well trained healthcare

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workers such as enrolled nurses.

Therefore, we compared point-of-care Xpert® HIV-1 viral load testing with same-day counseling and task shifting to enrolled nurses against standard-of-care laboratory viral load testing for achieving viral suppression and retention in care for HIV-positive adults receiving ART.

Methods

Trial Oversight and Participants

We conducted the STREAM (Simplifying HIV TREAtment and Monitoring) Study as a single site, open-label, two arm, non-inferiority randomized controlled trial in Durban, South Africa from February 2017 to October 2018. Details of the research protocol have been published.[14] The study received ethical approval from the University of KwaZulu-Natal (BFC296/16) and University of Washington (STUDY00001466), and was registered with ClinicalTrials.gov as number NCT03066128 on February 22, 2017.

The study site was the CAPRISA Ethekwini Clinical Research Site and the neighbouring Prince Cyril Zulu Clinic, a large urban public clinic that provides HIV and primary care services for a diverse, mobile population of more than 10,000 patients. Eligible study participants were HIV-positive adults aged ≥18 years who presented for their first routine HIV viral load test at six months after ART initiation. We enrolled participants best suited to receive differentiated HIV care by excluding those who were pregnant, had active tuberculosis, or required acute medical care by a physician. However, if participants became pregnant or were diagnosed with tuberculosis during follow-up, they were included in the final analysis.

Randomization

After obtaining written informed consent, we randomized participants (1:1) to receive either point-of-care viral load testing with same-day counseling and task shifted care by an enrolled nurse (registered nurse in the United States), or standard-of-care laboratory-based viral load testing and care by a professional nurse (nurse practitioner in the United States). The study statistician generated an allocation sequence with random numbers using SAS 9.4 (SAS Institute Inc., Cary, NC). Sequentially numbered, sealed, opaque envelopes containing a study arm

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allocation and participant identification number were opened once an eligible, consenting participant was enrolled.

Study Procedures

At enrollment, we collected sociodemographic, medical information, and other potential risk factors for viral failure or loss to follow-up, which included the WHO Alcohol Use Disorder Identification Tool (AUDIT-C), WHO violence against women instrument (female participants only), and Patient Health Questionnaire-2 (PHQ-2) to screen for depression. All participants were followed for 12 months and received care according to South African HIV treatment guidelines, including testing for viral load and creatinine at enrolment, and viral load, creatinine, and CD4 cell count after 6 months.[15] Any participant with a viral load >1,000 copies per mL received enhanced adherence counselling and repeat viral load testing after two months. If the repeat viral load was >1,000 copies per mL, the participant was offered to switch to a standard second-line ART regimen. We performed retrospective HIV drug resistance testing at enrolment and at 12 months for all participants with a viral load >1,000 copies per mL at those time points. Participants in both arms were reimbursed 100 South African Rand (ZAR) per clinic visit, in accordance with South African research guidelines.[16]

In the intervention arm, participants with viral suppression at enrollment and no comorbidities were seen by an enrolled nurse, rather than a professional nurse. In South Africa, enrolled nurses receive two years of training and are less highly qualified than professional nurses, who have four years of training and are the standard providers of HIV care. For this trial, enrolled nurses had received the standard South African Nurse Initiated and Managed ART (NIMART) training, which covers basic HIV management, ART side effects, adherence counseling, and appropriate referral systems.[17] At routine clinical visits, enrolled nurses performed vital signs, screened for tuberculosis, assessed adherence by asking about missing one or more ART doses in last four days, and issued pre-dispensed ART packages. If enrolled nurses detected clinical symptoms or abnormal vital signs, then a participant was referred up to a professional nurse for more comprehensive clinical management. All routine testing in the intervention arm was performed onsite using point-of-care Xpert® HIV-1 viral load, Statsensor® Xpress-I (Nova

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Biomedical, Waltham, MA, US) for creatinine, and Pima™ (Alere, Waltham, MA, US) for CD4 cell count. Participants were asked to wait in the clinic for the point-of-care test results, and waiting times were minimized by initiating point-of-care testing at the start of the clinical visit. Therefore, the intention was to deliver results to the participants on the same day and during the same clinical visit.

In the standard-of-care arm, participants were seen by a professional nurse, who had also received NIMART training. The nurse performed the same procedures, but sent all blood specimens to the routine National Health Laboratory Service for viral load testing using m2000 RealTime (Abbott, Chicago, IL, US). In accordance with standard practice in the South African health care system, participants were expected to receive their viral loads at their next clinical visit, which is scheduled at the clinicians discretion and typically occurs after four weeks (28 days) or eight weeks (56 days).

Based on South African policy, the study clinic participated in a program for clinically stable participants to collect ART at community pick-up points, such as private pharmacies and community-based organizations.[18] Participants in both arms were eligible for referral into the program if they were non-pregnant, clinically stable, both their enrolment and month 6 viral loads were <40 copies per mL and CD4 count >200 cells per µL. Once referred, participants collected ART every two months at community pick-up points and were reviewed at the clinic by a professional nurse after six months. All blood testing occurred at the clinic. Participants not eligible for community-based ART delivery continued with bi-monthly clinical visits. Any participant more than two weeks late for a scheduled clinic or community pick-up point visit received one phone call from the clinical team and resumed ART collection at the clinic, per South African guidelines.[14]

Study Outcomes

The primary outcome was a composite measure of retention in care with viral suppression (<200 copies per mL) after 12 months. We used this composite because both components are necessary to achieve positive treatment outcomes for HIV-positive adults. “Retained in care” was defined as collecting ART at the study clinic or a community pick-up point between 44-56 weeks

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after enrollment. Participants not retained in care at 56 weeks were defined as not retained in care, and were then tracked by the study team up to 60 weeks for viral load testing. All viral load testing for the primary outcome was performed using a laboratory-based Cobas 6800/8800 machine (Roche, Basel, Switzerland).

Several *a priori* secondary outcomes detailed in the study protocol[14] included: viral suppression using thresholds of 1,000 and 50 copies per mL; viral suppression and retention at any clinic; presence of HIV drug resistance mutations among participants with viremia at study exit. We used laboratory and clinical records to assess the timing of viral load test results available in health information systems, when test results were communicated to participants, and when participants were referred into the community-based ART delivery program.

Sample Size and Statistical Analysis

The study sample size was determined using a non-inferiority hypothesis for the intervention arm compared to the control arm, assuming 80% of adults in the control arm would be retained with viral suppression at 12 months. Using a non-inferiority margin of -10%, 390 participants were sufficient to provide 80% power to rule out a decrease of 10%, based on a one-sided 95% confidence interval. If non-inferiority was successfully demonstrated, we planned to assess superiority, as stated in the study protocol.[14] We recorded all clinical data using standardized electronic case report forms in the iDataFax system (DF/Net Research Inc., Seattle, USA). All data entry underwent three stages of quality control including immediate source document review, internal quality audits, and weekly quality reports.

The primary analysis was intention-to-treat among the population enrolled in the study and compared the proportions who achieved the composite primary outcome by estimating the absolute risk difference between the intervention and control arms. Non-inferiority of the intervention arm was defined as the one-sided 95% Newcombe-Wilson score confidence interval for the difference in proportions to exclude a non-inferiority margin of -10%.[19,20] Superiority was assessed with Fisher's exact test, and two-sided 95% confidence intervals were generated for the difference in proportions. We separately compared each component of the primary outcome by arm, as well as secondary binary outcomes, using the same methods. For time-to-event

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outcomes, we compared arms using hazard ratios (HRs) generated from Cox proportional models, except where differences were so extreme that all events in the intervention arm occurred before all events in the control arm, resulting in perfect separation of events. We could not compute a HR in such cases and report a log-rank test p-value instead. We used Kaplan-Meier curves to estimate time to referral into the community-based ART delivery program for each study arm. We compared health care utilization variables using Fisher's exact test and t-tests where appropriate. We conducted all analyses using SAS 9.4.

Role of the funding source

Cepheid Inc. loaned the GeneXpert® instruments for this study at no cost. Cepheid and the funder of the study had no role in the study design, data collection, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit the study results for publication.

Results

Study Participants

Between 24th February 2017 and 23rd August 2017 we screened 657 participants, of whom 267 were ineligible or chose not to enroll, and 390 were enrolled, randomized and evaluated for the primary outcome (Fig 1 and Supplementary Table 1). The median age was 32 years [interquartile range (IQR) 27-38] and 235 (60%) were female (Table 1). Most participants earned less than 4,000 South African Rand (USD ~$280) per month, took public transportation to the clinic, and estimated their travel distance and time to be more than five kilometers, but less than 60 minutes.

Among this cohort of participants enrolled six months after ART initiation, 123 (32%) had been diagnosed HIV-positive at least 12 months earlier, and 18 (5%) reported receiving ART before initiation of the current regimen. The median CD4 cell count was 366 [IQR 204-546] cells per µL at ART initiation, and 468 [IQR 309-666] cells per µL at study enrollment. Of the 18 participants with unsuppressed viral load (>1,000 copies per mL) at enrollment, 14 (78%) had evidence of any HIV drug resistance mutations. Sociodemographic, psychosocial, and clinical

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measures were similar between the two study arms.

Study Outcomes

After 12 months of clinical follow-up, 175 (89.7%) participants in the intervention arm and 148 (75·9%) in the standard-of-care arm were retained in care with viral suppression, a difference of 13·9% (95% CI 6·4-21·2, p<0·0040) (Table 2). Each component of the primary outcome was higher in the intervention arm than the standard-of-care arm: 10·3% higher rate of viral suppression (93·3% vs 83·1%, p=0·0025), and 7·7% higher rate of retention (92·3% vs 84·6%, p=0·026). There were no adverse events related to point-of-care HIV viral load testing or task shifting care.

We evaluated several secondary study end points. All secondary outcomes, using higher and lower viral load thresholds, and including retention in any clinic, showed improvements for point-of-care viral load testing with task shifting versus standard-of-care (Table 2). When the composite outcome included retention in care at any clinic (i.e. not just the Prince Cyril Zulu Clinic), which had less certainty, point-of-care viral load testing increased retention and viral suppression by 12·3%, from 78·5% to 90·8% (p=0·0011). When evaluating the composite outcome with the WHO viral load threshold of <1,000 copies per mL, or a more strict threshold of <50 copies per mL, the intervention group had 12·3% and 14·4% improvements in retention with viral suppression, respectively. When comparing each individual measure of HIV viral load <1,000 copies per mL or viral load <50 copies per mL, the intervention point-of-care viral load testing group had significantly higher rates of viral suppression. When restricted to those with a viral load result at study exit, the intervention had increased the proportion with viral suppression (<200 copies per mL) by 5·3%, from 91·0% to 96·3% (p=0.051). Reasons for not being retained in care are presented in Supplementary Table 2.

Communicating Viral Load Results to Participants

All 398 point-of-care viral load results except one were entered into the health information system on the same day, whereas laboratory-based results were entered into the record and available to clinicians a median of two days [IQR 1-4] after blood draw (Table 3).

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Overall, 397 of 398 (99·8%) point-of-care viral load results were communicated to participants by their provider, compared to 304 of 373 (81·5%) in the standard-of-care arm, an improvement of 18·3% (p<0·0001). Almost all (99·0%) point-of-care viral load results were communicated to participants on the same day; three participants received their result the next day and one received a result 7 days later. Laboratory-based viral load results were communicated at the participant's next clinical visit which was a median of 28 [IQR 28-54] days after the blood draw.

Follow-up HIV Treatment and Care

During the study, seven participants in the intervention arm and nine in the standard-of-care arm developed viral failure, defined as two consecutive viral loads >1,000 copies per mL. Among these, the intervention improved the median time to detection of viral failure from 123 [IQR 98-162] days to 55 [IQR 55-57] days. Of those with viral failure, six participants in the intervention arm were appropriately switched to second-line ART; three participants were switched on the same day and two participants were switched within one week. Among nine participants in the standard-of-care arm with viral failure, four (44%) were appropriately switched to second-line ART, a median of 76 days [IQR 20-134] after the second confirmatory viral load blood draw.

At study end, five participants in the intervention arm and seven participants in the standard-of-care arm had presence of any HIV drug resistance mutations. Overall, during the course of the study participants in the intervention arm had fewer total clinic visits and more visits with an enrolled nurse (p<0·0001; Supplemental Table 3).

Referral for Community-based ART Delivery Program

Patients were eligible for referral into the community ART delivery program if they met certain criteria, including a suppressed viral load, after 6 months of study enrollment, which was 12 months after ART initiation. Overall, 116 (59·5%) participants in the intervention arm and 52 (26·7%) in the standard-of-care arm were referred into the community-based ART delivery program, an increase of 32·8% (95% CI 23·2-41·6) (Table 2). Among those referred into the community-based ART delivery program, the time to referral for the intervention arm was 168

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days [IQR 168-175] and for the standard-of-care arm was 261 days [IQR 231-281] (Table 3). Overall, participants in the intervention arm had a 3·5-fold (95% CI 2·5-4·8) higher probability of referral into the community-based ART delivery program (Figure 2).

Discussion

In this randomized controlled trial that followed South African treatment and monitoring guidelines, point-of-care HIV viral load testing combined with task shifting to enrolled nurses improved viral suppression and retention in care for HIV-positive adults receiving ART. These gains were achieved in part by ensuring rapid turnaround of viral load results, which facilitated same day adherence counseling and led to a faster identification of viral failure and subsequent switch to second-line ART. Viral failure was identified significantly earlier in the intervention arm due to the cumulative delays for acting upon both the original and confirmatory laboratory viral load tests in the standard-of-care arm. In addition, point-of-care HIV viral load testing and task shifting allowed earlier identification of participants with viral suppression on the same day as their six month viral load was drawn. This meant they could be rapidly referred into differentiated care through the community-based ART delivery program. In interviews and focus groups, participants and healthcare workers from STREAM reported that point-of-care testing and task-shifting was acceptable. In settings where patient follow-up and HIV treatment outcomes remain suboptimal, using point-of-care viral load testing with task shifting could accelerate reaching the global UNAIDS target of 90% of people on ART achieving viral suppression.

Additional clinical trials are evaluating point-of-care HIV viral load testing, but have not yet reported results. Studies in Haiti and Uganda are evaluating HIV testing and outcomes in children, adolescents and adults.[21,22] Another South African study is comparing point-of-care to laboratory-based testing for the difference in the time to adherence counseling and resistance testing.[23] A clinical trial of HIV-positive adults in Nigeria is evaluating on-site Xpert® HIV-1 viral load testing for achieving viral suppression (<1,000 copies per mL) at one year after ART initiation.[24] Results from most of these trials are expected later this year.

We used the Cepheid Xpert® HIV-1 viral load test in our study, which has high diagnostic accuracy,[25] and there are other point-of-care HIV viral load platforms.[26,27] The SAMBA I/II semi-Q

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(Diagnostics for the Real World Ltd., Cambridge, UK) can be performed in 90 minutes on plasma or whole blood and has a lower limit of quantification of 1,000 copies per mL.[28] The m-PIMA, formerly Alere Q NAT, (Abbott, Chicago, IL, US) can complete testing in 70 minutes on plasma, and is currently the only point-of-care viral load test for both HIV-1 and HIV-2.[29]

Our study had several strengths and limitations. Point-of-care viral load testing and associated clinical care was performed by the research team, which may not always reflect implementation in routine clinical services. Study reimbursements may have increased retention in care, but we provided the same incentives for participants in both study arms to minimize differences. The study was designed as an open-label clinical trial, and research implementers were blinded to data by study arms. Study enrollment occurred at six months after ART initiation to coincide with the first viral load test in the routine South African ART monitoring schedule. Therefore, our results may not be generalizable to all patients initiating ART as they do not account for persons who default early in their HIV care. These people will require additional interventions to ensure retention until they are due their first viral load test. In addition, as our intervention contained two components, we cannot be certain to what extent point-of-care testing, or task shifting to enrolled nurses was responsible for the improved clinical outcomes. Finally, the study was conducted at a single clinical site serving an urban population of HIV-positive adults in South Africa, and additional studies may be necessary to determine achievable outcomes in other clinics or countries. Further assessment of the impact on quality of life, wider health systems costs, and cost-effectiveness is also warranted.

In conclusion, point-of-care HIV viral load testing combined with task shifting improved treatment outcomes in an urban clinic in South Africa. To accommodate the rapid expansion of ART, efficient methods to monitor HIV-positive people on ART will be required in resource-limited settings. These innovative models of HIV care may only be sustainable if they do not increase the existing burden on HIV care providers, laboratories, and health systems. By improving and expediting delivery of viral load results to patients and their care providers, HIV treatment programs may use point-of-care testing for reducing barriers to achieve viral suppression.

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Contributors

PKD and NG conceived the trial and are the Co-Principal Investigators. PKD, NG, JD, JQA, KT, NS, HN, KM, PM, RVB, KN, SAK and CC designed the study. NG, JD, PKD, NS, JQA, LV, HN, KM, PM, KN and SAK implemented the study and acquired the data. KT, LV and DD performed the statistical analysis. All authors critically revised the manuscript and consented to final publication.

Declaration of interests

Dr. Paul Drain reports receiving consulting or speaking fees from Gilead Science, and research support from the NIH, CDC, Gilead Sciences, and the Bill and Melinda Gates Foundation, during the conduct of the study. Drs. Naidoo, Abdool Karim, and Donnell report grants from the NIH during the conduct of the study. Dr. Donnell also reports grants from USAID, outside of the conduct of this study. All authors declare that they have no competing interests.

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Data Sharing Statement

Data will be available beginning 12 months following article publication. Proposals for individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices), will be accepted for up to 36 months following article publication. Investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose may have access to data for individual participant data meta-analysis. After 36 months the data will be available in our university's data warehouse but without investigator support other than deposited metadata. Information regarding submitting proposals and accessing data may be found at *(link to be provided)*.

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Figure 1. CONSORT diagram for eligibility, enrollment and outcomes.

* See Supplementary Table 1 for detailed reasons for study exclusion.

Figure 2. Kaplan Meier estimates of time from study enrollment to referral into a community-based ART delivery program by intervention and standard-of-care arms.

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