Study protocol and statistical analysis plan

Antiretroviral Improvement among Medicaid Enrollees (AIMS): An Insurance-based Data to Care Initiative for Medicaid Enrollees in Virginia

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STUDY PROTOCOL AND PROCEDURES

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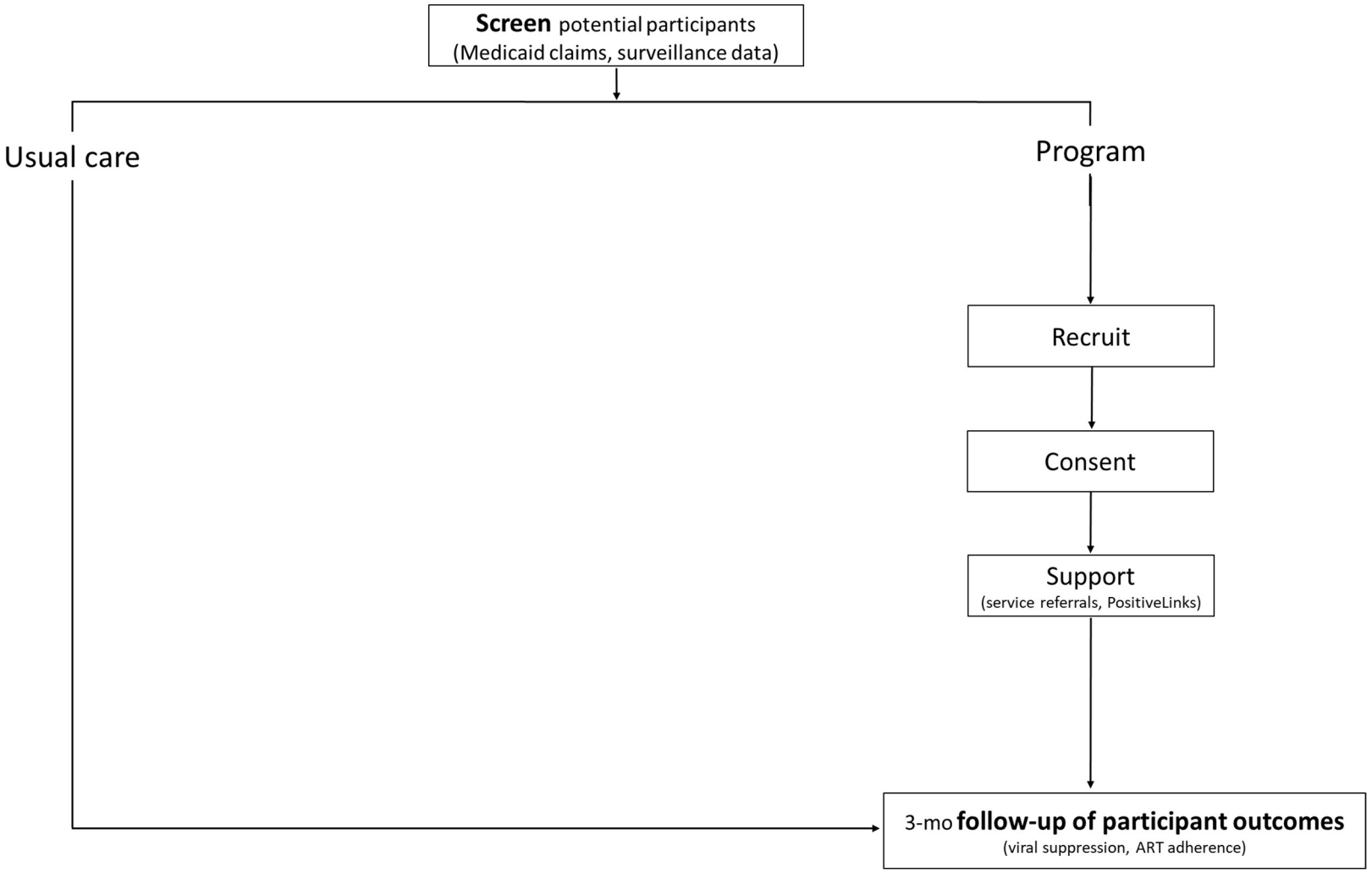
Contents

Overview

This protocol proposes to implement and evaluate Antiretroviral Improvement among Medicaid enrolleeS (AIMS), an insurance-based Data to Care initiative for evidence-based quality improvement. The initiative will involve two arms (program and usual care) and be implemented statewide among eligible Virginia Medicaid enrollees. The intervention will address barriers to prescribing or filling ART prescriptions by offering patient-level support depending on need. Patient-level support will be offered to patients who have a late ART prescription refill(s) by >30–365 days. Patient-level support will involve direct linkages and referrals, which will intensify as the gap in ART prescription(s) fills increases. For those with a late ART prescription refill(s) for a more extended period (>60–90 days), patient-level support will also involve warm health technology via PositiveLinks, a mobile app program promoting better health through self-monitoring tools, educational resources, direct messaging with program staff, and a confidential user community board (Dillingham et al. *AIDS Patient Care STDs* 2018; Laurence et al. *JMIR Form Res* 2019). The usual care arm will receive no study-related patient-level support, consistent with usual care at the state-level in Virginia.

An overview of study processes is shown in **Figure 1.** Below we discuss study procedures for the usual care and program arms, including patient-level support. We begin by briefly summarizing of screening and recruitment of eligible potential participants. We then explain the approach for each arm, including consent. We end with a description of the evaluation outcomes, analytic approach, and other analytic considerations.

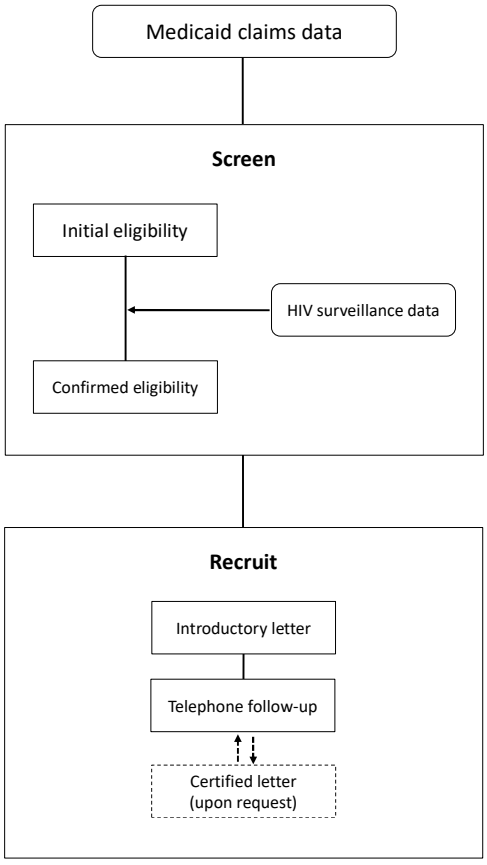
Figure 1. Overview of AIMS program evaluation study procedures



Screening

Potential participants will be identified via screening and then recruited. Screening will involve applying the selection criteria to the Medicaid claims and HIV surveillance data to identify potential participants. We will screen for potential participants given the study's goal is real-time identification of Medicaid members living with HIV and at early risk of falling out of care (as indicated by a late ART prescription refill(s)). Potential participants identified via screening will then be recruited. A simple schematic of screening and recruitment processes for potential participants is shown in **Figure 2**. Screening and recruitment will occur according to existing interagency and contractual agreements, which will collectively authorize Virginia Commonwealth University (VCU) personnel to implement and evaluate the AIMS program for evidence-based quality improvement on behalf of Virginia Medicaid.

Figure 2. Schematic of screening and recruitment for eligible potential participants



Screening will involve: 1) Initial identification of eligible potential participants using the Medicaid claims, and 2) Data integration with HIV surveillance data and confirmation of potential program participant eligibility. Screening activities will occur on a monthly basis during study enrollment, which is anticipated to be 6 months.

Initial eligibility. We will use the Medicaid claims to identify a preliminary sample of eligible potential participants. We will select from the Medicaid claims those enrollees who satisfy inclusion criteria: current enrollment in Virginia Medicaid, continuous Virginia Medicaid enrollment for >9 months, current

age 19–64 years, non-dual eligible for Medicare, identified as living with HIV according to the HIV case identification algorithm (Aim 1), and a late ART prescription refill(s) by >30–365 days in the prescription claims. 'Late ART prescription refill(s) by >30–365 days' refers to the most recent ART prescription(s) that is >30–365 days in the prescription claims after the expected date of refill or renewal.

We will exclude enrollees who have a record of third-party health insurance during the past 3 months. We will exclude enrollees who have a missing phone number and/or mailing address. We will exclude those experiencing within-class ART switches due to medication toxicity (defined as a new within-antiretroviral class ART prescription claim >30 days of the expected date of ART prescription refill or renewal). We will also exclude those enrollees experiencing ART resistance and thus switching to a new regimen (defined as a claim for an antiretroviral drug in a new ART class occurring >30 days of the expected date of ART prescription refill or renewal). We will exclude enrollees whose linked HIV provider is a provider practicing at a facility offering PositiveLinks. The study will exclude enrollees who do not have a record in Virginia's HIV surveillance data, as a record in the HIV surveillance data confirms HIV status. The study will exclude enrollees who do have a record of an ART prescription(s) in the Virginia HIV surveillance data, but did not have a record of an ART prescription(s) in the claims data, as an additional confirmatory check on study eligibility. We will exclude enrollees who do not speak English, as PositiveLinks has not been validated in languages other than English.

An initial database of eligible potential participants will be constructed and include: first and last name, social security number, complete or partial address, race/ethnicity, sex at birth, and date of birth; and expected date of ART prescription fill, refill, or renewal; and an indicator for a late ART prescription refill(s) by >30–365 days). Analysis will be conducted by authorized VCU personnel and saved on the Virginia Medicaid servers per an amendment to an existing Interagency Agreement between Virginia Medicaid and VCU.

Confirmed eligibility. The initial database of eligible potential participants will be integrated with an extract of HIV surveillance data from the Virginia Department of Health. The integrated data will be used to confirm HIV status of eligible potential participants, their current/prior ART prescription(s) from state health department program databases, and potential participant eligibility for the study. Authorized Virginia Medicaid personnel will securely transfer the initial database of eligible potential participants to the Virginia Department of Health per an existing Interagency Agreement. Data integration and potential program participant eligibility will occur on a monthly basis during the enrollment period. After data transfer, authorized VCU personnel will use deterministic and probabilistic methods to link the two databases using the following variables: first and last name, social security number, complete or partial address, race/ethnicity, sex at birth, and date of birth. We note that complete information about current or prior ART prescriptions, which we are using to confirm potential participant eligibility where possible, is not available for all Virginians living with HIV; this is because only some Virginians have accessed state programs providing antiretroviral prescriptions. Given Medicaid's comprehensive ART prescription coverage, we anticipate that Virginia Department of Health databases with ART prescription will be used primarily to ascertain if a potential participant has previously received ART prescriptions.

Recruitment

Recruitment activities for eligible potential participants will involve: 1) a mailed introductory letter to eligible potential participants, 2) follow-up phone calls and text messaging about the study, and 3) certified letters (on request). For each monthly screening of potential participants, recruitment activities will occur over approximately a two-week period. Contact information for eligible potential participants will be available in the Medicaid claims data. We emphasize that recruitment activities are designed to maintain participant privacy and confidentiality regarding HIV status (e.g., the printed introductory letter will not make specific mention of HIV). National data suggest that nearly 4 of 5 people living with HIV report feelings of any HIV-related stigma, with approximately 60% indicating that they hide their status from others and 2/3's noting that it is difficult to disclose their status (Baugher *AIDS Behavior* 2017). A recent systematic review indicates that about one-fifth of US adults living with HIV do not disclose their status to anyone, with higher rates of non-disclosure to sexual partners, family, and friends (Obermeyer *Am J Publ Health* 2011). A vast literature documents the negative consequences—including discrimination, violence, and rejection from friends, family, and employers—due to stigma and unintentional disclosure of HIV status (Obermeyer *Am J Publ Health* 2011).

We emphasize that recruitment occurs only for participants in the Program arm. Recruitment does not apply to the Usual Care arm.

Mailed introductory letter. Linkage coordinators will mail eligible potential participants a hard copy letter that introduces the study. The letter will include safeguards—including a general description about the nature of the study and general evaluation team contact information—to protect confidentiality and minimize the risk of HIV status disclosure. For example, the letter will state that the program is about adherence to prescribed medication, versus adherence to prescribed *HIV* medication. The introductory letter will include limited personal information or study-specific contact information in order to maintain confidentiality. However, the letter will include a unique ID to use during identity verification that will occur in follow-up phone conversation(s) (see below).

Follow-up phone conversations(s) and text message. Linkage coordinators will follow-up with eligible potential participants via text and phone to introduce the program. Similar to the mailed introductory letter, generalized information will initially be shared about the study to protect confidentiality and minimize the risk of HIV status disclosure. The text message will contain a link to a program-specific website with introductory text in order to describe the study and promote study credibility; website text will not reveal HIV status nor will it collect or report personally identifiable information. In order to share more detailed information about the purpose of the call, the linkage coordinator will request identity verification. Identity verification will protect eligible potential participant confidentiality by minimizing the risk that the linkage coordinator is speaking with someone other than the intended potential program participant, which could reveal HIV status through disclosure of study details. The linkage coordinator will request the unique participant ID provided on the eligible participant's introductory letter; the unique ID will serve as an initial sufficient, but not necessary, condition for identity verification. Additional required identity verification will include full name (first, middle, and last legal name) and date of birth. Identity verification aligns with existing approaches for other programs in which recruitment is program-initiated. For example, identity verification is required for Virginia in the Centers for Disease Control and Prevention (CDC)-sponsored Medical Monitoring Project, a cross-sectional, nationally representative survey on the clinical and behavioral characteristics of people diagnosed with HIV (CDC Medical Monitoring Project Protocol, 2015–2017). Up to three contact attempts will be made by phone per recruitment month. If an eligible potential participant does not

answer the phone, the linkage coordinator will leave a brief voicemail that provides a general description of the program and callback information; no information that could reveal HIV status will be included in the voicemail. Additionally, the callback number and phone number appearing on caller ID will not be linked to HIV or to the AIMS study through an online search. Eligible potential participants who are successfully contacted but prefer not to provide identity verification information will be offered a certified letter that explains the purpose of the call, provides a general description of the program, and gives study team contact information. During each recruitment month, eligible potential participants who are not successfully contacted after three phone-based attempts or who decline a certified letter will not be contacted further; up to 6 recruitment phone calls will occur across all months an eligible potential participant can enroll in the study. Up to one text message per recruitment month will occur, or up to two across all study months eligible for recruitment. Eligible potential participants who verify their identity will be asked if they are available to hear more about the study at that time, which will initiate informed consent procedures. Eligible potential participants who are unavailable upon contact will have the option to schedule a follow-up call with the linkage coordinator; calls will be scheduled at a time convenient for the eligible potential participant. All subsequent calls will require identify verification (full name and date of birth) in order to protect program participant confidentiality.

Certified letter. The linkage coordinator will offer to mail a certified letter about the study to eligible potential participants who are successfully contacted but do not verify their identity. The letter is intended to legitimize the study and personalize contact with the potential participant. The certified letter will be similar to the mailed introductory letter, although it will have the option to include some tailored language referencing a prior conversation between the eligible potential participant and the linkage coordinator. The letter will include safeguards—including a general description about the nature of the study and general study team contact information—to protect confidentiality and minimize the risk of HIV status disclosure. Eligible potential participants who are sent a certified letter will be re-contacted by the linkage coordinator according to procedures described above.

Procedures: Usual care arm

The Usual Care arm will involve an artificial control sample created through propensity score matching. No contact will occur with these individuals and they will receive no study-specific intervention, consistent with state-level care for late ART prescription refill(s) for Virginia Medicaid enrollees living with HIV in Virginia. Detail for other processes and procedures for this arm are below.

Screening. Screening for controls will occur over the month enrollment period and as described above.

Recruitment. Recruitment of eligible potential participants in the control (Usual Care arm) does not apply. No contact will occur with these individuals.

Informed consent. Informed consent procedures do not apply. Only existing, secondary health information will be used. This health information will be de-identified, with no code key available; consent and HIPAA authorization do not apply.

Follow-up. A 3-month follow-up period will begin on the first date an eligible control is confirmed as having a late ART prescription refill(s) by >30–365 days.

Procedures: Program arm

Overview. Patient-level support in the program arm seeks to improve timely filling of ART prescriptions among participants with late ART prescription refill(s) by >30–365 days. The program arm will consist of up to two phases, which will be distinguished by the barriers primarily addressed in each phase. Both phases will involve phone consultations to discuss barriers to prescription adherence. Both phases also will provide referrals to resources that address participant barriers to timely filling of ART prescriptions. However, discussion with participants whose ART prescriptions fills have been late for a more extended period (>60 days) will focus on more complex barriers to filling ART prescriptions (e.g., substance use, unstable housing) and these participants will be additionally offered PositiveLinks, a warm health technology support to promote better health for people living with HIV. The phone consultations will be delivered by a linkage coordinator.

Patient-level support in the program arm will involve: 1) Screening, recruitment of eligible potential participants, 2) Informed consent, 3) Courtesy notification letter and study information sheet for providers, 4) Program implementation, and 5) Follow-up.

Screening, recruitment, and arm assignment. Screening and recruitment will occur as described previously.

Informed consent. Informed consent procedures will be conducted verbally by the linkage coordinator and follow identity verification. Informed consent will occur via phone at a time that is convenient for the eligible potential participant. Thus, informed consent may occur immediately following identity verification or at subsequently scheduled time. The complete informed consent process will precede program implementation. Subsequent telephone contact will involve reminders that participants may withdraw from the study at any time and for any reason without penalty; they will also involve opportunity for questions.

Courtesy notification letter and information sheet for providers. A courtesy notification letter and study information sheet will be securely faxed to each participant's primary HIV provider. If attempts to fax a provider are unsuccessful, a courtesy notification letter and study information sheet will be mailed to the provider. Contact information for providers will come from the Medicaid claims, the National Provider and Plan Enumeration System (NPPES) Provider Lookup tool (https://npiregistry.cms.hhs.gov/), the Virginia Board of Medicine practitioner and license databases (https://www.vahealthprovider.com/index.asp), and/or via an online search. The letter will briefly summarize the study, indicate that the provider has one or more patients with a late ART prescription refill(s) >30–365 days, and note that the study team has contacted the participant on behalf of Virginia Medicaid. The letter is intended as a courtesy notification to providers, in line with traditional health department Data to Care program activities involving patient contact. We emphasize that names of the provider's patient participants will not be listed in the letter. The letter will be accompanied by a more detailed information sheet about the study. Courtesy notification letters and information sheets will be sent monthly during the study's enrollment period. A provider will receive up to one courtesy notification letter, regardless of the number of patient participants.

Program implementation. Patient-level support for the program arm will occur in up to two phases. These phases will be defined by the number of days an ART prescription(s) fill is late—either >30–60 days or >60 days after the expected fill date. Operationally, the phases will be distinguished by the barriers focused on during the phone consultation and the level of support offered to participants. Study

enrollment can occur in either phase. Both phases will involve phone consultations to discuss participant barriers to timely filling of ART prescriptions and referrals to resources to address these barriers. The phone consultations will be delivered by a linkage coordinator. Detailed information on each phase follows.

Phase 1. Phase 1 is for participants with late ART prescription refill(s) by >30–60 days. The phone consultation will involve a 30-minute discussion of the participant's barriers to filling their ART prescription and referrals to resources that may address these barriers. The consultation will use a conversational format guided by scripted prompts. During the consultation, the linkage coordinator will document data on each participant's self-reported barriers to filling ART prescriptions. Referrals will be made to existing resources that are already offered through the participant's Medicaid managed care organization or through pharmacists, their HIV provider, or local community resources. If a participant self-reports multiple barriers to filling ART prescriptions, the participant will be asked to prioritize the barriers; this will allow the linkage coordinator to provide referral information that aligns most closely with participant preferences. Whenever possible, the primary referral will involve a warm hand-off, where the linkage coordinator introduces the participant directly to the referral resource in real-time. This approach is designed to engage the participant and maximize success in the referral process. If a warm hand-off is not possible at the time of the consultation, a follow-up call can be scheduled to make the warm hand-off; referral contact information will be offered to the participant after 3 unsuccessful warm hand-off attempts. Participants will additionally be given contact information for referrals involving 1-2 other prioritized barriers. The referral resource, referral date, and referral time will be documented by the linkage coordinator. Approximately ten business days after the Phase 1 referral, the participant's ART prescription claims will be followed in the Medicaid claims data. The 10-business-day threshold will allow adequate time for an ART prescription fill and prescription claim reimbursement. If the participant has an ART prescription claim after this 10-business-day period, the participant will not be contacted further. If the participant has no ART prescription claim after the 10-business-day period, the participant will be eligible for Phase 2.

Phase 2. Phase 2 is for participants with late ART prescription refill(s) by >60 days. Phase 2 will involve a more intensive phone consultation, in which more complex barriers may be assessed. Three phone contact attempts will be made in the same manner as in Phase 1. Participants who do not respond to these contact attempts, who do not verify their identities, or who do not either consent to participate or assent to continue to participate will not be contacted further. The linkage coordinator will guide a 30-minute consultation similar in format to Phase 1. In Phase 2, however, more complex barriers, such as substance use and mental health concerns, will be probed and referrals made accordingly. Participants in Phase 2 will also be offered PositiveLinks, an evidence-based mobile app designed to support ART adherence and retention in care (https://www.positivelinks4ric.com/). PositiveLinks is based on theories of behavior change and provides 1) daily check-ins on mood, stress, and medication adherence, which promote self-monitoring; 2) educational resources for users; 3) direct messaging with study linkage coordinators; 4) an anonymous message board to connect with peers living with HIV to provide and receive social support; and 5) contact information for patients' providers and pharmacies. A major strength of the app is its support of self-monitoring, which addresses intrapersonal barriers to ART adherence. The app contains data security measures designed to protect patient privacy and confidentiality (e.g., phone calls to providers made through the app do not appear in the phone's call log). Further details on the app's development, user functions, and security features are available in the uploaded supporting documents. We emphasize that all study participants will be enrolled in Virginia Medicaid, and contracted Medicaid managed care organizations provide smartphones for enrollees (see

https://www.virginiamanagedcare.com/choose/compare-plans); therefore, we do not anticipate that smartphone ownership will be a barrier to participants' enrolling in PositiveLinks.

Follow-up. A 3-month follow-up period will begin on the date of the final consultation (**Table 1**).

Table 1. Start date of 3-month follow-up for participants receiving patient-level support

Phase(s) received	**Start of 3-month follow-up**
Phase 1 only	Date of final phase 1 consultation
Phase 2 only	Date of final phase 2 consultation
Phases 1 and 2	Date of final phase 2 consultation or joining of PositiveLinks*

* Most recent date will be selected; does not include direct messaging support provided via PositiveLinks.

Outcomes

Outcomes will be at the participant level. The primary outcome will be HIV viral suppression, defined as the most recent HIV RNA viral load <200 copies/mL at 3-month follow-up. In the usual care arm, 3-month follow-up will be the first date an eligible control is confirmed as having a late ART prescription refill(s) by >30–365 days; in the program arm, 3-month follow-up will be as shown in Table 1. The secondary outcomes will be adherence (defined as the proportion with ART prescription claims covering >90% of enrolled coverage days) and the number and percentage of participants reinitiating late ART prescription.

Statistical analysis

Descriptive statistics. We will evaluate the balance of demographics and other patient characteristics, as well as the measures between the 2 treatment groups (those enrolled in the Program arm, and those in the Usual Care [control] group). We will compare the means and medians of the continuous variables and test the differences between the treatment samples using t-tests and Kruskal-Wallis tests. Systemic differences between the enrolled participants enrolled and the control might introduce selection bias.

We will use propensity score methods to control for potential confounding patient or provider characteristics that may affect the acceptance to enroll in the study and, consequently, the outcome of interest (HIV viral suppression, adherence, and reinitiation). Propensity score methods help us balance the distribution of the covariates between treatment and control groups, reducing the selection bias and allowing for more accurate causal inference when assessing the impact of the treatment. Propensity scores (PS) will be calculated as the predicted probabilities of being in the treatment group. Logistic regression model predicting being in the enrolled in the study will be used. A wide range of patient (age, gender, race, Medicaid enrollment, etc.), provider (specialty), hospital and geographical (region, rurality) characteristics will be considered in the regression model. We will use the PS to match the treatment group to the control group. We will calculate the inverse probability weights (IPW) using these PS. We will evaluate the effect of the program in the PS matched samples on the binary outcomes—including HIV RNA viral load <200 copies/mL (primary outcome), adherence (secondary outcome), and reinitiation (secondary outcome)—by comparing the proportions between the Program arm and the Usual Care arm. We will use Chi-squared tests to evaluate the statistical significance of the effects of treatments on proportions. We will also use logistic regression models to test for the program effects, adjusting for all potential confounders that might affect the outcome and bias the results.

Sample size and statistical power considerations

We expect to enroll 100 participants in the Program arm. This sample size provides adequate power to detect differences in HIV viral suppression (i.e., HIV viral load <200 copies/mL), the primary outcome, across arms. Assuming a 50% rate of viral suppression in the control group, with 100 subjects in the control group, we will be able to detect a difference of .28 in the rate of viral suppression with greater than 80% power. This requires a sample size of 350 participants in each arm. However, an estimated 30% of the sample will be missing HIV viral load data (Crepaz et al. *MMWR Morb Mortal Wkly Rep* 2018). This translates into dropping the power to 70%. According to our experience with these data, and the

inclusion and Virginia Medicaid–Virginia Department of Health matching protocols, we note that no missing data are allowed.

Other data and analyses

Other data to be collected through interactions with participants include the quality improvement initiative's process data. These data will be used to track study progress and facilitate recruitment and enrollment (e.g., number and timing of contact attempts, mailing address for optional certified letter), current ART use to determine final eligibility (i.e., confirmation that the participant has not refilled their ART prescription), and barriers discussed and referrals made.

Additionally, PositiveLinks app metadata and usage data will be collected through the PositiveLinks app. App metadata include: number of app launches, number of app log ins, response rates for daily queries about medication, response rates for daily queries about mood, response rates for daily queries about stress, response rates for weekly quizzes, number of posts to community message board, number of direct messages to linkage coordinator, and number of times visiting resources section. The text of community board posts will also be collected.

Descriptive statistics will be used to summarize recruitment and enrollment, barriers endorsed, referrals made, and PositiveLinks app usage. We may examine correlates of these variables and/or consider these variables as confounders in the primary evaluation analyses. Community board posts from the PositiveLinks app will be examined using textual analysis methods.

Data management

Data management and statistical analysis will be performed using Terradata 16.10, REDCap 10.9.4, and SAS® Software version 9.4 (or most recent VCU- and agency-approved software releases available). Statistical analysis will occur at Virginia Medicaid, Virginia Department of Health, VCU, University of Virginia, and CDC. Intermediate datasets will be stored on Virginia Medicaid servers, Virginia Department of Health servers, and University of Virginia servers. Final limited and de-identified datasets will be stored at Virginia Medicaid, as well as Virginia Department of Health, and also securely transferred to VCU and CDC.