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Study Protocol(s) for Antiretroviral Improvement among Medicaid Enrollees (AIMS): A Cluster-Randomized Controlled Trial Leveraging Real-time Administrative Claims to Support Antiretroviral Prescription Adherence

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Abstract

Introduction: Retention in care and antiretroviral therapy (ART) adherence are major clinical and public health challenges in the treatment of HIV in the United States. Traditional data to care (D2C) approaches use health department surveillance data to promote retention in HIV care, with

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Declaration of Interest Statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Drs. Dillingham and Ingersoll declare that they are on the Board of Directors of Warm Health Technology (WHT). WHT disseminates a version of PositiveLinks, which is used in the AIMS study, to clinics outside Virginia. WHT is a wholly owned subsidiary of University of Virginia's Licensing and Ventures Group, a non-profit entity. Drs. Dillingham and Ingersoll do not own WHT, and they comply with University of Virginia's conflict of interest review processes and requirements. Remaining authors declare no conflicts of interest on this work.

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challenges in the timeliness of data and inconclusive findings. Earlier identification of people with HIV who are at risk of loss from care—such as when an ART prescription is not filled—represents a new direction for D2C (D2C-Rx or prescription-based D2C).

Methods: We designed the Antiretroviral Improvement among Medicaid EnrolleeS (AIMS) study, a D2C-Rx initiative in Virginia, which leveraged real-time administrative claims from Virginia Medicaid and HIV surveillance data from Virginia Department of Health (April 2023–June 2024). AIMS was a statewide cluster-randomized, controlled trial comparing a phased, multi-level program of support (intervention) to usual care, among Virginia Medicaid enrollees without current ART prescriptions. Support included a provider-level component for those with no prior ART prescription and patient-level component for those with a >30–90-day late ART prescription refill(s). We hypothesized that AIMS would increase HIV viral suppression and improve ART adherence at 12 months compared to usual care. We describe the original study protocol and discuss changes implemented to the study design and program implementation. We also consider key methodologic contributions, as well as limitations and challenges to patient- and provider-level enrollment, such as ART prescription data accuracy.

Ethics and Dissemination: This study was reviewed and approved by the Institutional Review Board of Virginia Commonwealth University (HM20018229).

Registration: The trial is registered at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05477485) (NCT05477485).

Keywords

HIV; data to care; administrative claims; adherence

INTRODUCTION

Retention in care and antiretroviral therapy (ART) adherence are among the largest clinical and public health challenges in the treatment of HIV in the United States. Regular engagement in care and medication adherence are critical to achieving viral suppression,¹ preventing morbidity and mortality,^{2,3} and preventing onward transmission of the virus.^{4,5} Despite the importance of retention in care for positive health outcomes and epidemic control, only half of those diagnosed with HIV, in the United States, are retained in care.⁶

Data to Care (D2C) is a public health strategy supporting retention in care by leveraging HIV surveillance and other data.^{7,8} States generally require that laboratory test results collected during routine HIV care, including CD4 cell count and HIV RNA viral load tests, be reported to state health departments' HIV surveillance programs. Absence of these test results, for a given individual, can indicate failure to link to care after diagnosis or loss from care. Once a person with HIV (PWH) is identified as out of care, the state health department can conduct case investigation and outreach to facilitate the individual's engaging, or re-engaging, with HIV care (Figure 1).

Early D2C findings from state health departments have been inconclusive.^{9–11} One challenge limiting traditional D2C success has been the lag time in reporting HIV viral load and CD4 test results to health departments. Earlier identification of PWH at risk of loss from care—such as when an ART prescription is not filled—represents a promising new direction

for D2C (“D2C-Rx” or prescription-based D2C, Figure 1). Unlike laboratory test results, however, ART prescription information is not routinely reported to state health departments. More complete and timely data on filled ART prescriptions are instead held by other state or federal agencies, private insurers or managed care organizations, and pharmacies, necessitating novel and complex data linkages that require cross-agency cooperation and consideration of relevant data protection laws and regulations.

We designed the Antiretroviral Improvement among Medicaid EnrolleeS (AIMS) study, an insurance-based D2C initiative in Virginia, which leverages real-time administrative claims from Virginia Medicaid and HIV surveillance data from Virginia Department of Health (VDH). The AIMS study is a statewide cluster-randomized, controlled trial comparing a phased, multi-level program of support (intervention) to usual care, among Virginia Medicaid enrollees without current ART prescriptions. Support includes a provider-level component for those with no prior ART prescription and patient-level component for those with a >30–90-day late ART prescription refill(s). While the study broadly targeted PWH with late prescription fills, the study had the potential to address two populations in particular need of support: those living in the South, where over half of new HIV diagnoses in the United States occur,¹² and those with lower socioeconomic status.^{13,14} We hypothesize that the AIMS program increases HIV viral suppression and improves ART adherence at 12 months compared to usual care. We first describe the original study protocol and subsequently discuss changes implemented to the study design and program implementation.

STUDY DESIGN AND METHODS

Selection criteria

Patient-level: We included adults 19–63 years living with HIV and enrolled in Virginia Medicaid who had a late ART prescription refill by >30–90 days (Box 1). We excluded those with coverage from other health service payers, including older adults who are insured through Medicare, and those whose claims indicated ART discontinuation due to toxicity or resistance.

Provider-level: The provider-level inclusion criterion was that their linked potential patient-participant(s) meets all selection criteria except having a late prescription; instead, the potential patient-participant has no history of a prior ART prescription. There were no provider-level exclusion criteria.

Sample selection and arm assignment

Cluster randomization of providers: Cluster randomization occurred at the provider level and concurrently with initial potential participant screening (Figure 2). For each identified Medicaid enrollee with HIV, an HIV provider was identified and linked using the National Provider Identifier (NPI) from each HIV-related service or prescription claim, provider taxonomy, and provider frequency in the enrollee’s claims. To prevent contamination across study arms, HIV providers were cluster-randomized to the program or usual care arm. Contamination could occur in cases where patients assigned to usual

care have providers who received the provider-level support (type II statistical error). Imbalance in observed and unobserved factors across study arms was minimized by stratified cluster-randomization based on provider characteristics (e.g., HIV patient volume) and patient characteristics (e.g., distribution of providers' patients by age, sex, race, ethnicity, urbanicity).

Screening: For Screening Step 1 (initial eligibility, Figure 3), we used the Virginia Medicaid claims to identify a preliminary sample of potential patient-participants, defined as current Virginia Medicaid enrollees 19–63 years with an HIV care marker (i.e., at least one claim with an HIV diagnosis code, HIV-related service code or national drug code for ART). For Screening Step 2 (confirming eligibility), HIV status of potential patient-participants was confirmed using an extract of HIV surveillance data from VDH. An additional eligibility check determined if a more recent ART prescription may have come from state health department programs (e.g., Ryan White and AIDS Drug Assistance Program). Screening occurred monthly.

Patient assignment to arm and component: Once confirmed as eligible, potential patient-participants were assigned to a study arm (program versus usual care) based on cluster randomization of their HIV provider (Figure 2). Among eligible potential patient-participants assigned to the program arm, those with a late ART prescription by >30–90 days were assigned to the patient-level support component of the program arm; those with no late ART prescription were assigned to the provider-level support component of the program arm.

Recruitment overview and materials

Sequence: Recruitment of patient-participants in the patient-level support program arm occurred after screening and assignment and throughout trial implementation. Recruitment occurred over approximately two weeks each month. Recruitment of providers for the provider-level support component followed the same timing.

Deferred recruitment, taking place after the program arm's 12-month follow-up, occurred for potential patient-participants in the usual care (control) arm and for patients of providers in the program arm.

Patient-participant recruitment procedures

Mailed introductory letters. Linkage coordinators mailed eligible potential patient-participants a hard copy letter introducing the study. The letter included safeguards—e.g., a general study description—to protect confidentiality and minimize risk of HIV status disclosure.

Follow-up phone conversations. Linkage coordinators followed up with potential patient-participants via phone to introduce the program. To protect confidentiality and minimize risk of HIV status disclosure, only generalized study information was shared before the linkage coordinator requested identity verification (full legal name, date of birth).¹⁵ Up to three contact attempts were made by phone within the month. If the potential patient-participant

was eligible for the study in a subsequent month, an additional three phone-based contact attempts were made. No further contact attempts were made after 6 unsuccessful contact attempts.

Certified letter. The linkage coordinator offered to mail a study-related certified letter to potential patient-participants who were contacted but chose not to verify their identity. The letter legitimized the study, personalized contact with the potential participant, and included safeguards to protect confidentiality and minimize risk of HIV status disclosure.

Provider-participant recruitment procedures: A linkage coordinator securely faxed an introductory letter and study information sheet to eligible provider-participants. Within ten business days, the linkage coordinator called the provider's office, confirmed fax receipt, and requested a short informational appointment with the provider or provider's clinical staff to provide information about the study and answer questions.

Informed Consent Procedures, by Participant Group

Program arm, patient-level support: Informed consent and HIPAA authorization procedures were conducted verbally by a linkage coordinator and followed identity verification (Table 1).

Program arm, provider-level support: Providers interested in participating were verbally consented by the linkage coordinator. Post-consultation activities included retrospective consent for the eligible patient-participant (i.e., the patient of the provider-participant receiving the provider-level support).

Usual care: Usual care procedures involved informed consent and follow-up. To minimize response bias, consenting procedures for use of the controls' health information were deferred, identical to patients of supported provider-participants in the program arm.

Intervention Procedures, by Participant Group

Program arm, patient-level support: Patient-level support in the program arm sought to improve timely filling of ART prescriptions among participants with late ART prescription refill(s) by >30–90 days. The program arm consisted of up to two phases (Phase I for persons >30–60 days late filling their prescription, Phase II for persons >60–90 days late), which were distinguished by the barriers primarily addressed in each phase (Table 1). Both phases involved phone consultations with a linkage coordinator to discuss barriers to ART adherence (e.g., medication side effects, lack of transportation); both provided referrals to resources that addressed participant barriers to timely filling of ART prescriptions. Discussions with Phase II participants focused on more complex barriers to filling ART prescriptions (e.g., substance use, unstable housing). These participants were additionally offered PositiveLinks, a warm health technology support using evidence-based mobile health platforms to promote better health for PWH.¹⁶⁻²⁰

Provider informational letters. A courtesy notification letter and study information sheet were securely faxed to each potential participant's linked HIV provider. The letter

summarized the study, indicated that the provider has a patient(s) with a late ART prescription refill(s) >30–90 days, and noted that the study team has contacted the participant on behalf of Virginia Medicaid. The courtesy notification letter aligned with traditional health department D2C programs involving patient contact. No patient names were provided.

Phone consultations and referrals. For both phases (>30–60 days, >60–90 days), the phone consultation involved 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 used a conversational format guided by scripted prompts. During the consultation, the linkage coordinator documented each patient-participant's self-reported barriers to filling ART prescriptions. Referrals were made to existing resources already offered through the patient-participant's Medicaid managed care organization, pharmacist, HIV provider or, using a study-specific database, local community. Patient-participants were asked to prioritize their barriers, so that referral information aligned with patient-participant preferences. When possible, the primary referral involved a warm hand-off, where the linkage coordinator provided a direct referral in real-time to engage the patient-participant and maximize referral success.^{21,22} Patient-participants were given contact information as a 'cold' referral for secondary/tertiary barriers.

PositiveLinks. Phase II patient-participants were offered PositiveLinks, an evidence-based mobile application ("app") designed to support ART adherence and retention in care.^{16–20,23} PositiveLinks was based on theories of behavior change²⁴ and provided 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 with HIV to provide and receive social support; and 5) contact information for patients' providers and pharmacies. A strength of the app was its support of self-monitoring, which addresses intrapersonal barriers to ART adherence. All patient-participants were enrolled in Virginia Medicaid and contracted Medicaid managed care organizations provide smartphones for enrollees; therefore, smartphone ownership was not a barrier to patient-participant enrollment in PositiveLinks.

Program arm, provider-level support: Provider-level support in the program arm sought to improve ART prescribing by providers and providers' knowledge about adherence support. Provider-level support involved a 30-minute peer-to-peer clinician consultation by phone. Consultations were delivered by HIV clinical experts (physicians, nurse practitioners and physician assistants) with a high volume of HIV patients and who provided HIV leadership in Virginia. Provider-level support involved: introductory letter and study information sheet, informational appointment and provider-participant consent, peer-to-peer consultation, post-consultation activities related to the provider-participant, and post-consultation activities.

Informational appointment. The linkage coordinator reviewed the call's purpose, summarized the study and answered questions. After consent, the linkage coordinator scheduled a meeting for the provider-participant and the clinician peer consultant.

Peer-to-peer clinician consultation. Peer-to-peer clinician consultations were supportive, conversational and tailored to the needs of the provider-participant. For example, the consultation might involve reinforcement of knowledge on HIV clinical guidelines for ART initiation and strategies to optimize ART adherence. Using a script of prompts, the clinician consultant: determined the provider-participant's experience and comfort with the treatment and care of PWH; discussed reasons for patients' lack of ART prescription fills (e.g., provider-participant did not prescribe ART, patient refusal); shared best practices on ART initiation; and/or shared guideline- and evidence-based recommendations that address underlying barriers to patient ART initiation and adherence. The clinician consultant may have suggested patient referral or navigation services to address patients' unmet needs affecting ART adherence (e.g., food insecurity).

Post-consultation activities: provider-participant. The clinician consultant documented the provider-participant's barriers to ART prescribing and recommended resources in a questionnaire. Resources were provided via follow-up email from the linkage coordinator to the provider-participant. For example, suggested resources for a provider-participant whose limited knowledge of substance use disorder impacts their ART prescribing might include: Centers for Disease Control and Prevention (CDC) guidance on alcohol screening and brief interventions;²⁵ a referral to the HealthHIV Primary Care Training/Certification Program;²⁶ and a referral to My Brother's Keeper, a training program involving patient/provider communication, particularly surrounding sensitive or difficult topics.²⁷

Post-consultation activities: patients of supported provider-participants. Eligible patients of providers offered provider-level support were recruited and invited to consent to using their health information in the study. To minimize response bias, recruitment and consenting procedures for retrospective use of health information were deferred until 12 months after the peer-to-peer clinician consultation. Informed consent procedures were conducted verbally by the linkage coordinator, following identity verification.

Usual care: Potential patient-participants assigned to the usual care arm (controls) received no study-specific intervention, which was consistent with state-level care for missing or late ART prescription refill(s) for Virginia Medicaid enrollees with HIV.

Analysis plan

Outcomes: Outcomes were at the patient-participant level. The primary outcome was HIV viral suppression, defined as the most recent HIV RNA viral load <200 copies/mL at 12-month follow-up. In the usual care arm, 12-month follow-up was the first date an eligible control was confirmed as having no prior ART prescription or a late ART prescription refill(s) by >30–90 days; in the program arm, the 12-month follow-up date varied by support and phase (Table 2). The secondary outcome was adherence, defined as a proportion of days covered (PDC) of ≥90%. The PDC was a pharmacy claims-based metric reflecting the proportion of days for which a person has medication available during a measurement period. We additionally explored retention in care (defined as two or more care markers [e.g., CD4 count, HIV RNA viral load, medical visit] over 12 months and ≥90 days apart)

and ART persistence (defined as the number of days between the first ART prescription claim following the date of enrollment and a late ART prescription claim >30 days).

Sample size: A sample size of 1,000 patient-participants (500 per arm) provided adequate power to detect meaningful differences in HIV viral suppression across arms. We conservatively considered a power of 80% to detect a 10-percentage point difference between study arms, assuming a 50% rate of viral suppression in the control group.²⁸ Assuming 30% of the sample will be missing viral load data,²⁸⁻³⁰ a sample size of 500 participants per arm was required. We anticipated peer-to-peer consultations for 15–40 providers randomized to the program arm and who had eligible patient-participant(s) with no prior ART prescription claim. No sample size estimate was calculated for provider-participants receiving peer-to-peer consultations; patient-participants of these provider-participants were included in the sample size calculation and were analyzed as part of the program arm.

Statistical analysis: Using descriptive statistics, we evaluated the balance of demographics, other patient characteristics, and outcomes between the study arms. We compared means and medians between the treatment samples using t-tests and Kruskal-Wallis tests.

We performed an intent-to-treat analysis to test hypotheses. We evaluated the effect of the program on the binary outcomes—including HIV viral suppression (primary outcome), adherence (secondary outcome), and retention (exploratory outcome)—by comparing the proportions between the program and usual care arms. We used Chi-squared tests to evaluate the statistical significance of the effects of treatments on proportions. We also used logistic regression models to test for program effects, adjusting for potential confounders. The differences in the means of persistence between the program and usual care groups were tested using a t-test, with a linear regression model used to evaluate the effect after adjusting for confounders.

Administrative claim databases are subject to data missingness.³¹ Multiple imputation is a common approach to address this limitation. We applied multiple imputation using predictive mean matching to address missing data, assuming missingness at random.³² Multiple imputation typically assumes that variables are normally distributed, but we used a predictive mean matching approach that does not make assumptions regarding the distribution of the data.³³

Data use agreements and access

Data were accessed via data use agreements between state agencies and between state agencies and VCU. Agreements specified the data to be accessed and transferred as well as study personnel authorized to do so. To conduct data analysis, select VCU personnel were granted affiliate status at each agency, authorized to view or access study-specific data, used agency-supported computers (if required), and adhered to VCU and agency-specific data security and confidentiality standards when working with the data.

Data management and statistical analysis were performed using Teradata 16.10, REDCap 10.9.4, and SAS® Software version 9.4. Statistical analysis occurred at Virginia Medicaid and VDH. Intermediate datasets were stored on Virginia Medicaid servers, VDH servers, and University of Virginia servers. Final limited and de-identified datasets were stored at Virginia Medicaid and VDH, as well as securely transferred to VCU and the CDC.

Ethics and dissemination

This study was reviewed and approved by the Institutional Review Board of Virginia Commonwealth University (HM20018229) and data collection approval through the Office of Management and Budget (0920-1361). The trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05477485) (NCT05477485).

DISCUSSION

Changes to design during implementation

Low patient-participant recruitment (i.e., two patient-participants enrolled in first three months) during the early project resulted in study design changes. These changes are in Figure 2 and the trial registration profile, and are described below in chronological order. Changes were reviewed and approved by the IRB.

Six months after recruitment start: We revised the consent form and procedure to address discordance between self-reported ART adherence and adherence in the claims data. Early on, multiple potential patient-participants whose insurance claims data indicated a late ART prescription reported being up-to-date on their prescription and therefore did not need to enroll in the study. Given patient self-report of a late prescription or adherence challenges was never an eligibility criterion, we revised the consent form and procedure scripts to indicate that the study seeks to understand patient experiences related to ART prescription filling. This change did not impact our interpretation of the secondary outcome (ART adherence), as our assessment of adherence was based on the claims data and not self-report. Notably, we did not find an explanation for the discrepancy between the claims data and self-reports from potential patient-participants. We hypothesize that the discordance may be due to internalized stigma regarding prescription filling or adherence, unrecognized adherence challenges, and/or stockpiling of untaken medications—all potential barriers the AIMS program is designed to address.

We also addressed data limitations in the claims data. We updated eligibility criteria to exclude patient-participants with missing or incorrect contact information.

Finally, we revised the recruitment protocol to include SMS text messages for patient-participants. The text message contained a website link (<https://adhere.vcu.edu/>) with introductory text to describe the study and promote study credibility. Up to 2 texts per potential patient-participant could occur across recruitment months.

Nine months after recruitment start: We removed the provider intervention after nine months during which no provider-participants were recruited (Figure 2). We found that providers and their clinic staff were frequently unable to talk or take messages unless in

regard to a specific patient. Yet due to privacy and confidentiality protections, we were unable to reveal names of specific patients who had not received an ART prescription. In removing the provider intervention, any potential impact of provider engagement on patient outcomes was no longer part of the intervention arm. We updated our definition of the program to include the patient intervention only, such that we examined the effect of the newly defined program on the outcomes, versus usual care.

Given continued difficulties in recruiting patient-participants, we also relaxed some eligibility criteria (Box 1), adapted the study design to a new quasi-experimental design and reduced target enrollment to 100 patient-participants per arm (Figure 2). For the new quasi-experimental design, the usual care arm was changed to an artificial control constructed using propensity score matching. The individuals included in the new usual care arm were de-identified for analysis and therefore required neither consent nor HIPAA authorization. Follow-up in the revised study design was decreased to 3 months. To adjust for the effect decreased sample size would have on the study's statistical power, we adjusted the analysis plan by lowering the target power to 70%, increasing the required effect size for detection to 25%, and adopting a one-sided test with a higher significance level (0.10).

Key methodological contributions

Real-time D2C using claims data: AIMS, as an early example of D2C-Rx, was built on traditional D2C approaches by using Medicaid claims to identify PWH without ART prescriptions and offer tailored support interventions. Various programs have used pharmacy data or prescription claims to improve medication adherence,³⁴ including Medicare or Medicaid Medication Therapy Management Programs;³⁵⁻³⁷ another D2C-Rx program, Link-Up Rx, has used pharmacy data in conjunction with HIV surveillance data to implement a D2C re-linkage program through a specialty pharmacy.³⁸ AIMS was the first program to our knowledge to target prescription adherence for Medicaid enrollees with HIV using claims data.

AIMS itself had novel features: Distinguishing PWH who have never been prescribed ART from those who have missed an ART prescription refill facilitated tailored support for prescription adherence barriers at the provider- or patient-level. Additionally, given ready availability of pharmacy claims, AIMS identified individuals with late ART prescriptions in nearly real-time and at precise intervals of lateness. Partnering with a state Medicaid program allowed for implementation statewide, versus through a single clinic, pharmacy, or managed care organization, and leveraged Medicaid's status as the largest single provider of health insurance for this population nationally, covering nearly half (45%) of all diagnosed PWH.³⁹ Finally, use of Medicaid claims facilitated rapid assessment of prescription filling behavior after delivering the intervention—and if necessary, re-intervention in a phased approach.

Secure cross-agency data transfers: A multi-stage data access and transfer procedure was created to satisfy institutional and agency requirements for data security, which in many cases were determined directly by state legislation.⁴⁰ Specifically, the Virginia Administrative Code protects information about Medicaid enrollees, allowing release of

member information for certain activities such as plan administration (12 VAC 30-20-90), and the Code of Virginia governs allowable purposes for cross-agency data sharing (Va. Code § 2.2-3801). The project depended on matching identifiable data between Virginia Medicaid and VDH by an academic third party. In accordance with state legislation, as well as institutional and agency requirements, our process (Figure 3) allowed for release of individual-level information.

Limitations and challenges

Study design: While the cluster-randomized controlled trial design can provide internal validity, we could not guarantee trial results would generalize to other states or health departments. This is important in the context of Medicaid, which is funded jointly by federal and state governments but is administered at the state level. State-level administration allows Medicaid agencies flexibility to implement new program improvement initiatives and tailor services to their state populations, but it also introduces variation between states that can affect generalizability of Medicaid programs. The AIMS program may be considered yet another example of the wide variability across states in Medicaid Medication Therapy Management programs.³⁷

AIMS program: First, while the program offered holistic patient support, it did not address or isolate the effects of individual interventions to decrease barriers to ART prescription and adherence, such as stigma or logistical and financial barriers. Thus, as originally designed, the study could not test differences between the provider-level and patient-level components of AIMS, nor of the different phases within the patient-level component. Study design changes limited our ability to incorporate and test the AIMS provider-level component as part of the full intervention. Further, decreasing the sample size would make detecting smaller differences, between study arms, challenging. However, we believe this holistic program of support best represents how such an initiative like AIMS would be implemented at state health departments or Medicaid agencies. The multi-level AIMS program is in line with recommendations for adherence interventions to address both provider- and patient-level factors⁴¹ and draws upon evidence-informed strategies to improve retention in care, such as motivational interviewing, removing structural barriers to care, and linkage to community resources at the patient level, as well as brief messages delivered by providers.^{42,43} AIMS also combines elements of existing Medicaid practices and recommendations, including quality improvement initiatives and continuing medical education which address provider behavior⁴⁴ and Medication Therapy Management programs that focus on patient behavior.⁴⁵

Second, minor variation in the benefits of the different managed care organizations with which Virginia Medicaid contracts, as well as in community resource availability across jurisdictions, may alter the specific support offered.

Enrollment challenges: We faced significant challenges with phone-based enrollment. These challenges necessitated a dramatic reduction in recruitment targets from a planned initial sample size of 500 to 100 per arm. Further developmental work, such as pilot studies

and focus groups, may have provided insights to study design that prevented the need for such changes.

CONCLUSIONS

The AIMS study began as a statewide, cluster-randomized controlled trial of a D2C-Rx program, advancing a novel procedure that leveraged real-time ART prescription claims to deliver support or relinkage services earlier than traditional D2C models. Problems with recruitment of both patients and providers necessitated major changes to the study design and sample during implementation. We present the full protocol, as originally devised, and as amended, to demonstrate the evolution of a large-scale trial and to share our decisions and rationales regarding methodological concerns that future researchers and program implementers may face.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1.**Patient-level inclusion and exclusion criteria**

Original protocol	Final amended protocol*
Inclusion criteria	
• Currently enrolled in Virginia Medicaid • Continuously enrolled in Virginia Medicaid for the preceding ≥ 12 months • Not dually eligible for Medicare • Identified as living with HIV according to a case identification algorithm that matches Virginia Medicaid and Virginia Department of Health data • Current age 19–63 years • Most recent refilling ART prescription refill(s) is late by >30–90 days OR no history of ART prescription in Virginia Medicaid claims data	• Currently enrolled in Virginia Medicaid • Continuously enrolled in Virginia Medicaid for the preceding <u>≥ 9 months</u> • Not dually eligible for Medicare • Identified as living with HIV according to a case identification algorithm that matches Virginia Medicaid and Virginia Department of Health data • Current age <u>19–64</u> years • Most recent refilling ART prescription refill(s) is <u>late by >30–365 days</u>
Exclusion criteria	
• Any record of non-Medicaid health insurance or other health care service payer in the past 12 months • New prescription claim(s) within 30 days of most recent late ART prescription claim(s) that suggests ART prescription was discontinued due to ART toxicity (within-class switch) • Service claim(s) for resistance testing and other ART prescription claim(s) within 30 days of most recent late ART prescription claim(s) for ART drug(s) not previously prescribed (indicating the previous ART prescription was discontinued due to ART resistance) • Enrollee's linked HIV provider practices at a healthcare facility currently offering PositiveLinks (a component of the intervention) • No record in the Virginia HIV surveillance data • Non-English speaking • History of prior ART prescription from state-administered health program (applies to eligible patient-participants with no history of an ART prescription claim)	• Any record of non-Medicaid health insurance or other health care service payer in the past <u>3 months</u> • New prescription claim(s) within 30 days of most recent late ART prescription claim(s) that suggests ART prescription was discontinued due to ART toxicity (within-class switch) • Service claim(s) for resistance testing and other ART prescription claim(s) within 30 days of most recent late ART prescription claim(s) for ART drug(s) not previously prescribed (indicating the previous ART prescription was discontinued due to ART resistance) • Enrollee's linked HIV provider practices at a healthcare facility currently offering PositiveLinks (a component of the intervention) • No record in the Virginia HIV surveillance data • Non-English speaking • <u>Missing or incorrect contact information</u>

Abbreviations: ART: antiretroviral therapy. * Changes to the final amended protocol are bolded and underlined.

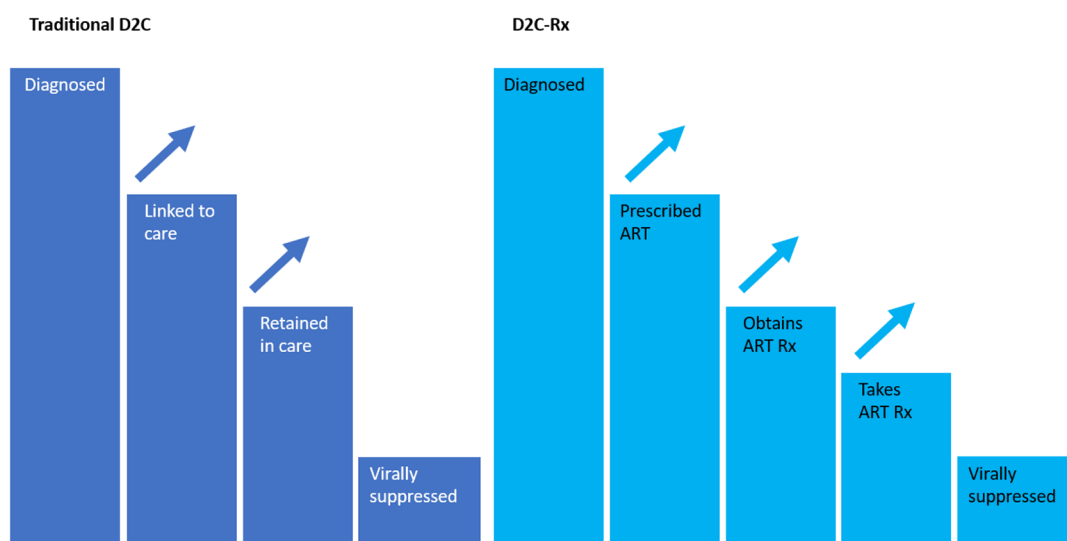
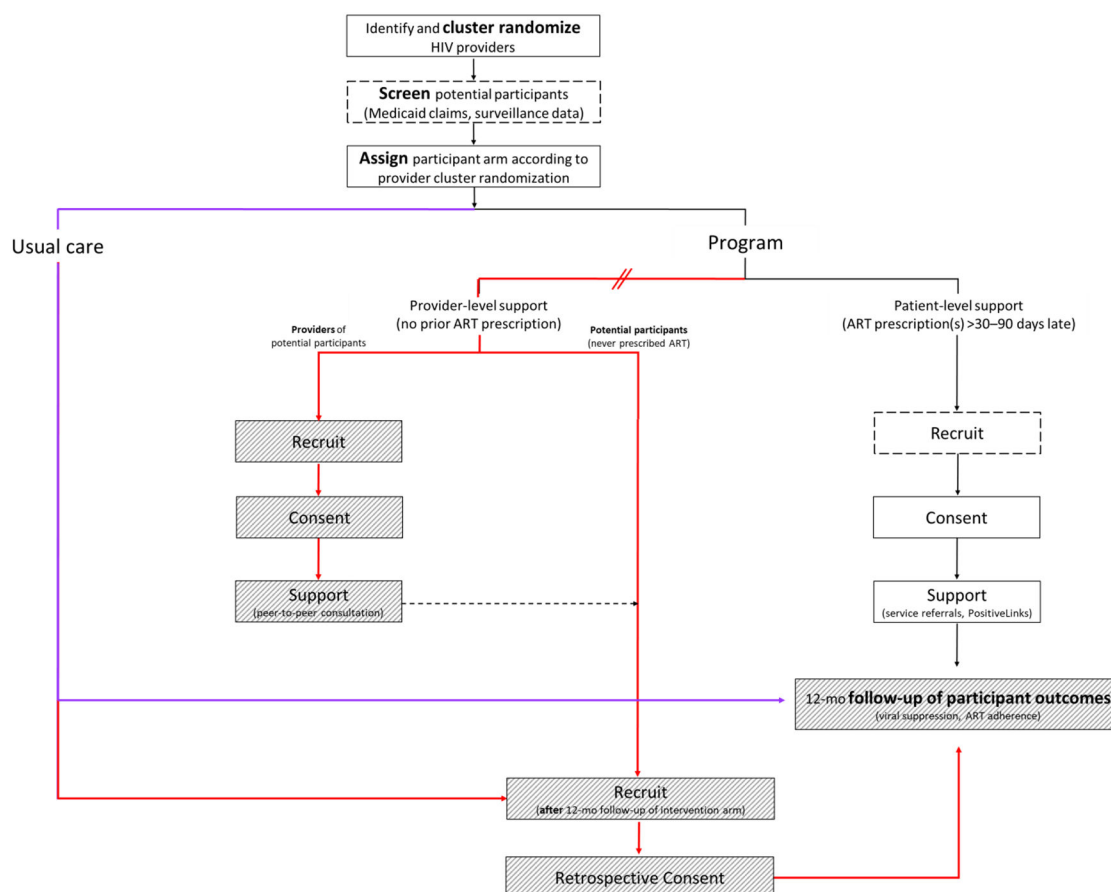


Figure 1.

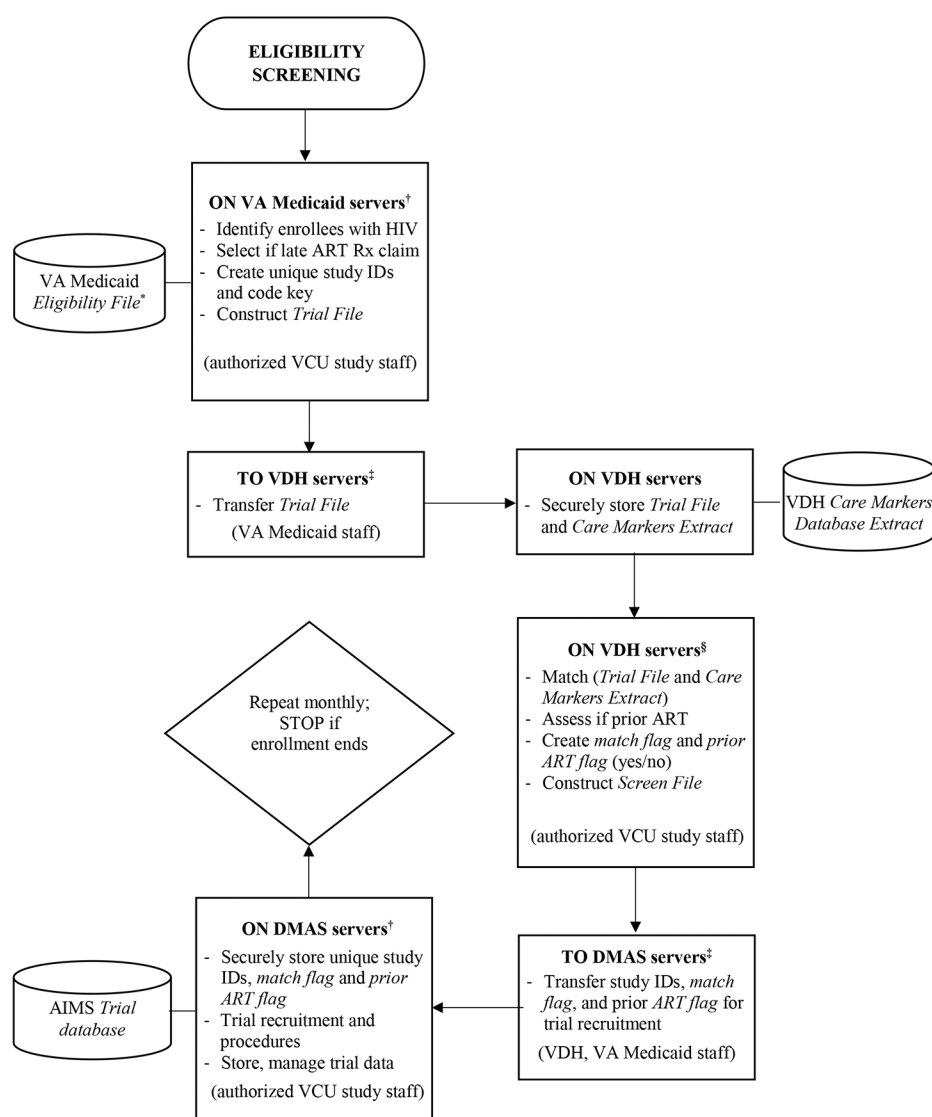
Data to Care approaches that rely on antiretroviral therapy (ART) prescription data (D2C-Rx) allow intervention at stages along the ART adherence continuum, rather than focusing on care engagement itself as the precursor to viral suppression

Arrows represent losses at each step where Data to Care programs can intervene to re-engage people with HIV. ‘Traditional’ Data to Care follows the continuum of HIV care, while D2C-Rx, leveraging data on filled prescriptions in addition to surveillance and other data sources, follows the continuum of ART adherence. D2C-Rx can deliver targeted support to ensure that people with HIV receive ART prescriptions from their providers, fill their prescriptions at pharmacies, and take ART as directed. In addition to intervening earlier, D2C-Rx may address specific barriers to ART adherence at both the patient level (e.g., transportation to the pharmacy) and the clinic or provider level (e.g., lack of provider knowledge about ART regimens).

Abbreviations. ART: Antiretroviral therapy. D2C-Rx: Data-to-Care using ART pharmacy claims. Rx: Prescription medication.

**Figure 2.****Study schematic**

Shown is a schematic of the original study design and protocol, as well as adaptations to the study design over time. Adaptations include: 1) Changes to screening criteria and recruitment (e.g., text messaging) denoted by the dashed boxes, 2) Removal of the provider-level support intervention, including potential participants with no history of antiretroviral therapy (ART) prescriptions and their linked providers, as denoted in red and by boxes with hatched lines, and 3) Change to the methods (i.e., propensity score matching) used to identify participants for the usual care arm.

**Figure 3.**

Study eligibility screening of secondary data: a process map

Potentially eligible Medicaid enrollees are first identified as living with HIV, and then as eligible for the trial, on Medicaid servers. A dataset containing necessary direct identifiers (e.g., name, social security number, date of birth) and a study identifier is then securely transferred to Virginia Department of Health, where it is matched with HIV surveillance data to confirm HIV status and antiretroviral therapy (ART) prescription history. Finally, a dataset containing study identifiers, matching results, and ART prescription history confirmation is transferred back to Medicaid servers.

Abbreviations: VA: Virginia. ART: antiretroviral therapy. Rx: prescription. ID: identification. VCU: Virginia Commonwealth University. VDH: Virginia Department of Health. DMAS: Department of Medical Assistance Services (a.k.a. VA Medicaid). AIMS: Antiretroviral Improvement among Medicaid enrolleeS.

Table 1.

Interventions received in the original protocol, by participant group

Arm	Group	Intervention received	Consent
Usual care	--	None	Retrospective
Program	Providers offered peer consultation	• Peer-to-peer clinician consultation to educate provider on topics such as HIV clinical guidelines for ART and strategies for supporting patient ART adherence • Follow-up email containing referrals and resources for further education	Prospective
	Participants of providers offered peer consultation	None	Retrospective
	Participants receiving patient-level support	• Courtesy letter sent to provider informing them that patient was late filling their ART prescription(s) • 30-minute phone consultation with linkage coordinator to assess barriers to ART prescription adherence – Phase I (>30-60 days late): focused on barriers such as forgetting, transportation to pharmacy, not understanding purpose of medication – Phase II (>60-90 days late): focused on more complex barriers such as substance use, mental health, unstable housing • Warm and cold referrals to Medicaid MCO, provider, pharmacy, or community resource • Phase II only: Offered PositiveLinks	Prospective

Abbreviations: ART: antiretroviral therapy. MCO: managed care organization.

Table 2.

Study components, with designated start dates for 12-month follow-up and data collection, AIMS study, April 2023 – June 2024^{*}

Arm	Group	Start of 12-month follow-up in data	When follow-up data may be collected
Usual care	--	First date of no prior ART prescription or a late ART prescription refill(s) by >30–90 days	After 12-month follow-up of patient-level component of program arm and retrospective consent
Program	Providers offered peer consultation	N/A – outcomes assessed at participant-level only	N/A – outcomes assessed at participant-level only
	Participants of providers offered peer consultation	Most recent of the following: Date provider is offered peer consultation Date provider receives peer consultation	After 12-month follow-up of patient-level component of program arm and retrospective consent
	Participants receiving patient-level support	Most recent of the following: Date of phase 1 consultation Date of phase 2 consultation Date of joining PositiveLinks	After prospective consent and for subsequent 12 months

Abbreviations: ART: antiretroviral therapy. *Study components in original protocol.