

Patient Education and Decision Support for Long-acting Injectable HIV Antiretroviral Therapy: Protocol for Tool Development and Pilot Testing in New York Ryan White HIV/AIDS Program Medical Case Management Programs

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Patient Education and Decision Support for Long-acting Injectable HIV Antiretroviral Therapy: Protocol for Tool Development and Pilot Testing in New York Ryan White HIV/AIDS Program Medical Case Management Programs

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Abstract

Background: Long-acting injectable (LAI) HIV antiretroviral therapy (ART) presents a major opportunity to facilitate and sustain HIV viral suppression, thus improving health and survival among people with HIV (PWH) and reducing the risk of onward transmission. However, realizing the public health potential of LAI ART requires reaching patients who face barriers to daily oral ART adherence. Ryan White HIV/AIDS Program Part A medical case management programs provide an array of services to address barriers to HIV care and treatment among low-income PWH. These programs are effective at improving engagement along the continuum of care, but findings of limited program impact on durable viral suppression highlight the need to further innovate and hone strategies to support long-term ART adherence.

Objective: This study aims to adapt and expand Ryan White medical case management service strategies to promote LAI ART awareness, access, patient-centered decision-making, and adherence, with the larger goal of improving health outcomes in the populations that could most benefit from alternatives to daily oral ART regimens.

Methods: Based on findings from patient and provider focus groups and discrete choice experiments, as well as feedback from advisory board meetings, our team developed patient education materials and a patient-provider decision tool to pilot at six partnering medical case management programs. Implementation outcomes, measured through provider interviews, surveys, and service reporting, will guide the further specification of strategies to integrate LAI ART options into medical case management program implementation.

Results: The study was funded in late April 2021 and received IRB approval in May 2021 under Protocol 20-096. Focus groups were conducted in late 2021 (N=21), discrete choice experiments ran from June 2022 to January 2023 (N=378), and tools for piloting were developed by May 2023. The trial (May 2023 through January 2024), has enrolled over 200 patients.

Conclusions: This study will produce evidence regarding the acceptability, feasibility, appropriateness, and effectiveness of a package of patient-oriented tools for comparing LAI ART and daily oral ART options. Study strengths include formative work to guide tool development, a mixed-methods design, and the testing of tools in real-world safety-net service settings. Clinical Trial: ClinicalTrials.gov NCT05833542; <https://clinicaltrials.gov/study/NCT05833542>

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Title: Patient Education and Decision Support for Long-acting Injectable HIV Antiretroviral Therapy: Protocol for Tool Development and Pilot Testing in New York Ryan White HIV/AIDS Program Medical Case Management Programs

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Key Words: HIV; implementation science; long-acting injectables; patient decision aid; medical case management; antiretroviral therapy

Abstract

Background: Long-acting injectable (LAI) HIV antiretroviral therapy (ART) presents a major opportunity to facilitate and sustain HIV viral suppression, thus improving health and survival among people with HIV (PWH) and reducing the risk of onward transmission. However, realizing the public health potential of LAI ART requires reaching patients who face barriers to daily oral ART adherence and thus can clinically benefit from alternative treatment modalities. Ryan White HIV/AIDS Program Part A medical case management programs provide an array of services to address barriers to HIV care and treatment among economically and socially marginalized PWH. These programs have demonstrated effectiveness at improving engagement along the continuum of care, but findings of limited program impact on durable viral suppression highlight the need to further innovate and hone strategies to support long-term ART adherence.

Objective: This study aims to adapt and expand Ryan White medical case management service strategies to integrate LAI ART regimen options, with the larger goal of improving health outcomes in the populations that could most benefit from alternatives to daily oral ART regimens.

Methods: In three phases of work involving patient and provider participants, this study employs role-specific focus groups to elicit perceptions of LAI versus daily oral ART; discrete choice experiment surveys to quantify preferences for different ART delivery options and related supports; and a non-randomized trial to assess the implementation and utility of newly developed tools at six partnering Ryan White HIV/AIDS Program Part A medical case management programs based in urban, suburban, and semi-rural areas of New York. Findings from the focus groups and discrete choice experiments, as well as feedback from advisory board meetings, informed the design and selection of the tools: (1) a patient-facing, two-page fact sheet including “frequently asked questions” and a side-by-side comparison of LAI with daily oral ART; (2) a patient-facing informational video available online; and (3) a patient-provider decision aid. Implementation outcomes, measured through provider interviews, surveys, and service reporting, will guide the further specification of

strategies to integrate LAI ART options into medical case management program workflows.

Results: The study was funded in late April 2021 and received IRB approval in May 2021 under Protocol 20-096. Focus groups were conducted in late 2021 (N=21), discrete choice experiments ran from June 2022 to January 2023 (N=378), and tools for piloting were developed by May 2023. The trial (May 2023 through January 2024), has enrolled over 200 patients.

Conclusions: This study is designed to produce evidence regarding the acceptability, feasibility, appropriateness, and utility of a package of patient-oriented tools for comparing and deciding between LAI ART and daily oral ART options. Study strengths include formative work to guide tool development, a mixed-methods approach, and the testing of tools in real-world safety-net service settings.

Trial Registration: ClinicalTrials.gov NCT05833542; <https://clinicaltrials.gov/study/NCT05833542>

INTRODUCTION

Since 1990 the federal Ryan White HIV/AIDS Program (RWHAP) has funded cities/counties (via Part A) to cover HIV medical care and support services for those without alternative resources. The RWHAP is an essential platform for reducing health disparities among people with HIV (PWH) and scaling up evidence-based strategies to strengthen the HIV care continuum [1, 2]. RWHAP service recipients account for over half of United States (US) PWH [1, 3-6], and nearly 75% of US PWH in HIV care attend facilities receiving RWHAP funds [2]. The central role of the RWHAP in the US response to HIV has been re-affirmed in the Ending the HIV Epidemic Plan [7]. In New York (NY), RWHAP Part A (RWPA) services primarily represent people who identify as Black (53%) or Latino/a/x (37%), groups disproportionately affected by the US HIV epidemic [8, 9]. Among those retained in HIV care in 2022, New York City (NYC) PWH enrolled in RWPA services were less likely than other NYC PWH to be virally suppressed (83% vs 93%) or experience durable viral suppression (defined as all viral loads <200 copies/mL) in 2022 (71% vs 86%). RWPA medical case management (MCM) programs are specifically designed to reduce barriers to HIV care and treatment through the coordination of medical and social services and the provision of antiretroviral therapy (ART) adherence support. The NYC Health Department oversees RWPA MCM services to >4,000 PWH per year in 29 programs in NYC and the suburban and semi-rural Tri-County area (Putnam, Rockland, and Westchester) north of NYC. Though these programs have shown effectiveness at engaging PWH in care and treatment, substantial room for improvement in HIV viral suppression outcomes remains, highlighting the need to further innovate and hone strategies to increase long-term ART adherence [10-14].

Long-acting injectable (LAI) ART has been heralded as a major biomedical advance that could close gaps in the HIV care continuum, minimize HIV transmission risk, reduce racial/ethnic HIV outcome disparities, and accelerate the end of the HIV epidemic by making viral suppression attainable for those who struggle with daily oral ART adherence. After phase 3 clinical trials found a long-acting cabotegravir and rilpivirine injectable combination (CABENUVA) to be comparable in safety and efficacy and superior in patient satisfaction to daily oral ART [15-18], the US Food and Drug Administration (FDA) approved a monthly CABENUVA regimen in January 2021 [19] and a bimonthly regimen in February 2022 [20]. LAI ART addresses some important adherence barriers by eliminating the requirement for daily dosing; patients have also noted that it can remove the daily reminder/stressor of HIV status and mitigate the risk of inadvertent HIV status disclosures [21-29]. Even so, there are challenges around LAI ART implementation that must be systematically addressed. Commonly reported patient barriers include concerns over effectiveness [30-35], side effects [30, 31, 34-36], dosing frequency [32, 34, 35], getting to a clinic for each injection [33, 37, 38], and needles [31, 36]. Providers have voiced concerns related to staffing resources, organizational logistics, patient readiness for LAI ART, adherence to injection appointments, and injection tolerability [34, 39, 40]. In the face of these challenges, uptake of LAI ART since its FDA approval has fallen short of expectations. As of the end of September 2023, approximately 20,000 people in the US (including Puerto Rico) were on CABENUVA (Cinthyia Avalos Meléndez of Viiv Healthcare, e-mail to author, December 14, 2023). This represents just under 2% of the approximately 1.1 million people living with diagnosed HIV in the US and its dependent areas [41]. Optimizing the public health impact of LAI ART will require implementation science to identify and tailor interventions to facilitate LAI uptake and engagement, particularly for the most marginalized patients. Without the necessary groundwork to assess and promote access, acceptability, and uptake in underserved populations, biomedical innovations tend to benefit those who are already relatively advantaged and can even exacerbate health disparities [42-44].

This paper describes the protocol for a mixed-methods study designed to prepare RWPA MCM programs for extending LAI ART options to patients who have struggled to achieve or maintain viral suppression on daily oral ART and who have been underrepresented in the phase 3 clinical trials. Specifically, we summarize the formative and survey research stages completed to guide the selection and development of LAI ART-related educational and decision-support tools, and we present the methods for a pilot test in progress to evaluate and refine these tools for future scale-up.

METHODS

Study Overview, Aims, and Partners

The APPLI (Assessing Perceptions and Preferences around Long-acting Injectables) study is organized into three consecutive phases of work, each of which corresponds to a specific aim: (1) elicit perceptions, barriers, facilitators and expectations of LAI versus daily oral ART delivery options, in focus groups with RWPA MCM patients, core staff and prescribing providers; (2) quantify preferences and drivers of engagement in ART delivery and support strategies, including options for LAI and daily oral ART, via discrete choice experiments (DCEs) with approximately 200 patients and 200 providers; and (3) select and pilot strategies to promote LAI ART uptake, adherence and impact in real-world care settings. Each aim corresponds to distinct data collection activities, summarized in Table 1.

The study functions as an academic-government-provider collaboration, with a university-based lead agency working closely with a health department and six NY RWPA MCM service-provider agencies that were engaged as partners from the outset. The six provider agencies were purposively selected to represent the full range of NY RWPA MCM service settings (hospitals, community health centers, and social services community-based organizations) and the distinct geographic regions within the NY RWPA eligible metropolitan area. Three of the agencies have headquarters in NYC, which includes five counties: New York (Manhattan), Bronx, Kings (Brooklyn), Queens, and Richmond (Staten Island). The other three have headquarters in the Tri-County area north of NYC: Westchester, Rockland, and Putnam. All six agencies had an annual caseload of at least 70 RWPA MCM patients at the time of study proposal development. Although the FDA had not approved LAI ART until after the study proposal was submitted, LAI ART prescription was beginning when the project started and was being considered for some MCM enrollees at the partner agencies by the second year of the project, in the months immediately preceding the pilot.

Table 1. Study data sources, participants, content, data collection periods, and purpose by aim/phase

Aim/ phase	Data source	Participants	Content	Time frame	Purpose
1	Focus groups	16 MCM providers (case managers, patient navigators, administrators, and a prescribing provider)	- Awareness and perceptions about LAI ART - Implementation barriers and facilitators (for providers) - Acceptability of LAI ART (to	October – December 2021	Inform design of discrete choice experiments and gather preliminary data on LAI ART acceptability or concerns

		5 MCM patients	patients)		
2	Discrete choice experiment surveys	177 MCM providers 201 MCM patients	- Preferred program features: type of ART, service location and mode, adherence support, rewards - Awareness and acceptability of LAI ART - Appropriateness and feasibility of LAI ART (for providers) - Case vignettes with questions about LAI ART candidacy and potential benefit (for providers)	June 2022 – January 2023	Understand drivers of decisions about ART regimens and adherence supports; quantify preferences for specific ART regimen, ART delivery, and ART adherence support or reinforcement options
3	Brief provider surveys	12 MCM providers (one administrator and one direct service provider per partnering agency)	Pilot intervention acceptability, appropriateness, and feasibility, and organizational readiness for implementation	Three rounds (baseline, midpoint, final), May 2023 – February 2024	Quantify role of specific factors for pilot implementation using standard measures for comparison to the literature
3	Individual provider interviews	12 MCM providers (one administrator and one direct service provider per partnering agency)	Providers' experience of the pilot, barriers/facilitators or other factors for pilot tool implementation, and any recommendations	September 2023 – February 2024	Qualitatively assess pilot implementation factors and outcomes and desired changes to piloted tools
3	Program data on patients enrolled and pilot-	≥180 MCM patients from 6 partnering agencies	Patient descriptive data, assessments of patient ART regimen and adherence, and detail on pilot	May 2023 – January 2024, with follow-up on LAI	Quantitatively assess pilot implementation outcomes such as reach,

	related service delivery		services delivered (tools and dates used, as well as patient responses on ART regimen choices)	ART adherence through September 2024	effectiveness, adoption, and implementation and variation by agency, intervention condition, or stage of pilot
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Completed Data Collection

Aim 1 focus groups

The first study phase was directed at eliciting patient and provider perceptions and expectations of LAI versus daily oral ART, including barriers and facilitators to LAI ART use/delivery. The focus group guide was designed to explore potential influences (organized by domain from the Consolidated Framework for Implementation Research, or CFIR [45]) on LAI ART implementation outcomes. Implementation outcomes were defined using RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) measures [46]. The focus groups' primary purpose was to identify key intervention attributes (features of possible LAI ART implementation tools) to be included in the DCEs.

We set out to conduct focus groups of up to nine participants each with NYC English-speaking patients, Tri-County English-speaking patients, Spanish-speaking patients, MCM administrators (who determine use of program resources), MCM direct support-service providers (who help develop and carry out patient care plans), and MCM program-affiliated primary care providers (who have discretion to prescribe LAI ART). Patient focus group eligibility required being 18 years of age or older, currently enrolled in a RWPA MCM program at one of the six partnering agencies, comfortable conversing in Spanish or English, and virally unsuppressed (viral load ≥ 200 copies/mL) at most recent viral load test. Providers were eligible if they filled a core MCM role (administrator, direct support-service provider, or primary care/prescribing provider) with any of the six partnering agencies. Provider focus group recruitment yielded 15 providers in two focus groups (administrators and direct-service providers, respectively) plus one individual interview with a prescribing provider. Patient recruitment was more challenging and yielded one Tri-County participant and four NYC participants after no-shows. Partner agencies had relatively few virally unsuppressed adults enrolled in MCM at the time of recruitment and noted that those patients were harder to engage in research. No Spanish-speaking patient enrolled, despite months of recruitment. Each participant received a \$25 gift card in appreciation of their time and input.

Focus group interview discussions were audio-recorded, transcribed, and coded in Dedoose, using thematic analysis [47]. In a combined inductive-deductive approach, the qualitative analysts applied pre-defined codes derived from the CFIR and RE-AIM constructs, and also used grounded exploration to interpret category meanings [48] and attend to emergent themes salient to participants. Separately for patient and provider transcripts, initial codes were identified in independent review of one focus group transcript, by two study team members in dialogue with a senior investigator with extensive experience conducting qualitative research. The draft (patient or provider) codebook was then independently applied to a second transcript, with discrepancies resolved in consensus sessions to optimize inter-rater reliability, yielding the final codebook that was applied to the entire dataset. Findings were presented for study advisory board input and used for consensus- and evidence-based selection of four potential intervention attributes (with three to four levels each) for inclusion in the DCEs.

Patient and provider participants highlighted the potential for LAI ART options to reduce HIV stigma and adherence burden; providers noted that ART administration via injection by a health care

worker offered protection against medication diversion. Both sets of participants mentioned COVID-19 vaccine-related attitudes and insurance pre-authorization processes as barriers, and providers expressed concerns about risks of missed injection appointments. Patients and providers desired more information and clearer messaging about LAI ART. Focus group participants also discussed MCM services that could be expanded to support LAI ART delivery: directly observed therapy, appointment transportation or accompaniment, reminder calls or texts, home visits, and financial incentives (e.g., rewards for receiving an injection on time). These strategies, along with perceived LAI ART facilitators (less frequent injections, peer support, and post-injection follow-up communications from MCM staff) were integrated as treatment package features for the DCE surveys.

Aim 2 discrete choice experiment (DCE) surveys

DCE methods: DCEs offer an efficient means of assessing preferences and priorities for intervention-related attributes [49], which can guide intervention design and packaging to encourage uptake, engagement and maintenance among the intended users. DCE participants are shown a series of choice sets juxtaposing two or more different hypothetical scenarios. Each scenario is comprised of intervention attributes, further defined by some number of levels, which are randomly combined to create hypothetical intervention alternatives. Participants are asked to choose the single preferred alternative for each choice set presented, recognizing trade-offs between the desirable or undesirable characteristics of each. Through repetition of this process over several choice sets representing many possible combinations of attribute variations, investigators can identify which attributes and attribute levels participants value most. Latent class multinomial logit regression is used to estimate utilities, which are measures of preference for levels within attributes. Positive values of utilities indicate greater preference.

DCE survey design: The above-described focus groups informed the team's selection of four attributes: (1) type of ART, (2) service location/mode, (3) adherence support, and (4) rewards. The latter three were alternative-specific attributes, defined according to type of ART (daily oral or LAI). Focusing on three implementation outcomes identified by Proctor and colleagues as salient during the adoption phase of an innovation-decision process [50], we also included the brief (four-item) 'acceptability of intervention measure' (AIM) on the provider and patient survey, and included the 'intervention appropriateness measure' (IAM) and the 'feasibility of implementation measure' (FIM) on the provider survey [51]. Contextual items at the end of the patient survey covered prior awareness of LAI ART and any experience with LAI ART, and contextual items at the end of the provider survey covered length of time delivering MCM and vignettes about hypothetical patients as potential candidates for LAI ART.

Survey recruitment: Eligibility for the patient DCE survey required being 18 years of age or older and enrolled in RWPA MCM services at any of the six partnering agencies. As with the focus groups, contact attempts for patient recruitment were conducted through MCM program staff at the partnering agencies. Eligibility for the provider DCE survey required having a RWPA MCM care team job role (i.e., case manager/care coordinator, patient navigator/peer/community health worker/health educator, program director/manager/administrator with duties beyond clerical or data support, or prescribing provider). Given the target of 200 participants per survey (patient or provider) and the availability of fewer than 50 eligible providers at the six partner agencies, all 29 RWPA MCM programs were engaged for the provider survey. We offered the provider survey in English and the patient survey in English, Spanish, and Haitian Creole.

Patient survey participants and preliminary results: From June 2022 through January 2023, 201 NY RWPA MCM patients with median age of 54 years (inter-quartile range [IQR]: 42 to 62) and median MCM enrollment of 31 months (IQR: 11 to 45) completed the DCE. Most (92%) were Black or Latino/a/x; 40% identified as women. One-quarter self-reported imperfect adherence to daily oral

ART. Two-group latent class analysis identified a smaller subset of patients with a strong preference for daily oral ART and a larger subset preferring LAI ART. Both groups preferred higher-value monetary incentives and transportation to primary care or injection appointments over other rewards or supports for adherence. Nine out of ten participants reported currently taking daily oral ART. Half of participants indicated they had heard of LAI ART prior to taking the survey, but under 5% (9 of 201) reported having tried it.

Provider survey participants: From July 2022 through January 2023, 177 NY RWPA MCM staff completed the DCE. Most participating staff identified as women (n=127, 72%), were 40-59 years old (n=92, 52%), and had been providing RWPA MCM services for more than 2 years (n=124, 70%). The largest racial/ethnic group among participating staff was Latino/a/x or Hispanic (n=73, 41%), followed by non-Hispanic Black/African American (n=50, 28%), and non-Hispanic White/Caucasian (n=32, 18%). The most frequent job types were patient navigator (n=68, 38%), case manager/care coordinator (n=46, 26%), program director (n=33, 19%), and prescribing provider (n=21, 12%). As of the end of 2023, data from the provider DCE survey were in the early analysis stage.

Advisory Board (AB)

After receiving notice of grant award (April 2021), the study team convened an AB for input in July 2021; February, May, and November 2022; and January, April, and August 2023. AB members, who consult on study tools, implementation, results interpretation, and dissemination, include clinical and non-clinical direct service providers and administrators (from all six partnering provider agencies and a seventh interested MCM agency); Health Department staff; external researchers; and members of the HIV Health and Human Services Planning Council of NY (RWPA community planning body). In the January and April 2023 meetings, AB members provided critical input on the tools for inclusion in the pilot, including feedback on the content and visual design of draft versions.

Pilot-testing of ART Regimen Decision-making Supports

Selection/design of tools to be piloted

The third aim and phase of this study focuses on the synthesis and application of findings from Aims 1 and 2, to develop LAI ART implementation tools and pilot-test them with partnering agencies, while gathering data to inform tool refinement for future research and scale-up. Tools were developed in consultation with MCM program staff and other AB members familiar with MCM service settings, MCM patient needs, and/or decision-support processes. The selection and design of tools for the pilot were guided by a combination of focus group findings, AB input, and preliminary patient DCE results. In addition to indirectly informing tool development by highlighting attributes for inclusion in the DCEs, focus group findings and AB input directly influenced the study team's decision to develop patient-facing educational materials. The latter decision stemmed from focus group participants' emphasis on the need for clearer messaging about LAI ART and AB members' requests for materials that could be reviewed by patients on their own. AB members called attention to a general lack of patient-facing materials about LAI ART beyond the drug manufacturer's consumer-directed materials, which partnering program staff viewed as non-relatable for many of their patients. Finally, the AB advocated for including a patient-facing video, to present and compare ART regimen options in an engaging and entertaining medium while minimizing the time required during MCM visits for ART regimen-related education and decision-making processes.

The limited familiarity of patient DCE participants with LAI ART reinforced the need for clear, patient-facing educational materials describing LAI ART and directly comparing it with daily oral ART. Divergent patient preferences for daily oral versus LAI ART suggested a difference in perception between LAI ART phase 3 clinical-trial participants and patients seen in our safety-net

MCM program settings, which may reflect some of the patient-level factors limiting LAI ART uptake in practice. The mixed reception of LAI ART in the DCE reinforced the potential value of a decision-support tool to assist patients in weighing the advantages and disadvantages of available regimen types and assessing the fit of each option with their individual preferences, needs, challenges, and strengths – as well as considering programmatic resources (such as transportation) that could reduce perceived barriers to treatment success. The study team developed a patient-provider ART regimen decision aid using the Ottawa Decision Support Framework [52] and tailored the tool to suit the RWPA MCM program context, the focus on ART regimen decisions, and the AB's emphases on brevity and accessibility.

Pilot trial design

The pilot includes primary data collection in brief provider surveys and semi-structured provider interviews drawing upon the CFIR, to assess factors (barriers and facilitators) for pilot tool implementation. In addition, we intend to utilize the provider interviews and program reporting on pilot enrollment and service delivery to evaluate pilot implementation outcomes, drawing upon RE-AIM measures: reach (types and numbers of patients enrolled), effectiveness (preliminary effects on LAI ART uptake and concordance between treatment plan pursued and patient choice as recorded on the decision aid), adoption (documentation of specific tools' use), implementation (alignment of reported tool use with study condition and guidance on tool use), and maintenance (ART adherence). Registered with ClinicalTrials.gov under Identifier NCT05833542, the pilot is a non-randomized, two-arm trial of newly developed tools with ≥ 180 RWPA MCM patients. It is structured to allow comparison of an intervention arm including both patient education materials and the decision aid ('decision-aid arm') with an intervention arm including only the patient education materials and usual-care approaches (whatever agencies may already be doing) for ART regimen decision-making ('education-only arm').

Study setting and participants

The pilot test is occurring at the six partnering RWPA MCM agencies. Characteristics and study arm assignments of the six agencies are summarized in Appendix Table 1. Cluster (agency-level) assignment was used for this study to minimize crossover between intervention conditions and avert the logistical and ethical dilemmas posed by assignment strategies that require providers to administer, maintain, and track different investigator-assigned intervention conditions within a single patient caseload [53-55]. *Provider eligibility:* Pilot-related primary data collection is limited to English-speaking/reading adults responsible for overseeing or delivering RWPA MCM services or prescribing ART for MCM patients at a partnering agency. At each agency, one administrative staff member (e.g., program director) and one direct service provider (e.g., case manager, patient navigator, or prescriber) has been engaged to participate in implementation-related data collection through brief surveys and semi-structured interviews. *Patient eligibility:* Patients must be currently enrolled in a partnering NY RWPA MCM program, ≥ 18 years of age, and able to understand materials in English or Spanish. Patient eligibility for an LAI ART prescription cannot be directly assessed by the study team and can be assessed differently by different providers and/or third-party payers; it may also change over time with the FDA label indications. However, the study team communicated to partnering programs that patients should not be included in the pilot if they have known or suspected resistance to cabotegravir or rilpivirine, since that was a contraindication for the LAI ART available as of the start of this pilot (CABENUVA). Based on AB feedback that translating pilot materials to Spanish without also translating to Haitian Creole would be viewed as inequitable, and given a lack of remaining time or resources to provide translations for tools (including audio for the video) in three languages, the pilot was launched with only English-language tool versions.

Intervention conditions

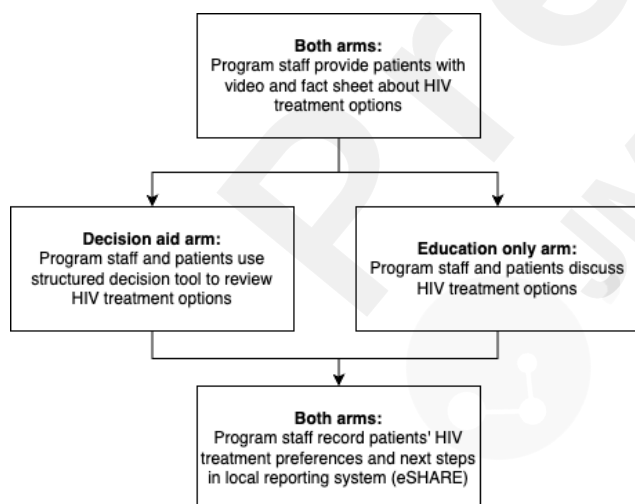
Education-only arm: Participants receive informational materials (including a fact sheet covering “frequently asked questions” and a short video) on their HIV treatment options and related support-service options. These materials provide a comparison of the risks and benefits of LAI and oral ART regimens, set expectations about clinic visits, present information about side effects, and provide additional resources to assist patients in preparing to discuss HIV treatment and support options with their medical case manager and prescribing provider. Participants receiving this intervention are offered these materials by a medical case manager or patient navigator and encouraged to review the materials on their own; they may also go over the materials with staff during an MCM program visit. All materials are at or below an eighth-grade reading level, use graphics to bolster understanding for different levels of health literacy, and follow accessibility guidelines for font choice and size.

Decision-aid arm: Prior to or during an MCM visit, participants receive informational materials (described above) on HIV treatment types and related support-service options. During an MCM visit, the participant and patient navigator or case manager/care coordinator also review the shared decision aid to weigh the participant’s treatment options and their fit to the participant’s interests, needs, assets, and constraints. The tool facilitates and records patient-provider agreement on a treatment plan, to be integrated into the broader MCM care plan signed by both patient and provider. Figure 1 illustrates the two intervention conditions and the workflow for each.

Non-random assignment: We used purposive sampling to assign three of the six partnering RWPA MCM agencies to the decision-aid arm (which includes the educational tools) and three to the education-only arm. Specifically, we ensured representation of at least two different agency types and MCM program sizes in each arm.

Blinding: Due to the need to engage service providers in the intervention through study team-led activities (e.g., orientation to the project-specific educational materials and/or the decision aid), study arm assignments were transparent to agency staff and study team members (though not to patients).

Figure 1. Intervention arms and workflows for the two-arm pilot trial



Data collection and management

Aim 3 (pilot testing) involves repeated primary data collection with two providers at each of the six partnering agencies and use of secondary data on pilot participants, service delivery, and outcomes. For Aim 3 pilot interviews with the implementing providers, oral informed consent is obtained in advance of the interview session, by phone or videoconference. Interviews are audio-recorded and transcribed for coding in Dedoose. Aim 3 provider survey data are collected and managed using the NYC Health Department REDCap server, a web-based application for designing and managing online surveys. All data will be stored on NYC Health Department servers and only

accessible with a valid login and password. The REDCap survey includes a consent form that can be printed and includes study team and IRB contact details; participants must indicate that they agree with the consent statement to proceed to the survey questions. REDCap survey data will be analyzed in R (version 4.3.2).

Patient data for the pilot will be drawn from the local RWPA data system, the Electronic System for HIV/AIDS Research and Evaluation (eSHARE), in the form of provider-reported enrollments, services, patient characteristics, assessed needs, regimen types, and adherence – data required for fee-for-service reimbursement in NY RWPA MCM contracts. eSHARE has been updated by the NYC Health Department to include pilot tools, so that partnering MCM agencies may enter pilot activities along with (and as distinct from) other MCM services. No patients are enrolled in RWPA MCM programs solely for the pilot; rather, patients already enrolled in MCM may be eligible to receive pilot-related services (ART regimen-related information and decision support with the tools developed for the project), along with the array of other MCM services. All patient- and service-level data are protected according to CDC physical and electronic data security and confidentiality policies [56]. Health Department staff extract and clean eSHARE data monthly, clean and freeze surveillance datasets quarterly, and conduct matches of program to surveillance data semi-annually. The deterministic matching algorithm has been previously described [57]. Through matching with surveillance data, patients are assigned a unique record number used to de-duplicate datasets, which are stripped of personal identifiers prior to analysis.

Study outcomes

LAI uptake (primary outcome): The primary outcome is defined as the proportion of pilot participants who start LAI ART (whether initiating ART, transitioning from a prior regimen, or transitioning from a period of non-ART use). The denominator includes patients not already on LAI ART at the start of the pilot trial; the numerator includes any of those in the denominator who begin LAI ART during the trial. Using program-reported (eSHARE) data on regimen type, uptake will be measured continuously for up to nine months (the duration of the pilot trial). *Concordance:* This outcome is defined as the proportion of participants whose intent (as documented via the decision aid) is carried through in terms of their subsequent treatment (self-administered daily oral ART, LAI ART, or some intermediate step, such as directly observed therapy to meet the current FDA label requirement for viral suppression). Using eSHARE data on decision-aid responses and subsequent regimen type and/or services related to ART adherence, concordance will be measured from the date of decision-aid completion for up to nine months. *LAI maintenance:* LAI maintenance is defined in terms of adherence to LAI ART, specifically the time from LAI initiation to first deviation from the injection schedule, among trial participants who initiate LAI ART during the trial. A deviation includes any injection more than one week ahead of or one week after the treatment target date, where the injection target date depends on whether the prescribed regimen is monthly or bimonthly. Using eSHARE data on ART regimen type and adherence (as well as case closure due to death), maintenance will be measured from first report of LAI ART to first reported deviation from the injection schedule or date of death from any cause, whichever comes first, assessed for up to nine months from first injection or up to eight months of follow-up injections (counting from the first possible deviation from a scheduled follow-up injection).

Other measures

To understand influences on implementation, we are assessing provider-perceived acceptability, appropriateness, and feasibility of the tools, at three points in the pilot: baseline, four to five months (midpoint) and nine months (end of pilot). Specifically, the provider survey includes the AIM, IAM, and FIM four-item scales that were used on the provider DCE survey [51]. However, for

the pilot survey, these three measures specifically refer to the pilot tools being implemented. The baseline and midpoint assessments also include a brief measure of organizational readiness for implementing change (ORIC), which captures commitment to change (five items) and perceived efficacy to change (seven items) [58], based on Weiner's theory of organizational readiness for change [59]. Because the ORIC measure is anticipatory, it will not be part of the final assessment. The midpoint and end-of-pilot interviews seek input from the same providers with a semi-structured instrument eliciting their experience of the piloted tools, including barriers, facilitators and suggested refinements. Interviews will lend context to the ORIC, AIM, IAM, and FIM results and guide tool refinements.

Sample size, data analysis, and power analysis

The original target was to enroll 180 patients, or 30 (on average) per partner agency. As of mid-November 2023, enrollment was already at 205. Using eSHARE data, we will describe trial participant demographics (e.g., gender, age, race/ethnicity, income, housing status) overall and by intervention arm. We will compare LAI ART uptake and, among those who start LAI ART, adherence by intervention arm, to assess the effects of the fuller package with the decision aid versus education alone. We will use log binomial regression to estimate risk ratios for uptake and adherence by intervention arm with generalized estimating equations (GEE) and a small-sample correction (due to the small number of clusters) to maintain the Type I error rate while accounting for clustering by site. To the extent possible given our sample size, we will adjust for potential confounders captured in eSHARE.

The brief provider survey measures will be analyzed through comparison of responses on the same measures over time (e.g., to assess change in perceived feasibility), as well as comparison of responses by intervention arm, agency type, and participant role. AIM, IAM, FIM and ORIC scores will also be analyzed in relation to levels of pilot service delivery as documented in eSHARE. To understand potential for sustainability and scale-up, we will explore qualitative provider interview themes related to acceptability and feasibility of the intervention. Qualitative and quantitative analyses will be integrated by examining thematic patterns reflecting RE-AIM and CFIR implementation constructs as they explain observed implementation outcomes [60].

Our pilot is designed to assess implementation of the newly developed tools and inform tool refinements. Data from the pilot will be used to generate estimates of LAI ART uptake that can, in turn, inform sample size and power calculations for a larger, controlled study of the refined tools' implementation and treatment outcomes. Accordingly, data from the pilot will be used to estimate the proportion of patients who start LAI ART and, among those initiating, the proportion who maintain LAI ART. With the original target of 180 patients (now exceeded), we will be able to estimate LAI uptake with precision (95% CI) as follows with the following levels of uptake:

Table 2. 95% confidence intervals (CIs) for long-acting injectable (LAI) antiretroviral therapy (ART) uptake among pilot participants overall and maintenance estimates for those who start on LAI ART, under LAI uptake percent assumptions

LAI ART Uptake	95% CI for LAI ART uptake	95% CI for LAI ART maintenance at 50%
5%	2.7-9.2	22.7-77.4
10%	6.4-15.2	29.0-71.0
15%	10.5-20.9	32.4-67.7

20%	14.8-26.4	34.5-65.5
30%	23.8-37.0	37.0-62.9
40%	33.1-47.3	38.8-61.3
50%	42.8-57.3	39.9-60.1

Assuming half of the people who initiate LAI ART maintain it at nine months, we will have the above precision estimates for the scenario of 50% LAI ART maintenance across a range of different levels of LAI ART uptake.

Ethical considerations

This study was approved by the NYC Department of Health and Mental Hygiene Institutional Review Board (IRB) under protocol: 20-096 and is registered with ClinicalTrials.gov (Identifier NCT05833542, pre-results). The pilot trial was granted a waiver of patient informed consent in accordance with the pre-2018 requirements set forth in 45 CFR 46.116(d), based on its reliance on secondary data analysis. Any changes to trial eligibility criteria, outcome measures, or analysis plans would be mutually agreed upon between the principal investigators, vetted with the AB, and submitted to the IRB as protocol modifications.

Informed consent was completed with each participant prior to their participation in primary data collection: focus groups, discrete choice experiment surveys, provider pilot interviews, or provider pilot surveys. No individual incentive was offered for provider pilot interviews or provider pilot surveys. Each focus group participant and each discrete choice experiment survey participant received a \$25 gift card.

Primary data collected for this study are stored on secured servers, without participant names or other personal identifiers. Study records can be linked to individual participants only by study team members, who retain a separate key linking study identifiers to other identifiers (e.g., eSHARE identifier codes). Patient names are stored in the most secured environment, accessible only to NYC Health Department staff authorized to view names and only during a time-limited, secured session in Citrix, which prohibits access to the internet, email, portable media such as flash drives, or printers. All records used in secondary analyses are also stripped of personal identifiers prior to their inclusion in datasets for analysis.

RESULTS

The study was funded in late April 2021 and received official IRB approval in May 2021 under Protocol 20-096. Focus groups were conducted in late 2021 and DCE data collection took place between June 2022 and January 2023. Patient education and patient-provider decision-aid tools were developed by May 2023, and the trial continues into 2024. Complete outcomes data are expected by October 2024 and will be submitted for publication by December 2024. Study results will be reported in accordance with the Consolidated Standards of Reporting Trials extension to cluster-randomized trials and disseminated through scientific conferences, peer-reviewed publications, and meetings with local stakeholders. The investigators have also been sharing this work with colleagues in other jurisdictions and will disseminate findings via NY's Ending the Epidemic Dashboard website.

DISCUSSION

Overview

As a biomedical advance that un-tethers HIV viral suppression from the requirement for daily

medication-taking, LAI ART could greatly increase opportunities for health, survival, transmission prevention, and health equity. However, realizing that potential will depend on reach to those who have difficulty achieving or maintaining viral suppression on daily oral ART regimens. In addition, at this relatively early stage of LAI ART availability through third-party payers, there is little information on how acceptable, appropriate, or feasible this treatment option may be for low-income, predominantly Black and Latino/a/x patients and their HIV service providers. The current study is designed to yield insights and field-tested strategies to help optimize the public health impact of LAI ART, with particular attention to the patient groups under-represented in clinical trials, disproportionately burdened by HIV-related morbidity and mortality, and most likely to benefit from gaining access to alternatives to daily oral ART. Based on focus group and AB members' calls for clear patient-facing information, and findings of limited LAI ART familiarity and divergent ART regimen-type preferences among patient DCE participants, we prioritized the development and testing of a patient-facing fact sheet and educational video, along with a patient-provider decision aid to guide conversations about treatment options and related supports.

Limitations and Strengths

Agencies were assigned to pilot intervention conditions purposively (with the intent of balancing the characteristics of agencies represented in each condition), rather than through randomization. Additional limitations include a lack of blinding (of agencies, providers, or investigators) to the agencies' assignments and a lack of control over agencies', providers', or patients' exposure to other initiatives or interventions that may affect the outcome. We are aware of at least one other NY-based pilot test of LAI-related support strategies [61], as well as a NY State Department of Health clinical quality-improvement committee focused on identifying and sharing LAI ART-related resources and best practices. However, the other NY-based pilot does not directly involve any of the agencies engaged in this trial. To our knowledge, APPLI is the first and only study to explicitly focus on the integration of LAI ART regimen options in RWPA or other RWHAP service settings, and the first to develop patient-directed LAI ART education materials or a patient-provider ART decision aid for use in a RWPA service population.

As with other HIV care quality-improvement activities led by the NYC Health Department, agency participation is voluntary, meaning that agencies in the pilot could implement their assigned intervention condition incompletely or decline to implement. To address this limitation, we are tracking multiple implementation measures.

Conclusions

The US National HIV/AIDS Strategy and National Institutes of Health have called for implementation science to produce evidence-based models of care [62, 63]. Reviews of HIV care continuum research have also noted the need for practice-based evidence to inform program and policy development [64-66]. The implementation-science design of this study has been selected to facilitate rapid research-to-practice translation of any LAI ART educational or decision-support tools that are found to be acceptable, feasible, and appropriate to these service settings, and that show preliminary evidence of patient benefit. Through a robust academic-government-provider partnership, products from this study will be incorporated into local HIV services planning and delivery, as well as future research.

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Disclaimers: The content of this manuscript is solely the responsibility of the authors and does not necessarily reflect the official views of the funding agencies supporting this project. The NIH and HRSA are not involved in the study design, conduct, or products, nor in the decision to submit this work for publication. Note: The cited personal communication from ViiV Healthcare, indicating approximately 20,000 people in the US (including Puerto Rico) on CABENUVA, is based on an estimate derived from the use of information under license from the following IQVIA information service: National Custom Patient with National Longitudinal Patient [LRx] for the period ending 2023-09-29. IQVIA expressly reserves all rights, including rights of copying, distribution and republication.

Data Availability: The full IRB protocol and statistical code will be made available upon request. NY State Public Health Law prohibits the study team from releasing a public-use dataset containing information tending to identify the subjects of its research. NYC Health Department staff retain sole custody of study datasets and designated staff are available to answer any inquiries. Please send an email to the study contact person with questions or requests for additional information.

Conflicts of interest: The authors have reported only federal government grants to their institutions for the work reported here. For work beyond this project, DN has received consulting fees from Gilead Sciences, Inc. and Abbvie, Inc., and RZ, SGK, and DN have received research grant funding from Pfizer to their institution.

Author contributions: MKI is the health department (DOHMH) Principal Investigator and led the conception of the overall study and the writing of the R34 proposal. RZ (CUNY) reviewed and edited all drafts of the grant proposal, led analyses on Aim 2 of the larger study, and contributed substantively to the preparation of the manuscript. TA (DOHMH) supervised the DOHMH analysts' work on Aims 1 and 3 of the larger study and contributed substantively to the study design and analysis plan. MP (DOHMH) and CE (DOHMH) conducted qualitative data collection for Aim 1 and Aim 3 and conducted qualitative analyses for Aim 1. SGK (CUNY) and MMP (UCSF) contributed substantively to the grant proposal and participated in ongoing planning. EAK (CUNY) contributed to the grant proposal and analysis plan and advised on study implementation. RZ (CUNY), TA (DOHMH), MP (DOHMH), and CE (DOHMH) prepared data, facilitated intervention implementation, participated in ongoing planning, and contributed to communications to service

providers and other stakeholders, while managing other aspects of the larger study. DN is the university-based, lead agency (CUNY) Principal Investigator and shares responsibility for the conceptualization and oversight of the overall study and this trial, serves as the primary contact with the grant funding agency, supervises CUNY team members on the grant, and guides dissemination. MKI drafted the manuscript, and all authors (MKI, RZ, TA, MP, CE, SGK, MMP, EAK, and DN) revised it for critically important intellectual content and provided final approval of the manuscript.

APPENDICES

Appendix Table 1. Partnering agency characteristics and intervention arm assignments for the pilot trial

Agency type	MCM location(s)	Estimated eligible patient count*	Intervention condition
CBO	Rockland	67	Decision aid
Community health center, PCMH	Westchester and Rockland; agency also has sites in all 5 NYC counties	70	Decision aid
Community health center, PCMH	Westchester; agency also has a site in Putnam	129	Decision aid
Community health center, PCMH	Bronx; agency also has a site in Queens	104	Education only
Public university hospital, PCMH	Brooklyn (Kings County)	234	Education only
CBO	Manhattan (New York County) and Brooklyn (Kings County)	96	Education only

* Based on program data reported for the March 2022 – February 2023 Ryan White HIV/AIDS Program grant year, and restricted to patients 18+ years of age with Spanish or English as their primary language.

CBO, community-based organization with health and social services but without primary medical care; PCMH, patient-centered medical home (as recognized by the National Committee on Quality Assurance); MCM, medical case management; NYC, New York City

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ABBREVIATIONS

AB: advisory board

AIM: acceptability of intervention measure

APPLI: Assessing Perceptions and Preferences around Long-acting Injectables

ART: antiretroviral therapy

CFIR: Consolidated Framework for Implementation Research

DCE: discrete choice experiment

eSHARE: Electronic System for HIV/AIDS Research and Evaluation

FDA: Food and Drug Administration

FIM: feasibility of implementation measure

IAM: intervention appropriateness measure

LAI: long-acting injectable PWH: people with HIV

MCM: medical case management

NY: New York

NYC: New York City

RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance

RWHAP: Ryan White HIV/AIDS Program

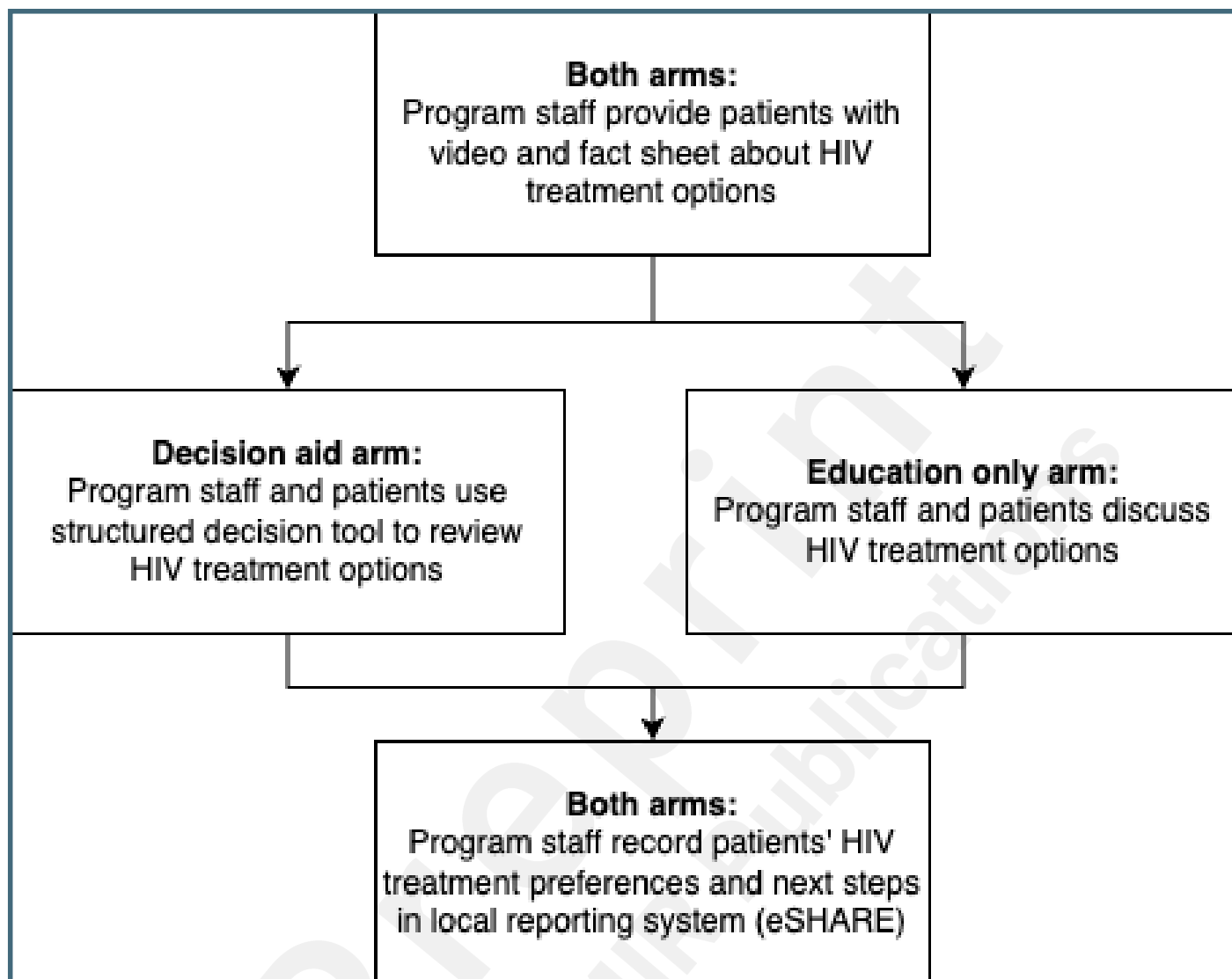
RWPA: RWHAP Part A

US: United States

Supplementary Files

Figures

Intervention arms and workflows for the two-arm pilot trial.



Multimedia Appendixes

Partnering agency characteristics and intervention arm assignments for the pilot trial.

URL: <http://asset.jmir.pub/assets/db7231b1b335e839432fa8d2340e99c2.docx>

LAI ART Pilot Fact Sheet.

URL: <http://asset.jmir.pub/assets/6e98cd92fc4be06fb443d21702e33a01.pdf>

LAI ART Pilot Video.

URL: <http://asset.jmir.pub/assets/ad305f09582d5c251ca11eab7784c46f.mp4>

LAI ART Decision Aid.

URL: <http://asset.jmir.pub/assets/4ae0cc52a0ec05b4bad1a82b84678392.pdf>



Related publication(s) - for reviewers eyes onlies

NYC Health Dept. Post-award IRB Approval.

URL: <http://asset.jmir.pub/assets/ea28308c63fa15d9a4ecd4f8c9bdb046.pdf>