BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054867
Article Type:	Original research
Date Submitted by the Author:	30-Jun-2021
Complete List of Authors:	Hodges, Jacqueline; University of Virginia Health System, Division of Infectious Diseases & International Health Waldman, Ava Lena ; University of Virginia Health System, Division of Infectious Diseases & International Health Koshkina, Olga; Irkutsk Regional Tuberculosis Referral Hospital Suzdalnitsky, Alexey; Irkutsk Regional Tuberculosis Referral Hospital Schwendinger, Jason ; University of Virginia Health System, Division of Infectious Diseases & International Health Vitko, Serhiy; University of Virginia Health System, Division of Infectious Diseases & International Health Plenskey, Alexey; Irkutsk Regional AIDS Centre Plotnikova, Yulia; Irkutsk Regional AIDS Centre Moiseeva, Elena; Irkutsk Regional Tuberculosis Referral Hospital Koshcheyev, Mikhail; Irkutsk Regional Tuberculosis Referral Hospital Sebekin, Sergey; Irkutsk Regional AIDS Centre Zhdanova, Svetlana; Scientific Centre for Family Health and Human Reproduction Problems Ogarkov, Oleg; Scientific Centre for Family Health and Human Reproduction Problems Heysell, Scott; University of Virginia Health System, Division of Infectious Diseases & International Health Dillingham, Rebecca; University of Virginia Health System, Division of Infectious Diseases & International Health
Keywords:	Tuberculosis < INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

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Practical considerations, challenges, and lessons learned in a multi-institution program to promote an integrated, mobile health-based approach for the care of people living with HIV and tuberculosis in Irkutsk, Siberia

Corresponding author:
Jacqueline Hodges
1215 Lee St, Charlottesville, VA 22903
Division of Infectious Diseases and International Health, University of Virginia
jch6sd@virginia.edu

Ava Lena Waldman
Division of Infectious Diseases and International Health, University of Virginia
ALW9T@hscmail.mcc.virginia.edu

Olga Koshkina
Irkutsk Regional Tuberculosis Referral Hospital
koshkina.1974@mail.ru

Alexey Suzdalnitsky
Irkutsk Regional Tuberculosis Referral Hospital
irksae@mail.ru

Jason Schwendinger
Division of Infectious Diseases and International Health, University of Virginia
jason.schwendinger@wht.care

Serhiy Vitko
Division of Infectious Diseases and International Health, University of Virginia
SV2U@hscmail.mcc.virginia.edu

Alexey Plenskey
Irkutsk Regional AIDS Centre
725590@gmail.com

Yulia Plotnikova
Irkutsk Regional AIDS Centre
plot18@yandex.ru

Elena Moiseeva
Irkutsk Regional Tuberculosis Referral Hospital
andrew959@mail.ru

Mikhail Koshcheyev
Irkutsk Regional Tuberculosis Referral Hospital
kme.57@mail.ru

Sergey Sebekin
Irkutsk Regional AIDS Centre
ssd@aids38.ru

Svetlana Zhdanova
Scientific Centre for Family Health and Human Reproduction Problems
svetnii73@gmail.com

Oleg Ogarkov
Scientific Centre for Family Health and Human Reproduction Problems
obogarkov@gmail.com

Scott Heysell
Division of Infectious Diseases & International Health, University of Virginia
SKH8R@hscmail.mcc.virginia.edu

Rebecca Dillingham
Division of Infectious Diseases & International Health, University of Virginia
RD8V@hscmail.mcc.virginia.edu

ABSTRACT

Objectives: Mobile health interventions for HIV self-management have been shown to improve HIV-related clinical outcomes and patient engagement in some but not all settings. We developed and tested a mobile health-based program to enhance integration of HIV and TB and promote a patient-centered approach in a region of high co-infection burden. Phases of program development included planning, stakeholder interviews, and platform re-build, testing and iteration.
Setting: In Irkutsk, Siberia, human immunodeficiency virus/tuberculosis (HIV/TB) co-infection prevalence is high relative to the rest of the Russian Federation.
Participants: Pilot testing occurred for a cohort of 60 people with HIV and TB.
Results: Key steps emerged to ensure the mobile health-based program could be operational and adequately adapted for the context, including platform language adaptation, optimization of server management, iteration of platform features, and organizational practice integration. Pilot testing of the platform re-build yielded favorable patient perceptions of usability and acceptability at 6 months (N=47 surveyed), with 18 of 20 items showing scores above 4 (on a scale from 1-5) on average. Development of this mobile health-based program for integrated care of infections highlighted the importance of several considerations for tailoring these interventions contextually, including language adaptation and technological capacity, but also, importantly, contextualized patient preferences related to privacy and communication with peers and/or providers, existing regional capacity for care coordination of different co-morbidities, and infection severity and treatment requirements.
Conclusions: Our experience demonstrated that integration of care for TB and HIV can be well served by using multimodal mobile health-based programs, which can enhance communication and streamline workflow between providers across multiple collaborating institutions and improve continuity between inpatient and outpatient care settings. Further study of the impact of this program on contextual disease-related stigma and social isolation as well as evaluation of implementation on a broader scale is currently under way.

ARTICLE SUMMARY

Strengths and limitations of this study

- A novel multimodal smartphone platform to support integrated HIV/TB care was designed, tested and iterated within the Irkutsk context.
- Pilot testing of the re-built platform yielded favorable perceptions of usability and acceptability following incorporation of local patient and provider feedback.
- Mobile health interventions should be tailored to the context where they are implemented, considering regional language and conventions, regional technological capacity, existing patient perceptions of peer and provider relationships, current care coordination systems, and regional severity and treatment requirements for infections targeted.
- Integration of care for TB and HIV is well served by using mobile health-based programs, which can streamline workflow between providers across multiple collaborating institutions and improve continuity between inpatient and outpatient care settings.
- Further platform testing in a larger cohort is necessary to consider how further care coordination and mitigation of stigma can be enhanced by the platform within the context of Irkutsk

INTRODUCTION

In Irkutsk, Siberia, there is a disproportionately high rate of co-infection with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and multidrug-resistant tuberculosis (MDR-TB) compared to the rest of the Russian Federation (RF)[1]. HIV/AIDS-related mortality persists as a major cause of premature mortality in the RF, particularly in TB co-infected patients[2]. Despite significant efforts by providers within the region to reduce yearly incidence, retain patients in care, and improve patient quality of life, progress continues to fall short of targets reached throughout the rest of Europe.

A range of factors influence patient engagement in HIV care globally, including sociodemographic disparities in care, limited transportation, a lack of trust in healthcare providers, and various psychosocial factors [3,4]. Several additional historical and socio-political factors impact HIV/TB co-infection in the RF, where disease-related stigma and misinformation potentiate social isolation and discourage patients from seeking and retaining in care[5-9]. For patients with comorbid substance use in the RF, stigma is further compounded in the form of criminalization policies, police abuse and exclusion from health care and employment opportunities[7,10]. A lack of integration of systems of care for HIV, TB and substance use also plays a role[11]. People living with HIV (PLWH) in Irkutsk must navigate additional geographic remoteness relative to regional HIV/AIDS treatment centers[12].

Mobile health (mHealth) interventions to enhance patient care have been shown to improve a variety of outcomes for PLWH[13-15]. For PLWH and TB, several different mHealth strategies have been trialed, typically involving automated text message appointment and medication reminders. One study combined reminders with enhanced phone communication with village health workers, aiming to increase initiation and adherence to antiretroviral therapy (ART)[16], while other studies deployed text reminders with additional educational quizzes and other health promotional material to enhance retention in TB treatment[17] as well as both HIV and TB care[18,19]. The strategies demonstrated acceptability in those contexts, however these interventions did not significantly improve outcomes related to treatment retention or death when studied[17,19]. To our knowledge, no mHealth strategies have been studied to enhance delivery of HIV and TB care within the Russian Federation.

A previously tested clinic-associated multi-feature smartphone platform called PositiveLinks demonstrated improvement in several HIV-related outcome measures for a population of PLWH seeking care at a Ryan White clinic in Virginia, USA[3,20-22]. Prior studies have identified a patient population in Irkutsk, Siberia with HIV/TB coinfection at high risk of disengagement with HIV care and low rates of early ART initiation[23,24]. We describe the planning, design and implementation of a multi-institution collaborative program aiming to use an integrated approach to enhance linkage of HIV/TB co-infected patients to HIV care and to promote sustained engagement in HIV and TB care. Integral to this effort was the adaptation of the PositiveLinks platform to be used in association with HIV/TB care in the unique context of Irkutsk. We share several programmatic considerations, challenges and experiences that emerged throughout program planning, design, testing, iteration and implementation in an effort to inform similar applications of integrated health care delivery enhanced by an mHealth-based approach in contextually related settings.

METHODS

Program Conception

Previous research efforts conducted by program team members have characterized patients hospitalized for active TB in Irkutsk who were co-infected with HIV[23]. Efforts to increase early ART initiation by streamlining the prescription and referral process during these hospitalizations have achieved some success[24]. The program described here was conceived with the aim to further promote cross-collaboration between HIV and TB clinicians and researchers in Irkutsk, in order to increase linkage to and engagement with care of PLWH and TB within the region. Adaptation of the PositiveLinks platform to Irkutsk was planned in order to facilitate a patient-centered approach, with the aim to test the adapted platform in a pilot cohort of patients previously identified as at risk for disengagement, followed by broader implementation throughout Irkutsk as well as dissemination to PLWH regardless of TB co-infection status.

Program Team
A long-term research collaboration exists between the Irkutsk Regional TB Referral Hospital (TB Referral Hospital), the Irkutsk Scientific Centre for Family Health and Human Reproduction Problems (Scientific Centre), and the University of Virginia. This collaboration includes several clinical TB care providers, researchers, a program coordinator, and a team member providing interpretation services and facilitation of cross-team communication. The program team was formed by addition of team members representing the Irkutsk Regional AIDS Centre, the primary provider of HIV/AIDS care in the region. Amongst those team members were several clinical HIV care providers, appointed intervention administrators, and a technical support officer. The program team was finalized by addition of members of the PositiveLinks multidisciplinary team based at the University of Virginia, including the PositiveLinks team lead, the project manager, and the lead technical support officer/platform developer.

PositiveLinks Platform
The PositiveLinks smartphone platform was originally designed to be accessed by PLWH in association with HIV care delivered at an outpatient clinic[25]. The platform provides several features including: 1) daily 'check-ins' or queries of stress, mood, and ART adherence; 2) appointment reminders; 3) tailored educational resources; 4) access to HIV-related laboratory results; 5) a community message board for anonymous peer messaging and 6) a direct messaging feature that allows patients to communicate with clinic care team members. Clinic staff are appointed to serve as app administrators, with access to a web-based portal that allows for monitoring of the community message board for inflammatory comments or identity disclosure, response to patient messages and uploading of labs and other documents.

Program Planning
Initial planning activities were conducted in Irkutsk during 2017, including program team meetings to discuss the logistics of program implementation and monitoring, partner organization visits, and finalization of institutional agreements. In conjunction with the initial planning activities in Irkutsk, 14 TB Referral Hospital and AIDS Centre providers underwent in-person training on portal usage and platform administration, patient enrollment and troubleshooting of user difficulties. Longitudinal program team meetings thereafter occurred bi-weekly and virtually by secure video calls throughout the remaining planning, pilot testing, and broader program implementation and dissemination phases.

Provider and Patient Interviews
During provider training sessions, program team members performed unstructured group interviews to engage providers on perceptions related to how the PositiveLinks platform could be adapted to meet the specific needs of their patient populations, as well as to elucidate logistical considerations for implementation of the intervention in the context. A total of 10 providers (clinical and non-clinical) from the TB Referral Hospital and AIDS Centre in Irkutsk were engaged through a series of additional unstructured group interviews with members of the intervention team. We primarily sought input on providers' priorities for HIV and TB management of their patients during these interviews.

Patient and Public Involvement
Twenty representative patients- ten patients with HIV treated at the AIDS Centre and ten patients with HIV and TB treated at the TB Referral Hospital- were interviewed by respective institutional providers on the program team regarding their priorities for self-management and monitoring of their HIV and TB. Responses were recorded and summarized into themes by the program team. Patients enrolled in the pilot study were also informally queried during study follow-up visits over the six months following enrollment on their perceptions of the functionality of various platform features in association with their outpatient care. Patient feedback was directly incorporated into platform re-build/iteration prior to and during pilot testing.

Platform Iteration and Testing
Patient and provider feedback on various aspects of the platform's design and functionality was gathered by study team members throughout both the planning and pilot study phases of the evaluation. Feedback was discussed and summarized by program team members during a series of working group meetings performed every two months during the first year. Following consensus reached from intervention team members, proposed modifications were provided to the team platform developer. Feature re-design was performed both during the planning phases and following pilot testing prior to intervention scale-up.

A pilot study was conducted to test the adapted platform in a subset of patients at risk for disengagement, with HIV and TB co-infection as well as substance use[26]. Patients admitted for active TB treatment at the TB Referral Hospital were offered enrollment from April 2018 to November 2019. Inclusion criteria included adults aged 18-64 years diagnosed with HIV (by laboratory testing for new diagnoses and chart review for patients with documented history), a history of using substances at the time of enrollment (confirmed by chart review or self-report), and residence in Irkutsk city. Patients unable or unwilling to use a smartphone or without cognitive ability to give informed consent were excluded. Written informed consent was obtained for all participants based on a protocol approved by the human subjects institutional review boards (IRB-HSR 20451) at the Scientific Centre for Family Health and Human Reproduction Problems and the University of Virginia (Clinical Trial Registration Number: NCT03819374).

Patients were provided a smartphone as well as a data plan if needed, and they underwent training on use of the platform followed by a short proficiency test. Patients were initiated or re-initiated on ART and enrolled in the intervention prior to discharge. Follow up HIV care was provided at the AIDS Centre and TB care at the TB Referral Hospital/associated clinics. Patients enrolled in the pilot study were provided a follow up survey at six months post-enrollment (twenty-item survey, scored on a Likert scale 1-5, 1=strongly disagree, 5=strongly agree) of perceptions related to platform usability and acceptability, originally adapted for PositiveLinks then modified for use with MOCT in Russian language[27]. In addition, administrators performed a preliminary qualitative review of a sample of community message board content posted anonymously by pilot study participants over the six-month follow up period.

Data Analysis

Patient and provider interviews were summarized in descriptive narrative form. Patient interview responses regarding HIV and TB treatment priorities were also recorded and themes were generated by consensus from at least two study team members. Community message board content was downloaded from the platform, translated into English, and themes from interviews were applied again by team member consensus. Platform survey scoring was analyzed using descriptive statistics. Analyses were performed with IBM SPSS Statistics for Mac, Version 26.0 (Statistical Package for the Social Sciences, IBM Corp, Armonk, NY, USA).

RESULTS

Several steps emerged that were critical to the process of planning and implementing the program, including 1) language adaptation of platform components, 2) optimization of server management, 3) iteration of platform features, and 4) program organizational practice integration. Below we detail how these various processes were specifically informed by stakeholder input.

Language and Contextual Adaptation

Interpretation services were provided by a bilingual US-based team member for all program meetings. Several Irkutsk-based team members were also bilingual (spoke both English and Russian). Our interpreter communicated the desired platform changes to US-based program team members following direct translation from Russian to English, based on Irkutsk-based program team member, clinical provider, and patient feedback. Initial patient feedback on language adaptation of platform components from English indicated that patients preferred the Russian term for ‘bridges’ or ‘moct,’ over ‘links.’ They felt that it more effectively reflected the aim of the platform to enhance integration of HIV and TB care and captured the context of Irkutsk, where several bridges cross the Angara River. Patients also felt there was a ‘carceral’ implication to the translated Russian word for ‘links,’ connoting being ‘locked up’ or ‘chained’ rather than a word connoting unification or partnership. Thus, the platform was named ‘MOCT.’ The title change also prompted re-design of the platform title logo to display a bridge as opposed to a chain link. Additional platform components needing adaptation to Russian convention included date and time formatting, calendar formatting (to a Monday to Sunday display) and alteration of the description of the community message board feature to a ‘chat’ board.

Server Management

Planning meetings conducted with the program team yielded discussion surrounding the setup and management of a suitable server. Initially, an on-site server was installed at the TB Referral Hospital. This

server was managed in part by the hospital's technical officer, while software and operating system updates were regularly updated by the team's US-based platform developer, each time requiring permission be requested to access the server remotely through access control software, which regularly changed the password. The server experienced intermittent system crashes; there was no monitoring system to track when or how long the system was down. There were also issues with connectivity when our US-based platform developer could not access and troubleshoot issues with the server remotely. Following platform testing during the pilot study and gathering of provider experiences with the platform and the server, the team upgraded to secure cloud services to host server data, maintaining access control software through which the US-based team platform developer could provide remote assistance. Ultimately, however, ongoing server management was primarily handled locally by AIDS Centre staff.

Platform Iteration

AIDS Centre and TB Referral Hospital providers and patients provided feedback regarding their priorities for management of HIV and TB, as well as how the platform could help meet these needs, in order to inform platform iteration. Patients were provided with the following three prompts to generate discussion: 1) What is the most important aspect of your health? 2) If you are living with HIV, what would be the most important part of your HIV care that you would like to monitor? 3) If you are recovering from TB, what would be the most important part of your TB care that you would like to monitor? Providers were similarly asked about their thoughts on their own priorities for HIV and TB management of their patients, as well as how best to measure the effectiveness of prescribed therapy and overall HIV and TB care for patients that would participate in the intervention. Themes that emerged from these conversations are detailed below and summarized in **Table 1.**

Table 1. Selected patient interview responses regarding priorities in management of HIV and TB, associated iteration of the PositiveLinks platform features performed in re-build of the MOCT platform, and example community message board posts following patient testing of the MOCT platform.

Themes	Example Patient Interview Responses	Resulting Platform Feature Iteration	Example Community Message Board Posts
Individual and community effectiveness of HIV and TB Care	*"CD4 numbers: I would like to know how many cells with AIDS I have"* *"Cure and then control"* *"Am I dangerous to others"* *"[monitoring]…about lab results periodically"* *"That my treatment was successful, the cells were respectively normal"* *"Improving health condition and major indicators: reducing viral load to undetectable levels, increasing CD4 lymphocytes"*	Added TB culture results to 'lab upload' feature in addition to maintaining upload feature for HIV viral load and CD4 results; educational resources related to monitoring treatment progress/efficacy were maintained, community message board and direct messaging features maintained to allow providers to re-enforce patient treatment goals	*"Your goal and ours is your recovery, and a full inpatient treatment stage is 70% of success" (provider)*
Transparency of care	*"I would like to know everything about my treatment"* *"Openness about treatment"* *"Truthfulness of tests and timely selection of medications"* *"More information about my treatment"*	Community message board made accessible to providers to distribute information to patients; educational resources tailored to setting and added for TB; clinic appointment reminders, provider contact information, direct messaging feature maintained	*"When prescribing antiretroviral therapy, its effectiveness, first of all, is assessed by reducing viral load. CD4 count increases more slowly" (provider)*

Well-being	*"Well-being"* *"Stay alive, get the joy of life"* *"Good mood"* *"Increased vital tonus (new work, new acquaintances)"*	Daily queries for mood, stress were maintained; community message board maintained for provision of peer support	*"I have problems with housing and animals" (patient)* *"I heard that in case of tuberculosis people are eligible for a separate housing. Does anyone know if it is true?" (patient)* *"The most important thing is to know what all of this is for, and I have my motivation - my CHILDREN. And I want to participate in their life, and after all to see my grandchildren grow" (patient)* *"I was in the hospital, it was very hard, but it's ok, I did it." (patient)*
Self-management	*"Stability and control over my own health condition"* *"I would like to control the treatment itself"* *"Self-discipline"* *"Rejection of bad habits"* *"Structuring life (correct priorities)"*	Providers added targeted messages to encourage self-management on community message board including those related to COVID-19 as the pandemic evolved; TB lab upload function and daily TB medication reminders added; maintained document upload feature	*"What is more important to increase cell count or to decrease viral load?" (patient)* *"If you don't take therapy, nothing will pass by itself, the load has decreased to 440, and I'm not going to stop there" (patient)* *"I have a question! Some drugs that are used for HIV also beat the coronavirus. Does this mean if I get infected, the infection will die immediately? Or can I not get infected at all?" (patient)*

Patients and providers emphasized "individual and community-level effectiveness of HIV and TB care." They wanted to support patients' knowledge of treatment progress and efficacy. Therefore, the 'labs upload' feature was maintained to facilitate tracking of CD4 cell counts and HIV viral load lab results, and TB culture conversion (from positive to negative) results were added to the platform as a key clinical indicator for PLWH co-infected with TB. By checking the portal's record of laboratory collection date and result, providers were able to monitor patients' progress and to reach out to patients behind schedule. Educational resources related to monitoring of HIV treatment progress and interpreting lab results were maintained, and similar resources were added for monitoring of drug-resistant TB treatment. Community-level effectiveness referred to shared desires expressed by patients and providers to see how the AIDS Centre's patient panel

was doing collectively in terms of lab monitoring and treatment progress. However, this was not able to be incorporated into the platform re-build for patient viewing, and it is being considered as the program expands.

Another theme involved the "transparency of care," as both providers and patients emphasized openness and transparency throughout the treatment course. Patients highlighted their desire to be given updated, accurate and honest information about their disease and their treatment course. Platform features maintained as a result included clinic appointment information, provider contact information, and the direct messaging feature as an open line for out-of-clinic communication. While patients in the US preferred that the community message board remain private for patients, with only administrators moderating content, patients in Irkutsk preferred to allow providers to view posts, write responses, and answer questions.

In regards to patient perceptions of the "most important aspect of their health," "well-being" emerged as a priority for several patients, suggesting that quality of life beyond treatment efficacy was critical. The daily query features for mood and stress were maintained as a result, as well as the community message board, which has previously shown utility as a source of peer support in other cohorts[21]. Peer support has been shown to contribute to improved psychosocial and emotional health and wellness, and was maintained in the platform re-build, as other cohorts demonstrated appreciation for this feature after utilizing it[28].

Finally, components of 'self-management' emerged as priorities for patients as well. Patients recognized the importance of self-efficacy and self-discipline, or taking control of their own treatment plan. Several features consistent with the goal of self-management were maintained including: the laboratory value upload function, daily medication reminders, and the option to upload documents for providers to access. For patients co-infected with TB, an additional anti-TB therapy reminder was built into the platform that included the possibility for patients to set up twice daily reminders for medications. To account for multiple-pill regimens, an option indicating having taken 'all, some or none' of their medications, rather than just a yes/no response (appropriate for single combination pill ART regimens), was developed.

Platform Re-build

The platform interface and features are shown following modification by the platform developer based on input gathered through our qualitative evaluation (**Figure 1).**

Usability and Acceptability

Patients' perceptions of platform usability and acceptability were assessed following 6 months of participation in the intervention (**Table 2)**. A total of 60 patients were enrolled in the pilot study and are described elsewhere[26]. The survey was completed by 47 participants (7 patients were lost to follow up, 2 were deceased by six months, 1 did not attend the 6-month assessment, and 3 attended the assessment but did not complete the survey). Categories of survey questions were grouped as follows: 1) Impact 2) Perceived Usefulness 3) Perceived Ease of Use and 4) User Control. On average, patients scored above 4 on a scale from 1 to 5 (5=strongly agree) for all but two survey items. The lowest scored items were both related to the perceived usefulness of the platform in facilitating 'quicker' or 'more timely' self-management of HIV-related symptoms.

Table 2: Usability and acceptability survey at six months following pilot testing for a cohort of participants (N=47). Each item is scored by participants on a scale from 1 (lowest) to 5 (highest).

Survey Item	Mean (SD)
Impact	
I think MOCT application would be a positive addition for persons living with HIV.	4.19 (1.28)
I think MOCT application would improve the Quality of Life of persons living with HIV.	4.15 (1.30)
MOCT application is an important part of meeting my information needs related to symptom self-management.	4.28 (1.26)
Perceived Usefulness	

Using MOCT application makes it easier to self-manage my HIV-related symptoms.	4.11 (1.43)
Using MOCT application enables me to self-manage my HIV symptoms more quickly.	3.98 (1.36)
Using MOCT application makes it more likely I can self-manage my HIV-related symptoms.	4.15 (1.32)
Using MOCT application is useful for self-management of HIV-related symptoms.	4.19 (1.33)
I think MOCT application presents a more equitable process for self-management of HIV-related symptoms.	4.15 (1.37)
I am satisfied with MOCT application for self-management of HIV-related symptoms.	4.17 (1.29)
I self-manage my HIV-related symptoms in a timely manner because of MOCT application.	3.94 (1.36)
Using MOCT application increases my ability to self-manage my HIV-related symptoms.	4.13 (1.31)
I am able to self-manage my HIV-related symptoms whenever I use MOCT application.	4.07 (1.44)
Perceived Ease of Use	
I am comfortable with my ability to use MOCT application.	4.09 (1.38)
Learning to operate MOCT application is easy for me.	4.30 (1.04)
It is easy for me to become skillful in using MOCT application.	4.17 (1.19)
I find MOCT application easy to use.	4.23 (1.15)
I can always remember how to log onto and use MOCT application.	4.38 (1.11)
User Control	
MOCT application gives error messages that clearly tell me how to fix a problem.	4.19 (1.25)
Whenever I make a mistake using MOCT application, I recover easily and quickly.	4.30 (1.18)
The information (such as on-line help, on-screen messages and other documentation) provided with MOCT application is clear.	4.40 (1.12)

Community Message Board Content

Following testing of the adapted platform in the pilot study for six months, a review of a sample of community message board content was performed. This assessment of conversations on the community message board between patients, as well as between patients and providers, allowed the study team to gauge whether the previously identified priorities were being met within the platform. Interactions on the community message board were mapped to the themes generated based on patient and provider interviews (See **Table 1**). With regard to "individual effectiveness of HIV and TB therapy," several community message board posts demonstrated that the feature was an opportunity for providers and other patients to re-enforce treatment goals. To enhance "transparency of care," providers distributed community educational resources and content verified as accurate and up to date on the board, including for those seeking COVID-19 related services after March 2020. In addition, patients were able to obtain support in interpreting and understanding their lab results by eliciting the opinions, experiences and knowledge of both peers and providers. As for the concept of "well-being," anonymous peer messaging allowed for patients to seek information and assistance related to non-medical needs, including housing, child care, and other concerns. They also had the opportunity to provide first-hand perspective and positive role-modeling. Providers provided encouragement as well. Finally, with reference to "self-management," the community message board afforded patients the opportunity to reach out to providers and peers, initiating conversations about their own needs and seeking information to help guide their own care.

Organization Practice Integration

In previous years, the TB Referral Hospital and AIDS Centre provided TB and HIV care that was largely separate, consistent with traditional systems of care delivery in the region[11]. Following formation of the multi-institution program team, local members of both organizations continued to meet on a biweekly basis

throughout the planning and platform testing phases. Several clinical providers from the TB Referral Hospital underwent training first and became familiarized with the provider portal, and, during subsequent provider training sessions, they assumed unprompted 'peer teacher' roles, which led to robust discussions of the platform and shared goals for its use between providers of the two organizations. Discussions fostered additional brainstorming regarding ways to incorporate TB care into the HIV-centered platform. Resulting components built into the mHealth strategy also triggered integration of other care efforts. Specifically, availability to both institutions of appointment information and direct messaging availability for providers at both organizations has streamlined the referral, linkage, and follow up processes for patients referred to the AIDS Centre from the TB Referral Hospital. Previously inaccessible patient information and lab results have become available to share between the organizations through the platform. Professional collaboration and regular communication between these organizations has continued following program scale-up beyond pilot testing.

Program Implementation and Platform Dissemination

Pilot study participants demonstrated improved rates of linkage to care at the AIDS Centre and ongoing engagement with the platform by six months as well as better rates of medication refill and a lower propensity towards developing the composite outcome of death and failure to achieve viral suppression at six months[26]. Following contextual evaluation of patient and provider perceptions and platform testing and modification, the program has been implemented across the Irkutsk oblast (federal region similar to state). Enrollment has expanded to four TB Referral Hospital filial (affiliated) clinics following hospital administrative approval and engagement of clinic leadership. Importantly, the MOCT platform has been disseminated to a broader population of PLWH living in Irkutsk oblast both with and without TB (**Figure 2**). Providers at filial clinics underwent similar group training sessions on patient enrollment, linkage coordination to the AIDS Centre, and MOCT administration. In addition to recruitment of HIV/TB coinfected patients at filial sites, patient recruitment has been expanded to all patients in care at the AIDS Centre, including those without TB. Following scale-up of the program, patients are able to seek enrollment in the platform across a large area served by the participating provider organization sites.

DISCUSSION

We examined the design, planning, and pilot testing of a multi-institution collaborative program using a mHealth approach to enhance the linkage and engagement of PLWH with or without TB in care In Irkutsk. Our aim was to elucidate potential considerations for groups hoping to apply similar strategies to the care of PLWH with or without TB in other contextually related settings. We identify several aspects of the project design and conduct that may have contributed to the successful uptake and high linkage rates observed following pilot testing[26]. Specifically, the team members were well-informed from prior experience and stakeholder feedback about the care systems already in place in Irkutsk. In addition, they iterated continuously from the planning to expansion and dissemination phases. Key components of the program's planning and implementation processes included language and contextual adaptation, server management, a cycle of platform iteration and testing before the MOCT platform was finalized, and organization practice integration.

Following language and contextual adaptation and patient and provider-informed iteration of the platform based on local priorities, pilot testing indicated high average scoring by the cohort on platform usability and acceptability at 6 months. The lower scored survey items (still above 3 out of 5) were both related to perceived usefulness of the platform in facilitating self-management 'more quickly' or in a 'more timely' manner. Patients did, however, generally rate the app highly as 'making it easier' or 'more likely' for them to self-manage symptoms on average. Notably, these survey items as well as several others within the category of 'perceived usefulness' became somewhat redundant following language adaptation of the survey.

Provider and patient input gathered throughout the planning and pilot testing phases on platform functionality revealed many shared priorities that aligned with the original platform features, although there were some modifications including added functionality related to TB management. Notable differences in patient testing of the platform included preferences by patients in Irkutsk to allow providers to contribute to discussions on the community message or 'chat' board. While patients in the US cohort appeared to prefer

privacy for peer discussions, as platform testing occurred, patients in Irkutsk began demonstrating an interest in gathering information and support from their clinical providers and peers simultaneously. This change highlights the need to consider how patient-provider and peer relationships vary across contexts when building this type of feature into a platform. Preliminary review of chat board content demonstrates patients directly engaged with providers and with one another to provide perspectives and encouragement surrounding their shared diagnoses. However, the direct impact of the platform on patients' perceived ability to navigate stigma and gain social support within this context requires further investigation.

This build of the platform required specific consideration of the additional burden of drug-resistant TB that patients face within the context, as well as the additional demanding medication regimens required for treatment. The platform was also tested for the first time in patients seen in both outpatient and inpatient settings, which allowed for elicitation of patient perspectives through the continuum of care delivery across those different settings. The platform provided a unique opportunity to prevent discontinuity of care following discharge from the TB Referral Hospital.[26] Various features were similarly helpful in preventing service disruptions related to COVID-19 for participants later in implementation. Conservative models estimate that COVID-19 related disruption in HIV and TB services in high-burden settings could increase HIV-related death by 10% and TB-related death by 20% in the 5 years following the pandemic.[29] With the MOCT platform, patients initiated chat board and messaging conversations querying specific ART impact on SARS-CoV-2, and appeared to use the features to navigate social isolation and barriers to service during periods of lockdown, indicating a potential role for these forms of mHealth-enhanced care in the current pandemic and in the years to come.

Importantly, the development of this program occurred in a specific sociopolitical environment within Irkutsk. Separated systems of care for TB and HIV exist there and in other regions of the Russian Federation, urban or otherwise, and our findings suggest they may benefit from similar integrated approaches to program development for the care of these co-morbid infections. Administrative approval of information sharing between collaborating institutions was obtained, and secure information sharing was made feasible in part because it was built into the mHealth strategy used. Organizational buy-in and approval and methods for secure and effective information sharing must be considered when planning similar integrated approaches to novel care delivery.

Recruitment of a dedicated bilingual program manager to the program team significantly streamlined cross-team communication. This team member's participation was critical for enhancing collaboration and data-sharing capabilities between program team members, as well as translation of various components of the platform to the local conventions, terminology, and patient/provider preferences. We also found that developing local capacity for technical support was instrumental for day-to-day troubleshooting. The recruitment of an experienced technology lead with mobile application development and systems administration skills to assist with program activities facilitated the launch and management of the server through the planning and pilot phases. However, sustaining ongoing server management through program expansion necessitated expansion of the technology lead's role to provision of training to local Irkutsk team members appointed to perform troubleshooting and manage user concerns that arose related to the platform.

Several challenges arose throughout the course of program development and implementation. While injection drug use is a major risk factor for transmission in the region[12], and pilot testing of the platform occurred in a cohort with substance use at high risk for disengagement, only limited resources related to local rehabilitation and harm reduction services were available to share on the platform reflecting systemic barriers to access within the region[11,30]. Well-being was identified as a management priority by patients, however aside from maintaining peer support functionality through the community message board, the platform re-build did not specifically measure patient access to more holistic care services (e.g. mental health, nutrition, employment services) following participation. Further efforts toward platform iteration are necessary to consider how further care coordination can be enhanced by the platform in a context where these services are not necessarily co-localized with outpatient HIV care. Several validated patient survey tools were considered for the purpose of data collection following pilot testing, however availability in Russian language was highly limited. The dearth of validated survey tools to assess mHealth interventions in different languages poses a broader challenge to assessment of platforms within contexts where they

remain novel. We were able to incorporate the majority of patient and provider feedback into the new MOCT platform build. However, patient access to regularly updated, aggregate community-level data was not feasible prior to platform dissemination, and is being considered as the program expands.

CONCLUSION

The development of this mHealth-based program, spanning efforts of multiple institutions in the US and Irkutsk, was a significant undertaking requiring advanced planning and coordination, consistent collaboration between program team members, participating providers, and beneficiary patients at all stages, and consideration of unique contextual factors. The major challenges and facilitating factors that arose for our program are likely to be relevant when creating or adapting mHealth-based, integrated care delivery programs in similar settings with high HIV/TB burden and geographic remoteness relative to treatment settings. Further evaluation of the program is planned following expansion and dissemination of the platform across Irkutsk, including 'real world' platform uptake and program effectiveness.

ACKNOWLEDGMENTS

We thank the patients who participated in this study, as well as all collaborators and staff at the Irkutsk Regional TB Referral Hospital and filial clinics, and Irkutsk AIDS Centre.

FUNDING INFORMATION

Funding for this study was provided by the National Institutes of Health (NIH) (R01DA04413, T32AI007046) and Russian federal R&D financing of the Scientific Centre for Family Health and Human Reproduction Problem.

COMPETING INTERESTS

Authors R.D., A.L.W., and J.S. provide consulting services to Warm Health Technology, Inc., an entity that supports dissemination of PositiveLinks. R.D. has also received an investigator-initiated grant from Gilead, Inc., which is unrelated to this study. The other authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Study conception: S.H., R.D. Protocol development: J.S., A.L.W., O.O., R.D., S.H. Study activities and follow-up: S.Z., O.K., A.S.,A.P., Y.P., E.M., M.K., S.V., A.L.W., J.S., S.S. Article conceptual development and preparation: J.H., A.L.W., R.D., S.H. Data analysis: J.H. Article review and contributions: all authors.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed for this study are available from the corresponding author, J.H., on reasonable request.

ETHICS APPROVAL STATEMENT

The study protocol was approved by the human subjects institutional review boards at the Scientific Centre for Family Health and Human Reproduction Problems and the University of Virginia (IRB-HSR 20451) (Clinical Trial Registration Number: NCT03819374).

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Figure 1. MOCT Platform features following adaptation. MOCT platform includes a dashboard (1), a community message or ‘chat’ board (2), direct provider messaging (3), educational/community resources (4), daily queries of mood (5), stress (6), adherence to HIV/TB medications (7), appointment and medication reminders (8), and HIV/TB lab results.

Figure 2. MOCT Program Activities. Program activities are summarized from conception and team formation to broader expansion across Irkutsk. MOCT is Russian for ‘bridge,’ and describes the platform following language translation and contextual adaptation. TB – tuberculosis; UVA – University of Virginia; TBH – TB Referral Hospital; HIV – human immunodeficiency virus; PLWH – people living with HIV; PL – PositiveLinks; AC - AIDS Centre

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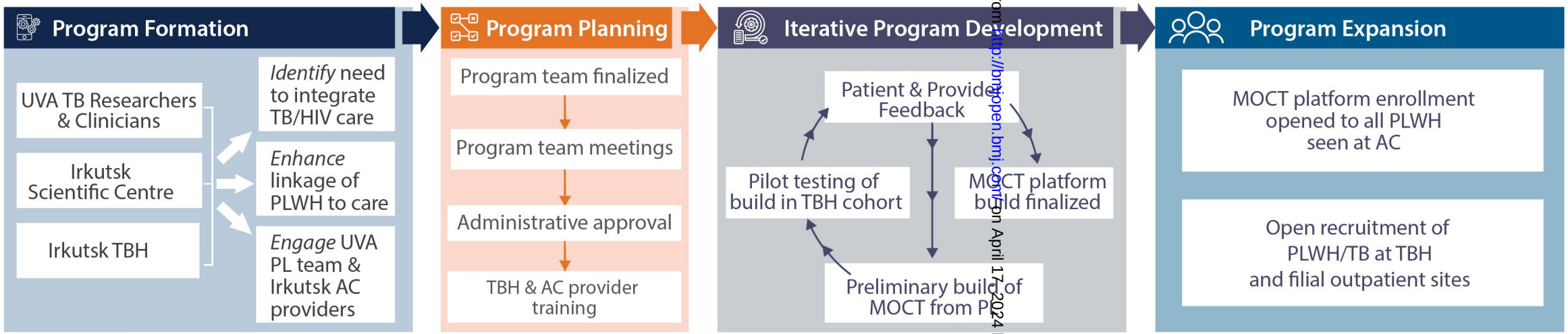

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Process evaluation for the adaptation, testing and dissemination of a mobile health platform to support people with HIV and tuberculosis in Irkutsk, Siberia

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054867.R1
Article Type:	Original research
Date Submitted by the Author:	20-Jan-2022
Complete List of Authors:	Hodges, Jacqueline; University of Virginia Health System, Division of Infectious Diseases & International Health Waldman, Ava Lena ; University of Virginia Health System, Division of Infectious Diseases & International Health Koshkina, Olga; Irkutsk Regional Tuberculosis Referral Hospital Suzdalnitsky, Alexey; Irkutsk Regional Tuberculosis Referral Hospital Schwendinger, Jason ; University of Virginia Health System, Division of Infectious Diseases & International Health Vitko, Serhiy; University of Virginia Health System, Division of Infectious Diseases & International Health Plenskey, Alexey; Irkutsk Regional AIDS Centre Plotnikova, Yulia; Irkutsk Regional AIDS Centre Moiseeva, Elena; Irkutsk Regional Tuberculosis Referral Hospital Koshcheyev, Mikhail; Irkutsk Regional Tuberculosis Referral Hospital Sebekin, Sergey; Irkutsk Regional AIDS Centre Zhdanova, Svetlana; Scientific Centre for Family Health and Human Reproduction Problems Ogarkov, Oleg; Scientific Centre for Family Health and Human Reproduction Problems Heysell, Scott; University of Virginia Health System, Division of Infectious Diseases & International Health Dillingham, Rebecca; University of Virginia Health System, Division of Infectious Diseases & International Health
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	HIV/AIDS, Patient-centred medicine, Public health
Keywords:	Tuberculosis < INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

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Process evaluation for the adaptation, testing and dissemination of a mobile health platform to support people with HIV and tuberculosis in Irkutsk, Siberia

Corresponding author:
Jacqueline Hodges
1215 Lee St, Charlottesville, VA 22903
Division of Infectious Diseases and International Health, University of Virginia
jch6sd@virginia.edu

Ava Lena Waldman
Division of Infectious Diseases and International Health, University of Virginia
ALW9T@hscmail.mcc.virginia.edu

Olga Koshkina
Irkutsk Regional Tuberculosis Referral Hospital
koshkina.1974@mail.ru

Alexey Suzdalnitsky
Irkutsk Regional Tuberculosis Referral Hospital
irksae@mail.ru

Jason Schwendinger
Division of Infectious Diseases and International Health, University of Virginia
jason.schwendinger@wht.care

Serhiy Vitko
Division of Infectious Diseases and International Health, University of Virginia
SV2U@hscmail.mcc.virginia.edu

Alexey Plenskey
Irkutsk Regional AIDS Centre
725590@gmail.com

Yulia Plotnikova
Irkutsk Regional AIDS Centre
plot18@yandex.ru

Elena Moiseeva
Irkutsk Regional Tuberculosis Referral Hospital
andrew959@mail.ru

Mikhail Koshcheyev
Irkutsk Regional Tuberculosis Referral Hospital
kme.57@mail.ru

Sergey Sebekin
Irkutsk Regional AIDS Centre
ssd@aids38.ru

Svetlana Zhdanova
Scientific Centre for Family Health and Human Reproduction Problems
svetnii73@gmail.com

Oleg Ogarkov
Scientific Centre for Family Health and Human Reproduction Problems
obogarkov@gmail.com

Scott Heysell
Division of Infectious Diseases & International Health, University of Virginia
SKH8R@hscmail.mcc.virginia.edu

Rebecca Dillingham
Division of Infectious Diseases & International Health, University of Virginia
RD8V@hscmail.mcc.virginia.edu

ABSTRACT

Objectives: We developed and tested a mobile health-based program to enhance integration of human immunodeficiency virus (HIV) and tuberculosis (TB) care and to promote a patient-centered approach in a region of high co-infection burden. Phases of program development included planning, stakeholder interviews, and platform re-build, testing and iteration.

Setting: In Irkutsk, Siberia, HIV/TB co-infection prevalence is high relative to the rest of the Russian Federation.

Participants: Pilot testing occurred for a cohort of 60 people with HIV and TB.

Results: Key steps emerged to ensure the mobile health-based program could be operational and adequately adapted for the context, including platform language adaptation, optimization of server management, iteration of platform features, and organizational practice integration. Pilot testing of the platform re-build yielded favorable patient perceptions of usability and acceptability at 6 months (N=47 surveyed), with 18 of 20 items showing scores above 4 (on a scale from 1-5) on average. Development of this mobile health-based program for integrated care of infections highlighted the importance of several considerations for tailoring these interventions contextually, including language adaptation and technological capacity, but also, importantly, contextualized patient preferences related to privacy and communication with peers and/or providers, existing regional capacity for care coordination of different co-morbidities, and infection severity and treatment requirements.

Conclusions: Our experience demonstrated that integration of care for TB and HIV can be well served by using multimodal mobile health-based programs, which can enhance communication and streamline workflow between providers across multiple collaborating institutions and improve continuity between inpatient and outpatient care settings. Further study of program impact on contextual disease-related stigma and social isolation as well as evaluation of implementation on a broader scale for HIV care is currently under way.

ARTICLE SUMMARY

Strengths and limitations of this study

- The study provides guidance related to the processes of adaptation, testing, and dissemination of mHealth strategies to support patients with HIV, including those co-infected with TB with unique needs in distinct contexts.
- This study specifically examines a smartphone app designed to provide patient support through multiple features, which is novel in that its functionalities extend beyond supports for daily medication adherence alone.
- Patient and provider feedback were elicited through iterative evaluation of platform adaptation and testing in Irkutsk, and these processes were facilitated thanks to the inclusion of program team members with dedicated roles related to providing language translation and technological assistance.
- Patient post-participation surveys were performed to assess usability and acceptability of the MOCT platform, however the tool used was not validated for the language and context.
- Further study using implementation science frameworks to elucidate specific reasons for patient and provider uptake or non-participation following broad platform dissemination is needed.

INTRODUCTION

In Irkutsk, Siberia, there is a disproportionately high rate of co-infection with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and multidrug-resistant tuberculosis (MDR-TB) compared to the rest of the Russian Federation (RF), with surveillance indicating over 125 new cases of co-infection registered per 100,000 people in the most recent publicly accessible reports[1]. HIV/AIDS-related mortality persists as a major cause of premature mortality in the RF, particularly in TB co-infected patients[2]. Despite significant efforts by providers within the region to reduce yearly incidence, retain patients in care, and improve patient quality of life, progress continues to fall short of targets reached throughout the rest of Europe.

A range of factors influence patient engagement in HIV care globally, including sociodemographic disparities in care, limited transportation, a lack of trust in healthcare providers, and various psychosocial factors [3,4]. Several additional historical and socio-political factors impact HIV/TB co-infection in the RF, where disease-related stigma and misinformation potentiate social isolation and discourage patients from seeking and retaining in care[5-9]. For patients with comorbid substance use in the RF, stigma is further compounded in the form of criminalization policies, police abuse and exclusion from health care and employment opportunities[7,10]. A lack of integration of systems of care for HIV, TB and substance use also plays a role[11]. People with HIV (PWH) in Irkutsk must navigate additional geographic remoteness relative to regional HIV/AIDS treatment centers[12].

Mobile health (mHealth) interventions to enhance patient care have been shown to improve a variety of outcomes for PWH[13-15]. For PWH and TB, several different mHealth strategies have been trialed. One study combined reminders with enhanced phone communication with village health workers, aiming to increase initiation and adherence to antiretroviral therapy (ART)[16], while other studies deployed text reminders with additional educational quizzes and other health promotional material to enhance retention in TB treatment[17] as well as both HIV and TB care[18,19]. The strategies demonstrated acceptability in those contexts, however these interventions did not significantly improve outcomes related to treatment retention or death when studied[17,19]. A multi-faceted mHealth strategy designed to support patients beyond tracking of daily medication adherence has not been studied for HIV/TB or TB mono-infection, despite a pressing need identified in recent years[20,21]. Furthermore, to our knowledge, no mHealth strategies have been studied to enhance delivery of HIV and TB care within the Russian Federation.

A previously tested clinic-associated multi-feature smartphone platform called PositiveLinks demonstrated improvement in several HIV-related outcome measures for a population of PWH seeking care at a federally-funded clinic in Virginia, USA[3,22-24]. Prior studies have identified a patient population in Irkutsk, Siberia with HIV/TB coinfection at high risk of disengagement with HIV care, low rates of early ART initiation, and high risk of short-term mortality[25,26]. We describe the planning, design and implementation of a multi-institution collaborative program aiming to use an approach to enhance linkage of HIV/TB co-infected patients to HIV care and to promote sustained engagement with and integration of HIV and TB care. Integral to this effort was the adaptation of the PositiveLinks platform to be used to support HIV/TB care in the unique context of Irkutsk. We share several programmatic considerations, challenges and experiences that emerged throughout program planning, design, testing, iteration and implementation in an effort to inform similar efforts to integrate health care delivery with the support of a contextually-tailored mHealth intervention.

METHODS

Program Conception

Previous research efforts conducted by program team members have characterized patients hospitalized for active TB in Irkutsk who were co-infected with HIV[25]. Efforts to increase early ART initiation by streamlining the prescription and referral process during these hospitalizations have achieved some success[26]. The program described here was conceived with the aim to further promote cross-collaboration between HIV and TB clinicians and researchers in Irkutsk, in order to increase linkage to and engagement with care of PWH and TB within the region. Adaptation of the PositiveLinks platform to Irkutsk was planned in order to facilitate a patient-centered approach, with the aim to test the adapted platform in a pilot cohort

of patients previously identified as at risk for disengagement, followed by broader implementation throughout Irkutsk as well as dissemination to PWH regardless of TB co-infection status.

Program Team

A long-term research collaboration exists between the Irkutsk Regional TB Referral Hospital (TB Referral Hospital), the Irkutsk Scientific Centre for Family Health and Human Reproduction Problems (Scientific Centre), and the University of Virginia. This collaboration includes several clinical TB care providers, researchers, a program coordinator, and a team member providing interpretation services and facilitation of cross-team communication. The program team was formed by addition of team members representing the Irkutsk Regional AIDS Centre, the primary provider of HIV/AIDS care in the region. Amongst those team members were several clinical HIV care providers, appointed intervention administrators, and a technical support officer. The program team was finalized by addition of members of the PositiveLinks multidisciplinary team based at the University of Virginia, including the PositiveLinks team lead, the project manager, and the lead technical support officer/platform developer.

PositiveLinks Platform

The PositiveLinks smartphone platform was originally designed to be accessed by PWH in association with HIV care delivered at an outpatient clinic[27]. The platform provides several features including: 1) daily 'check-ins' or queries of stress, mood, and ART adherence; 2) appointment reminders; 3) tailored educational resources; 4) access to HIV-related laboratory results; 5) a community message board for anonymous peer messaging, whereby users can give and receive emotional support, information and navigate stigma and 6) a direct messaging feature that allows for low barrier communication with clinic care team members outside of clinic. Clinic staff are appointed to serve as app administrators, with access to a web-based portal that allows for monitoring of the community message board for inflammatory comments or identity disclosure, response to patient messages, and uploading of labs and other documents. The platform automatically stores all activity data for the app's various features, and does not require continuous internet access for patients to interact with app features. Intermittent connectivity is, however, required for activity to be uploaded to cloud based servers and viewable to staff and other peers using the platform.

Program Planning

Initial planning activities were conducted in Irkutsk during 2017, including program team meetings to discuss the logistics of program implementation and monitoring, partner organization visits, and finalization of institutional agreements. In conjunction with the initial planning activities in Irkutsk, 14 TB Referral Hospital and AIDS Centre providers underwent in-person training on portal usage and platform administration, patient enrollment and troubleshooting of user difficulties. Longitudinal program team meetings thereafter occurred bi-weekly and virtually by secure video calls throughout the remaining planning, pilot testing, and broader program implementation and dissemination phases.

Provider and Patient Interviews

During provider training sessions, program team members performed unstructured group interviews to elicit providers' perceptions related to how the PositiveLinks platform could be adapted to meet the specific needs of their patient populations as well as to elucidate logistical considerations for implementation of the intervention in the context. A total of 10 providers (clinical and non-clinical) from the TB Referral Hospital and AIDS Centre in Irkutsk were engaged through a series of additional unstructured group interviews with members of the intervention team. We primarily sought input on providers' priorities for HIV and TB management of their patients during these interviews.

Patient and Public Involvement

Twenty representative patients- ten patients with HIV treated at the AIDS Centre and ten patients with HIV and TB treated at the TB Referral Hospital- were interviewed by respective institutional providers on the program team regarding their priorities for self-management and monitoring of their HIV and TB. Responses were recorded and summarized into themes by the program team. Patients enrolled in the pilot study were also informally queried during study follow-up visits over the six months following enrollment on their perceptions of the functionality of various platform features in association with their outpatient care. Patient feedback was directly incorporated into platform re-build/iteration prior to and during pilot testing.

Platform Iteration and Testing

Patient and provider feedback on various aspects of the platform's design and functionality was gathered by study team members throughout both the planning and pilot study phases of the evaluation. Feedback was discussed and summarized by program team members during a series of working group meetings performed every two months during the first year. Following consensus reached from intervention team members, proposed modifications were provided to the team platform developer. Feature re-design was performed both during the planning phases and following pilot testing prior to intervention scale-up.

A pilot study was conducted to test the adapted platform in a subset of patients at risk for disengagement, with HIV and TB co-infection as well as substance use[28]. Patients admitted for active TB treatment at the TB Referral Hospital were offered enrollment from April 2018 to November 2019. Inclusion criteria included adults aged 18-64 years diagnosed with HIV (by laboratory testing for new diagnoses and chart review for patients with documented history), a history of using substances at the time of enrollment (confirmed by chart review or self-report), and residence in Irkutsk city. Patients unable or unwilling to use a smartphone or without cognitive ability to give informed consent were excluded. Written informed consent was obtained for all participants based on a protocol approved by the human subjects institutional review boards (IRB-HSR 20451) at the Scientific Centre for Family Health and Human Reproduction Problems and the University of Virginia (Clinical Trial Registration Number: NCT03819374).

Patients were provided a smartphone as well as a data plan if needed, and they underwent training on use of the platform followed by a short proficiency test. Staff provided assistance as needed with installation of the app onto the phone provided or the patient's own phone. Patients were initiated or re-initiated on ART and enrolled in the intervention prior to discharge. Follow up HIV care was provided at the AIDS Centre and TB care at the TB Referral Hospital/associated clinics. Patients enrolled in the pilot study were provided a follow up survey at six months post-enrollment (twenty-item survey, scored on a Likert scale 1-5, 1=strongly disagree, 5=strongly agree) of perceptions related to platform usability and acceptability, originally adapted for PositiveLinks then modified for use with MOCT in Russian language[29]. In addition, administrators performed a preliminary qualitative review of a sample of community message board content posted anonymously by pilot study participants over the six-month follow up period.

Data Analysis

Patient and provider interviews were summarized in descriptive narrative form. Patient interview responses regarding HIV and TB treatment priorities were also recorded and themes were generated by consensus from at least two study team members. Community message board content was downloaded from the platform, translated into English, and themes from interviews were applied again by team member consensus. Platform survey scoring was analyzed using descriptive statistics. Analyses were performed with IBM SPSS Statistics for Mac, Version 26.0 (Statistical Package for the Social Sciences, IBM Corp, Armonk, NY, USA).

RESULTS

Several steps emerged that were critical to the process of planning and implementing the program, including 1) language adaptation of platform components, 2) optimization of server management, 3) iteration of platform features, and 4) program organizational practice integration. Below we detail how these various processes were specifically informed by stakeholder input.

Language and Contextual Adaptation

Interpretation services were provided by a bilingual US-based team member for all program meetings. Several Irkutsk-based team members were also bilingual (spoke both English and Russian). Our interpreter communicated the desired platform changes to US-based program team members following direct translation from Russian to English, based on Irkutsk-based program team member, clinical provider, and patient feedback. Initial patient feedback on language adaptation of platform components from English indicated that patients preferred the Russian term for 'bridges' or 'moct,' over 'links.' They felt that it more effectively reflected the aim of the platform to enhance integration of HIV and TB care and captured the context of Irkutsk, where several bridges cross the Angara River. Patients also felt there was a 'carceral' implication to the translated Russian word for 'links,' connoting being 'locked up' or 'chained' rather than a

word connoting unification or partnership. Thus, the platform was named 'MOCT.' The title change also prompted re-design of the platform title logo to display a bridge as opposed to a chain link. Additional platform components needing adaptation to Russian convention included date and time formatting, calendar formatting (to a Monday to Sunday display) and alteration of the description of the community message board feature to a 'chat' board.

Server Management

Planning meetings conducted with the program team yielded discussion surrounding the setup and management of a suitable server. Initially, an on-site server was installed at the TB Referral Hospital. This server was managed in part by the hospital's technical officer, while software and operating system updates were regularly updated by the team's US-based platform developer, each time requiring permission be requested to access the server remotely through access control software, which regularly changed the password. The server experienced intermittent system crashes due to connectivity issues; there was no monitoring system to track when or how long the system was down. There were also issues with connectivity when our US-based platform developer could not access and troubleshoot issues with the server remotely. Following platform testing during the pilot study and gathering of provider experiences with the platform and the server, the team upgraded to secure internal cloud services purchased from a Russian-based commercial vendor using program funding to host server data, maintaining access control software through which the US-based team platform developer could provide remote assistance. At the end of the first year of operations, however, ongoing server management was primarily handled locally by AIDS Centre staff.

Platform Iteration

AIDS Centre and TB Referral Hospital providers and patients provided feedback regarding their priorities for management of HIV and TB, as well as how the platform could help meet these needs, in order to inform platform iteration. Patients were provided with the following three prompts to generate discussion: 1) What is the most important aspect of your health? 2) If you are living with HIV, what would be the most important part of your HIV care that you would like to monitor? 3) If you are recovering from TB, what would be the most important part of your TB care that you would like to monitor? Providers were similarly asked about their thoughts on their own priorities for HIV and TB management of their patients, as well as how best to measure the effectiveness of prescribed therapy and overall HIV and TB care for patients that would participate in the intervention. Themes that emerged from these conversations are detailed below and summarized in **Table 1.**

Table 1. Selected patient interview responses regarding priorities in management of HIV and TB, associated iteration of the PositiveLinks platform features performed in re-build of the MOCT platform, and example community message board posts following patient testing of the MOCT platform.

Themes	Example Patient Interview Responses	Resulting Platform Feature Iteration	Example Community Message Board Posts
Individual and community effectiveness of HIV and TB Care	*"CD4 numbers: I would like to know how many cells with AIDS I have"* *"Cure and then control"* *"Am I dangerous to others"* *"[monitoring]…about lab results periodically"* *"That my treatment was successful, the cells were respectively normal"* *"Improving health condition and major indicators: reducing viral load to undetectable levels, increasing CD4 lymphocytes"*	Added TB culture results to 'lab upload' feature in addition to maintaining upload feature for HIV viral load and CD4 results; educational resources related to monitoring treatment progress/efficacy were maintained, community message board and direct messaging features maintained to allow providers to re-enforce patient treatment goals	*"Your goal and ours is your recovery, and a full inpatient treatment stage is 70% of success" (provider)*

Transparency of care	*"I would like to know everything about my treatment"* *"Openness about treatment"* *"Truthfulness of tests and timely selection of medications"* *"More information about my treatment"*	Community message board made accessible to providers to distribute information to patients; educational resources tailored to setting and added for TB; clinic appointment reminders, provider contact information, direct messaging feature maintained	*"When prescribing antiretroviral therapy, its effectiveness, first of all, is assessed by reducing viral load. CD4 count increases more slowly" (provider)*
Well-being	*"Well-being"* *"Stay alive, get the joy of life"* *"Good mood"* *"Increased vital tonus (new work, new acquaintances)"*	Daily queries for mood, stress were maintained; community message board maintained for provision of peer support	*"I have problems with housing and animals" (patient)* *"I heard that in case of tuberculosis people are eligible for a separate housing. Does anyone know if it is true?" (patient)* *"The most important thing is to know what all of this is for, and I have my motivation - my CHILDREN. And I want to participate in their life, and after all to see my grandchildren grow" (patient)* *"I was in the hospital, it was very hard, but it's ok, I did it." (patient)*
Self-management	*"Stability and control over my own health condition"* *"I would like to control the treatment itself"* *"Self-discipline"* *"Rejection of bad habits"* *"Structuring life (correct priorities)"*	Providers added targeted messages to encourage self-management on community message board including those related to COVID-19 as the pandemic evolved; TB lab upload function and daily TB medication reminders added; maintained document upload feature	*"What is more important to increase cell count or to decrease viral load?" (patient)* *"If you don't take therapy, nothing will pass by itself, the load has decreased to 440, and I'm not going to stop there" (patient)* *"I have a question! Some drugs that are used for HIV also beat the coronavirus. Does this mean if I get infected, the infection will die immediately? Or can I not get infected at all?" (patient)*

Patients and providers emphasized "individual and community-level effectiveness of HIV and TB care." They wanted to support patients' knowledge of treatment progress and efficacy. Therefore, the 'labs upload' feature was maintained to facilitate tracking of CD4 cell counts and HIV viral load lab results, and TB culture conversion (from positive to negative) results were added to the platform as a key clinical indicator for PWH co-infected with TB. By checking the portal's record of laboratory collection date and result, providers were able to monitor patients' progress and to reach out to patients who fell behind schedule. Educational resources related to monitoring of HIV treatment progress and interpreting lab results were maintained, and similar resources were added for monitoring of drug-resistant TB treatment. Community-level effectiveness referred to shared desires expressed by patients and providers to see how the AIDS Centre's patient panel was doing collectively in terms of lab monitoring and treatment progress. However, this was not able to be incorporated into the platform re-build for patient viewing, and it is being considered as the program expands.

Another theme involved the "transparency of care," as both providers and patients emphasized openness and transparency throughout the treatment course. Patients highlighted their desire to be given updated, accurate and honest information about their disease and their treatment course. Platform features maintained as a result included clinic appointment information, provider contact information, and the direct messaging feature as an open line for out-of-clinic communication. While patients in the US preferred that the community message board remain private for patients, with only administrators moderating content, patients in Irkutsk preferred to allow providers to view posts, write responses, and answer questions.

In regards to patient perceptions of the "most important aspect of their health," "well-being" emerged as a priority for several patients, suggesting that quality of life beyond treatment efficacy was critical. The daily query features for mood and stress were maintained as a result, as well as the community message board, which has previously shown utility as a source of peer support in other cohorts[23]. Peer support has been shown to contribute to improved psychosocial and emotional health and wellness, and was maintained in the platform re-build, as other cohorts demonstrated appreciation for this feature after utilizing it[30].

Finally, components of 'self-management' emerged as priorities for patients as well. Patients recognized the importance of self-efficacy and self-discipline, or taking control of their own treatment plan. Several features consistent with the goal of self-management were maintained including: the laboratory value upload function, daily medication reminders, and the option to upload documents for providers to access. For patients co-infected with TB, an additional anti-TB therapy reminder was built into the platform that included the possibility for patients to set up twice daily reminders for medications. To account for multiple-pill regimens, an option indicating having taken 'all, some or none' of their medications, rather than just a yes/no response (appropriate for single combination pill ART regimens), was developed.

Platform Re-build

The platform interface and features are shown following modification by the platform developer based on input gathered through our qualitative evaluation (**Figure 1).**

Usability and Acceptability

A total of 60 patients were enrolled in the pilot study. Briefly, in terms of usage of the app in the first six months, 51 (85%) logged in at least once, and 43 (72%) actively used an interactive feature, including responding to daily queries, private messaging or posting to the "chat" board. The cohort and additional usage details are described elsewhere[28]. Patients' perceptions of the platform's usability and acceptability were assessed following 6 months of participation in the intervention (**Table 2)**. The survey was completed by 47 participants (7 patients were lost to follow up, 2 were deceased by six months, 1 did not attend the 6-month assessment, and 3 attended the assessment but did not complete the survey). Categories of survey questions were grouped as follows: 1) Impact 2) Perceived Usefulness 3) Perceived Ease of Use and 4) User Control. On average, patients scored the platform above 4 on a scale from 1 to 5 (5=strongly agree) for all but two survey items. The lowest scored items were both related to the perceived usefulness of the platform in facilitating 'quicker' or 'more timely' self-management of HIV-related symptoms.

Table 2: Usability and acceptability survey at six months following pilot testing for a cohort of participants (N=47). Each item is scored by participants on a scale from 1 (lowest) to 5 (highest).

Survey Item	Mean (SD)
Impact	
I think MOCT application would be a positive addition for persons living with HIV.	4.19 (1.28)
I think MOCT application would improve the Quality of Life of persons living with HIV.	4.15 (1.30)
MOCT application is an important part of meeting my information needs related to symptom self-management.	4.28 (1.26)
Perceived Usefulness	
Using MOCT application makes it easier to self-manage my HIV-related symptoms.	4.11 (1.43)
Using MOCT application enables me to self-manage my HIV symptoms more quickly.	3.98 (1.36)
Using MOCT application makes it more likely I can self-manage my HIV-related symptoms.	4.15 (1.32)
Using MOCT application is useful for self-management of HIV-related symptoms.	4.19 (1.33)
I think MOCT application presents a more equitable process for self-management of HIV-related symptoms.	4.15 (1.37)
I am satisfied with MOCT application for self-management of HIV-related symptoms.	4.17 (1.29)
I self-manage my HIV-related symptoms in a timely manner because of MOCT application.	3.94 (1.36)
Using MOCT application increases my ability to self-manage my HIV-related symptoms.	4.13 (1.31)
I am able to self-manage my HIV-related symptoms whenever I use MOCT application.	4.07 (1.44)
Perceived Ease of Use	
I am comfortable with my ability to use MOCT application.	4.09 (1.38)
Learning to operate MOCT application is easy for me.	4.30 (1.04)
It is easy for me to become skillful in using MOCT application.	4.17 (1.19)
I find MOCT application easy to use.	4.23 (1.15)
I can always remember how to log onto and use MOCT application.	4.38 (1.11)
User Control	
MOCT application gives error messages that clearly tell me how to fix a problem.	4.19 (1.25)
Whenever I make a mistake using MOCT application, I recover easily and quickly.	4.30 (1.18)
The information (such as on-line help, on-screen messages and other documentation) provided with MOCT application is clear.	4.40 (1.12)

Community Message Board Content

Following testing of the adapted platform in the pilot study for six months, a review of a sample of community message board content was performed. This assessment of conversations on the community message board between patients, as well as between patients and providers, allowed the study team to gauge whether the previously identified priorities were being met within the platform. Interactions on the community message board were mapped to the themes generated based on patient and provider interviews (See **Table 1**). With regard to "individual effectiveness of HIV and TB therapy," several community message board posts demonstrated that the feature was an opportunity for providers and other patients to re-enforce treatment goals. To enhance "transparency of care," providers distributed community educational resources and content verified as accurate and up to date on the board, including for those seeking COVID-19 related services after March 2020. In addition, patients were able to obtain support in interpreting and

understanding their lab results by eliciting the opinions, experiences and knowledge of both peers and providers. As for the concept of "well-being," anonymous peer messaging allowed for patients to seek information and assistance related to non-medical needs, including housing, child care, and other concerns. They also had the opportunity to provide first-hand perspective and positive role-modeling. Providers provided encouragement as well. Finally, with reference to "self-management," the community message board afforded patients the opportunity to reach out to providers and peers, initiating conversations about their own needs and seeking information to help guide their own care.

Organization Practice Integration

In previous years, the TB Referral Hospital and AIDS Centre provided TB and HIV care that was largely separate, consistent with traditional systems of care delivery in the region[11]. Following formation of the multi-institution program team, local members of both organizations continued to meet on a biweekly basis throughout the planning and platform testing phases. Several clinical providers from the TB Referral Hospital underwent training first. Now familiar with the provider portal, these providers, during subsequent provider training sessions, assumed unprompted 'peer teacher' roles, which led to robust discussions of the platform and shared goals for its use between providers of the two organizations. Discussions fostered additional brainstorming regarding ways to incorporate TB care into the HIV-centered platform. Resulting components built into the mHealth strategy also triggered integration of other care efforts. Specifically, availability to both institutions of appointment information and direct messaging availability for providers at both organizations has streamlined the referral, linkage, and follow up processes for patients referred to the AIDS Centre from the TB Referral Hospital. Previously inaccessible patient information and lab results have become available to share between the organizations through the platform. Professional collaboration and regular communication between these organizations has continued following program scale-up beyond pilot testing.

Program Implementation and Platform Dissemination

Pilot study participants demonstrated improved rates of linkage to care at the AIDS Centre and ongoing engagement with the platform by six months as well as better rates of medication refill and a lower propensity towards developing the composite outcome of death and failure to achieve viral suppression at six months[28]. Following contextual evaluation of patient and provider perceptions and platform testing and modification, the program has been implemented across the Irkutsk oblast (a federal region similar to a state or province). Enrollment has expanded to four TB Referral Hospital filial (affiliated) clinics following hospital administrative approval and engagement of clinic leadership. Importantly, the MOCT platform has been disseminated to a broader population of PWH living in Irkutsk oblast both with and without TB (**Figure 2**). Providers at filial clinics underwent similar group training sessions on patient enrollment, linkage coordination to the AIDS Centre, and MOCT administration. In addition to recruitment of HIV/TB coinfected patients at filial sites, patient recruitment has been expanded to all patients in care at the AIDS Centre, including those without TB. Following scale-up of the program, patients are able to seek enrollment in the platform across a large area served by the participating provider organization sites.

DISCUSSION

We examined the design, planning, and pilot testing of a multi-institution collaborative program using a mHealth approach to enhance the linkage and engagement of PWH with or without TB in care In Irkutsk. Our aim was to elucidate potential considerations for groups hoping to apply similar strategies to the care of PWH with or without TB in other contextually related settings. We identify several aspects of the project design and conduct that may have contributed to the successful uptake and high linkage rates observed following pilot testing[28]. Specifically, the team members were well-informed from prior experience and stakeholder feedback about the care systems already in place in Irkutsk. In addition, they iterated continuously from the planning to expansion and dissemination phases. Key components of the program's planning and implementation processes included language and contextual adaptation, server management, a cycle of platform iteration and testing before the MOCT platform was finalized, and organization practice integration.

Following language and contextual adaptation and patient and provider-informed iteration of the platform based on local priorities, pilot testing indicated high average scoring by the cohort on platform usability and

acceptability at 6 months. The lower scored survey items (still above 3 out of 5) were both related to perceived usefulness of the platform in facilitating self-management 'more quickly' or in a 'more timely' manner. Patients did, however, generally rate the app highly as 'making it easier' or 'more likely' for them to self-manage symptoms on average.

Provider and patient input gathered throughout the planning and pilot testing phases on platform functionality revealed many shared priorities that aligned with the original platform features, although there were some modifications, such as including added functionality related to TB management. Notable differences in patient testing of the platform included preferences by patients in Irkutsk to allow providers to contribute to discussions on the community message or 'chat' board. While patients in the US cohort appeared to prefer privacy for peer discussions, as platform testing occurred, patients in Irkutsk began demonstrating an interest in gathering information and support from their clinical providers and peers simultaneously. This change highlights the need to consider how patient-provider and peer relationships vary across contexts when building this type of feature into a platform. Preliminary review of chat board content demonstrates patients directly engaged with providers and with one another to provide perspectives and encouragement surrounding their shared diagnoses. To date, mHealth interventions for TB with patient-provider messaging features have largely been centered on enhancing communication in order to encourage daily medication adherence.[31,32] The chat board and direct messaging features of MOCT were designed to encourage more holistic patient support in association with clinical care, including exchange of psychosocial support and low barrier communication to troubleshoot issues as they arise (housing, employment, etc), and align with the priority of overall 'well-being' identified by patient input. However, the direct impact of the platform on patients' perceived ability to navigate stigma and gain social support within this context requires further investigation.

This build of the platform required specific consideration of the additional burden of drug-resistant TB that patients face within the context, as well as the additional demanding medication regimens required for treatment. The platform was also tested for the first time in patients seen in both outpatient and inpatient settings, which allowed for elicitation of patient perspectives through the continuum of care delivery across those different settings. The platform provided a unique opportunity to prevent discontinuity of care following discharge from the TB Referral Hospital.[28] Various features were similarly helpful in preventing service disruptions related to COVID-19 for participants later in implementation. Conservative models estimate that COVID-19 related disruption in HIV and TB services in high-burden settings could increase HIV-related death by 10% and TB-related death by 20% in the 5 years following the pandemic.[33] With the MOCT platform, patients initiated chat board and messaging conversations querying specific ART impact on SARS-CoV-2, and appeared to use the features to navigate social isolation and barriers to service during periods of lockdown, indicating a potential role for these forms of mHealth-enhanced care in the current pandemic and in the years to come.

Importantly, the development of this program occurred in a specific sociopolitical environment within Irkutsk. Separated systems of care for TB and HIV exist there and in other regions of the Russian Federation, urban or otherwise, and our findings suggest they may benefit from similar integrated approaches to program development for the care of these co-morbid infections. Administrative approval of information sharing between collaborating institutions was obtained, and secure information sharing was made feasible in part because it was built into the mHealth strategy used. Organizational buy-in and approval and methods for secure and effective information sharing must be considered when planning similar integrated approaches to novel care delivery.

Recruitment of a dedicated bilingual program manager to the program team significantly streamlined cross-team communication. This team member's participation was critical for enhancing collaboration and data-sharing capabilities between program team members, as well as translation of various components of the platform to the local conventions, terminology, and patient/provider preferences. We also found that developing local capacity for technical support was instrumental for day-to-day troubleshooting. The recruitment of an experienced technology lead with mobile application development and systems administration skills to assist with program activities facilitated the launch and management of the server through the planning and pilot phases. However, sustaining ongoing server management through program expansion necessitated expansion of the technology lead's role to provision of training to local Irkutsk team

members appointed to perform troubleshooting and manage user concerns that arose related to the platform.

Several challenges arose throughout the course of program development and implementation. While injection drug use is a major risk factor for transmission in the region[12], and pilot testing of the platform occurred in a cohort with substance use at high risk for disengagement, only limited resources related to local rehabilitation and harm reduction services were available to share on the platform reflecting systemic barriers to access within the region[11,34]. Well-being was identified as a management priority by patients, however aside from maintaining peer support functionality through the community message board, the platform re-build did not specifically measure patient access to more holistic care services (e.g. mental health, nutrition, employment services) following participation. Further efforts toward platform iteration are necessary to consider how further care coordination can be enhanced by the platform in a context where these services are not necessarily co-localized with outpatient HIV care. Several validated patient survey tools were considered for the purpose of data collection following pilot testing, however availability in Russian language was highly limited. The dearth of validated survey tools to assess mHealth interventions in different languages poses a broader challenge to assessment of platforms within contexts where they remain novel. We were able to incorporate the majority of patient and provider feedback into the new MOCT platform build. However, patient access to regularly updated, aggregate community-level data was not feasible prior to platform dissemination and is being considered as the program expands.

CONCLUSION

The development of this mHealth-based program, spanning efforts of multiple institutions in the US and Irkutsk, was a significant undertaking requiring advanced planning and coordination, consistent collaboration between program team members, participating providers, and beneficiary patients at all stages, and consideration of unique contextual factors. Several modifications were made to optimize the platform based on patient and provider preferences, however PositiveLinks features developed for US-based cohorts that encourage psychosocial support of patients and that extend beyond medication adherence tracking, including the community chat board and direct messaging features, were also found to be beneficial during user testing of MOCT in Irkutsk. The major challenges and facilitating factors that arose for our program are likely to be relevant when creating or adapting mHealth-based, integrated care delivery programs in similar settings with high HIV/TB burden and geographic remoteness relative to treatment settings. Further evaluation of the program using rigorous implementation science methodology is planned following expansion and dissemination of the platform across Irkutsk, including 'real world' platform uptake and program effectiveness.

ACKNOWLEDGMENTS

We thank the patients who participated in this study, as well as all collaborators and staff at the Irkutsk Regional TB Referral Hospital and filial clinics, and Irkutsk AIDS Centre.

FUNDING INFORMATION

Funding for this study was provided by the National Institutes of Health (NIH) (R01DA04413, T32AI007046) and Russian federal R&D financing of the Scientific Centre for Family Health and Human Reproduction Problem.

COMPETING INTERESTS

Authors R.D., A.L.W., and J.S. provide consulting services to Warm Health Technology, Inc., an entity that supports dissemination of PositiveLinks. R.D. has also received an investigator-initiated grant from Gilead, Inc., which is unrelated to this study. The other authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Study conception: S.H., R.D. Protocol development: J.S., A.L.W., O.O., R.D., S.H. Study activities and follow-up: S.Z., O.K., A.S.,A.P., Y.P., E.M., M.K., S.V., A.L.W., J.S., S.S. Article conceptual development and preparation: J.H., A.L.W., R.D., S.H. Data analysis: J.H. Article review and contributions: all authors.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed for this study are available from the corresponding author, J.H., on reasonable request.

ETHICS APPROVAL STATEMENT

The study protocol was approved by the human subjects institutional review boards at the Scientific Centre for Family Health and Human Reproduction Problems and the University of Virginia (IRB-HSR 20451) (Clinical Trial Registration Number: NCT03819374).

EXCLUSIVE LICENSE STATEMENT

Figure 1. MOCT Platform features following adaptation. MOCT platform includes a dashboard (1), a community message or 'chat' board (2), direct provider messaging (3), educational/community resources (4), daily queries of mood (5), stress (6), adherence to HIV/TB medications (7), appointment and medication reminders (8), and HIV/TB lab results.

Figure 2. MOCT Program Activities. Program activities are summarized from conception and team formation to broader expansion across Irkutsk. MOCT is Russian for 'bridge,' and describes the platform following language translation and contextual adaptation. TB – tuberculosis; UVA – University of Virginia; TBH – TB Referral Hospital; HIV – human immunodeficiency virus; PWH – people living with HIV; PL – PositiveLinks; AC - AIDS Centre

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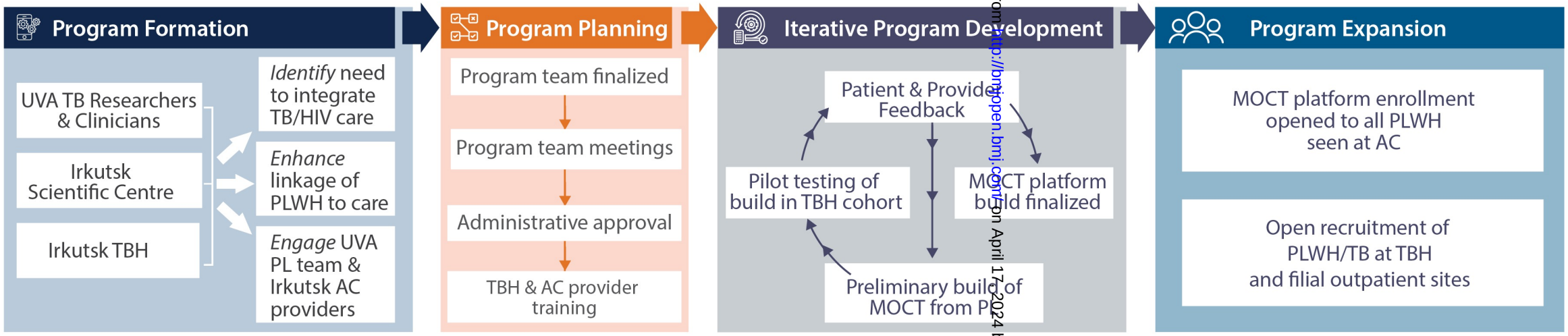
Figure 1. MOCT Platform features following adaptation. MOCT platform includes a dashboard (1), a community message or 'chat' board (2), direct provider messaging (3), educational/community resources (4), daily queries of mood (5), stress (6), adherence to HIV/TB medications (7), appointment and medication reminders (8), and HIV/TB lab results.

Figure 2. MOCT Program Activities. Program activities are summarized from conception and team formation to broader expansion across Irkutsk. MOCT is Russian for 'bridge,' and describes the platform following language translation and contextual adaptation. TB – tuberculosis; UVA – University of Virginia; TBH – TB Referral Hospital; HIV – human immunodeficiency virus; PLWH – people living with HIV; PL – PositiveLinks; AC - AIDS Centre



TIDieR Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	3	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	3-4	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	4,9	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	4-5	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	4	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	5	
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	5	

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	5	
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	4-8,11	
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	8-12	
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	8-9, 10-11	
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	8-9, 10-11	

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	5
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	4, 8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	6-10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.