Yunnan-ADARC HIV Prevention Program: Developing and Testing a Model to Implement and Sustain PrEP Delivery in China

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Research Aims & Abstracts

B-HAPPY is a multisite randomized stepped-wedge study to compare the effectiveness of two PrEP implementation strategy bundles: 1) Standard Implementation: comprising the strategies that the Yunnan CDC would usually use to introduce HIV prevention innovations in the absence of the proposed study; and 2) Enhanced Implementation: standard implementation enhanced by an approach guided by the Stages of Implementation Completion (SIC) framework to plan and implement PrEP.

We **hypothesize** that adding SIC-guided implementation onto standard health system implementation of PrEP will improve outcomes and lead to greater likelihood of a) implementation success and b) sustainment. **Successful implementation** will be defined as a site achieving Five-80% targets and maintaining them three months in a row: 1) Awareness of PrEP among 80% of MSM clients; 2) PrEP eligibility assessment for 80% of MSM clients; 3) PrEP linkage for 80% of MSM clients who wish to start and are medically-eligible; 4) PrEP initiation for 80% of MSM who linked to PrEP services; and 5) six-month PrEP continuation for 80% of those who remain PrEP-eligible. **Sustainment** will be defined as achieving the Five-80s continuously over 6-months.

To examine the implementation process and efficiency of the Enhanced versus Standard implementation approaches we will use SIC and COINS tools to monitor sites for implementation process and resource use. Outcomes will include proportion of implementation activities completed, duration of each implementation phase, and cost and resource allocation for completion of each implementation phase. Based on robust studies that assess implementation using the SIC, we **hypothesize** that time and

resources spent in Pre-Implementation will be associated with higher odds of successful implementation and sustainment

Scientific Abstract: Pre-exposure prophylaxis (PrEP), a key biomedical HIV prevention strategy, can significantly reduce HIV incidence in real-world settings. However, introduction and global scale-up of PrEP have been slow. Part of the challenge is that PrEP is typically introduced into existing health systems through a hit-or-miss process that is rarely studied. We propose the Biomedical HIV/AIDS Prevention Program, Yunnan (B-HAPPY), an implementation science study of the process of introduction and implementation of PrEP in a specific international health system facing high rates of HIV incidence among men who have sex with men.

B-HAPPY will introduce and evaluate the implementation of PrEP among over 1000 men who have sex with men, in eight sites in Yunnan, China. The study is guided by the Stages of Implementation Completion Framework (SIC) and will use SIC-associated assessment tools to measure progression across eight pre-defined stages of implementation, including documenting costs and required resources.

The study has two specific aims: 1) To evaluate whether the addition of Enhanced implementation strategies to Standard health system PrEP delivery improves client-services outcomes; 2) To compare the time, costs, and resources required for Standard versus Enhanced PrEP implementation. Enhanced PrEP implementation will rely on a centralized technical assistance strategy to deliver PrEP-related knowledge, skills, and best practices to clinics delivering PrEP. The outcome of the study will be an implementation blueprint that may be used across China and in other low- and middle-income countries to guide the introduction of PrEP into existing health systems.

Lay Abstract: B-HAPPY is an implementation science research project to study the process by which preexposure prophylaxis (PrEP) is introduced and integrated into a specific international health system facing high rates of new HIV infections among men who have sex with men. The study aims to (1) evaluate whether the addition of Enhanced implementation strategies to Standard health system PrEP delivery improves client-services outcomes; (2) compare the time, costs, and resources required for Standard versus Enhanced PrEP implementation. Enhanced PrEP implementation will rely on a systems analysis and improvement approach guided by the Stages of Implementation Completion (SIC) framework.

Study Purpose and Rationale

Pre-exposure prophylaxis (PrEP) is a key biomedical HIV prevention strategy that can significantly reduce HIV incidence in real-world settings. Yet globally, PrEP introduction and scale up have been slow. PrEP is typically integrated into existing health systems through a hit-or-miss process that is rarely studied, leaving a gap in understanding of implementation processes, and how sociopolitical and cultural contexts influence implementation. A scientific study of the process of introduction and implementation of PrEP in a specific international health system has the potential to produce actionable knowledge, and more efficient and effective implementation that will both reduce HIV incidence and costs within the existing system and accelerate access to effective prevention in similar health systems. PrEP implementation in the US and globally has taught us that clinical guidance is necessary but not sufficient for large scale implementation. Effective implementation has multiple components. Health systems must 1) build awareness and generate demand; 2) identify potential

beneficiaries; 3) offer and link people to services; 4) get pills to those who need them; and 5) support users to adhere both to pills and to regular check-ups. These five components comprise the PrEP Care Continuum (Kelly et al., 2015; Nunn et al., 2017). Studies are testing strategies for each of these components: for example, comparing methods for screening (Kelly et al., 2015), evaluating the impact of same-day initiation (Wendel, 2017) and testing different retention strategies (Amico & Stirratt, 2014; Holtzman et al, 2015; Fuchs et al., 2018). While knowledge generated in each of these studies is critical, not one is holistic enough to inform planning for large, state-run health systems seeking to integrate PrEP into services. What is needed are protocols to detail how to implement what the clinical protocol specifies.

HIV prevalence among Chinese MSM is estimated between 5% and 15% depending on region (Wu et al., 2013; Zhong et al., 2014; Xu et al, 2016; Chen et al., 2018; Ning et al., 2018). Estimated incidence —around 5 per 100 person-years nationally (Wang et al., 2014; Xu et al. 2016; Mao et al., 2018) and in Yunnan (Yunnan CDC, 2018)—is almost ten times the incidence among MSM in the US (Shang & Zhang, 2015; Rosenberg et al., 2016; Ma et al., 2017). There are an estimated 6-10 million MSM aged between 15-49 years old living in China (Wong et al., 2009) and the PI's recent modeling paper estimated 2.5 million PrEP-eligible MSM living in China (Zhang et al., 2018). By extending these assumptions to Yunnan, we estimate 80,000 PrEP-eligible MSM in that province alone. Under relatively conservative assumptions, our model estimated that hundreds of thousands of HIV infections could be averted over a twenty-year horizon and that delaying implementation by five years would reduce cost-effectiveness by 36% and lead to ~90,000 additional infections among MSM.

Implementation of PrEP in more effective ways than the standard approach of issuing clinical guidance, without robust implementation guidance, is urgently needed.

The Stages of Implementation Completion (SIC) Framework was derived from an 8-stage SIC assessment tool that consistently identifies key implementation activities needed to achieve sustainable outcomes. The SIC tool was originally developed for a large-scale randomized trial comparing two strategies to deliver a child-welfare intervention across two state systems (Chamberlain et al., 2011). Mixed-methods research suggests the utility of SIC as a general Implementation Framework: organizational stakeholders and leaders used it to guide planning for the adoption of a new health intervention (Palinkas et al., 2018). The SIC emphasizes identifying implementation activities most likely to help organizations plan for successful implementation and anticipate barriers that hinder success. SIC findings consistently demonstrate that challenges with implementation can be mitigated through completion of pre-implementation activities such as Readiness Planning (Palinkas et al., 2018). This study will use the SIC Framework to guide and study the implementation of PrEP in Yunnan China.

We propose to study this process in Yunnan Province, China, a key geography in the country's HIV initiatives. Yunnan has made great progress towards attaining 90-90-90 treatment targets, but there continue to be between 8,000~11,000 HIV diagnoses per year, and an estimated 5% annual incidence among men who have sex with men (MSM) (Yunnan CDC, 2018). Given the existing relationship of Aaron Diamond AIDS Research Center (ADARC) with the Yunnan government, we were approached to help design a study to identify an optimal implementation approach for PrEP. In collaboration

with the Yunnan CDC, we developed the Yunnan-ADARC HIV Prevention Program. This real-world study provides a unique opportunity to evaluate the use of supportive implementation strategies and frameworks to increase the chance for successful and sustained implementation. In preparation for this study, the Yunnan CDC secured a pledge for a donation of 2128 person-years of TDF/FTC from Gilead Sciences. By removing barriers to PrEP access for a period, lessons for health system integration can be identified and directly applied once PrEP can be procured when generic TDF/FTC becomes available by the third year of the proposed project.

B-HAPPY has two specific aims: 1) To evaluate whether the addition of Enhanced implementation strategies to Standard health system PrEP delivery improves client-services outcomes; 2) To compare the time, costs, and resources required for Standard versus Enhanced PrEP implementation. Enhanced PrEP implementation will rely on a systems analysis improvement approach (Sherr et al., 2014; Gimbel et al., 2016) to deliver PrEP-related knowledge, skills, and best practices to clinics delivering PrEP. The outcome of the study will be an implementation blueprint that may be used across China and in other low- and middle-income countries to guide the introduction of PrEP into existing health systems.

Study Procedures

All study procedures will be conducted at international site (Yunnan, China). All study procedures have been reviewed and approved by Yunnan CDC IRB. Columbia personnel might be involved in data collection (obtaining content, conducting interviews with clients and program staff) at international sites.

The overall study uses a stepped-wedge design to understand PrEP implementation at eight study sites in Yunnan, China. Each study site will go through four study periods. Sites will start with a six-month pre-baseline period, where PrEP is not offered but HIV prevention utilization data will be collected among MSM client population. HIV prevention utilization data will be captured by the PrEP M&E data system created by Yunnan CDC. Examples of indicators to be collected include number and frequency of HIV and STI tests, diagnoses, and treatment status. These metrics will be collected throughout all study periods. Each site will then have a different length of Baseline Period of standard PrEP implementation followed by a one-year Experiment Period with enhanced PrEP implementation.

The study procedures involve audio recording of research subjects. All study procedures will be performed at eight study sites by research staff who have completed human subject protection training after obtaining informed consent from participants. This study will not use previously collected biospecimens, data or records. Detailed study procedures are listed below:

Audio and/or video recording of research subjects: This study will conduct in-depth interviews with (1) MSM clients, and (2) program staff to understand their experience with PrEP implementation. Interview guides are submitted in English only as these are documents to guide the English-Chinese bilingual interviewers. Therefore, no Chinese version of the interview guide is attached. We will audio-record interviews with participants who provide permission for recording. Audio-recording is a very widely used technique in qualitative research. It allows researchers to fully engage and concentrate on the interview rather than writing notes, which may be a distraction for both the

interviewer and the participants. Audio-recording will help researchers keep accurate records of qualitative data and capture non-verbal expressions during the interview. Informed consent will be obtained before any study procedures are initiated. During the consent process, the interviewer will ask participant's permission for audio-recording. For detailed process of obtaining consent, please see section "Informed Consent Process". After informed consent is obtained, the interviewer will announce that the interview will begin and turn on audiorecording equipment. The interviewer will begin the interview by noting the time, date, and unique ID number for the interview. S/he will proceed to conduct the interview guided by the interview guides. The interview will be in-person or remotely one-on-one and is expected to last 45 to 60 minutes. All data will be confidential and protected. Compensation of 100 Yuan (approximately USD $16) will be provided upon completion of the interview. De-identified data will be sent to contractors external to Columbia University to support data analysis.

Study Design

B-HAPPY is a multisite randomized stepped-wedge trial to compare the effectiveness of two implementation strategy bundles: 1) Standard Implementation: comprising the strategies that the Yunnan CDC would usually use to introduce HIV prevention innovations in the absence of the proposed study; and 2) Enhanced Implementation: standard implementation enhanced by a SIC-guided approach to plan and implement PrEP. Eight sites will receive identical Standard Implementation during a six-month baseline period; additional strategies will be introduced to blocks of 2 sites in six-month increments. Importantly, the role of the SIC will shift between Baseline when

it will be used as an observational assessment tool only, and Enhanced, when it will be used both to guide implementation and to assess it. During Enhanced Implementation each site will receive Implementation Support to plan and introduce PrEP by following the eight stages of the PrEP-adapted SIC. Implementation Support will involve a centralized TA system developed using US-based PrEP experience. The support will utilize **a SIC-guided systems analysis and improvement approach** that focuses on addressing implementation issues identified through real-time analysis of client, provider/site, and implementation data. During the study, sites will participate in four study periods: a Pre-Baseline Period (Routine service with no PrEP implementation), a Baseline Period (Standard Implementation of PrEP), an Experiment Period (Enhanced Implementation of PrEP), and a Post-Experiment-Sustainment Period. Sites are randomized to the ***timing*** of the intervention phase—the intervention condition changes *over time* and the intervention effect is the difference in outcomes between the Baseline and Experiment Periods, and the Post-Experiment and Baseline Periods.

We hypothesize that adding SIC-guided implementation onto standard health system implementation of PrEP will improve outcomes and lead to greater likelihood of a) implementation success and b) sustainment. Successful implementation will be defined as a site achieving "Five-80%" targets and maintaining them three months in a row (Aim 1): *1) Awareness of PrEP among 80% of MSM clients; 2) PrEP eligibility assessment for 80% of MSM clients; 3) PrEP linkage for 80% of MSM clients who wish to start and are medically-eligible; 4) PrEP initiation for 80% of MSM who are linked to PrEP services; and 5) six-month PrEP continuation for 80% of those who remain PrEP-eligible.* Sustainment will be defined as achieving the Five-80% targets continuously

over 6 months. The study team set 80% targets for two reasons: 1) 80% targets are commonly used in observational facilitated training in implementation processes; 2) the PI's recently-published PrEP modeling analysis clearly showed the differential epidemiological impact a high real-world PrEP effectiveness would have compared to a low real world effectiveness: with 80% effectiveness, PrEP would lead to 345,000 infections averted over a 20-year horizon compared to 219,000 with 50% effectiveness and 87,900 with 20% effectiveness (Zhang et al., 2018), spurring the team to choose ambitious targets that could drive down infections among MSM. To examine the implementation process and efficiency of the Enhanced versus Standard implementation approaches we will use SIC and COINS tools to monitor sites for implementation process and resource use. Outcomes will include proportion of implementation activities completed, duration of each implementation phase, and cost and resource allocation for completion of each implementation phase (Aim 2). Based on robust studies that assess implementation using the SIC, *we hypothesize that time and resources spent in Pre-Implementation will be associated with higher odds of successful implementation and sustainment.*

Recruitment

All recruitment activities will take place at our international site (Yunnan, China) and will be conducted in Mandarin Chinese, the primary language of the region, by Chinese-speaking research staff. All research staff will complete the required human subject training before conducting any recruitment activities. All procedures related to recruitment have been reviewed and approved by Yunnan CDC IRB. Columbia personnel will not be involved in the recruitment of participants.

Two types of participants will be recruited for in-depth interviews in our study: (1) MSM clients of participating facilities; (2) program staff who are involved in PrEP implementation. We will conduct the interviews with clients and program staff in each study period, as a result, a total of four rounds of interviews will be conducted.

1. MSM clients. Overview: In each study period, we estimate prescreening over 96 MSM clients to achieve the enrollment goal of 48 evaluable study participants (6 clients per site, 8 sites). We estimate a 50% response rate based on our experience conducting qualitative research among MSM in China, and our consultation with local collaborators. Given the qualitative nature of the study, we may conduct fewer interviews with clients if data saturation is reached (i.e. adding more participants into the study does not result in new findings). The total number of participants for the client interview will be 192 (48 per study period * 4 study periods).

Two methods will be used for recruiting MSM clients: person-to-person, and handout/flyer.

Research staff will conduct recruitment activities through person-to-person methods at facilities that are participating in the PrEP implementation, e.g. community-based organizations (CBOs), STI clinic, HIV testing center, and HIV treatment clinic. In the waiting room of the facilities, staff will approach to male clients and explain the purpose of the interview study. It will be made clear that participation in the interview is totally voluntary; declining to participate in the interview will not have any negative impacts on access to HIV prevention services and PrEP care at sites.

If a client shows interest, staff will administer a set of screening questions to determine their eligibility to participate in the study. If eligible, research staff will conduct

a qualitative interview with the client directly in a private room in the facility, or schedule a time for interview in the future.

In addition to the in-person recruitment approach, we will also print handouts about the interview study and distribute them in the waiting room of the facilities. The handout will include a brief introduction of the study purpose and procedures, and contact information of site research staff. Clients who are interested in the interview study will contact research staff for screening.

2. Program staff. Overview: In each study period, we estimate prescreening over 60 program staff to achieve the enrollment goal of 40 evaluable study participants (5 per site, 8 sites). We estimate a 67% response rate based on our experience conducting qualitative research among health workers in China, and our consultation with local collaborators. The total number of participants for the client interview will be 160 (40 per study period * 4 study periods).

Given the qualitative nature of the study, we may conduct fewer interviews with program staff if data saturation is reached (i.e. adding more participants into the study does not result in new findings). We will recruit program staff through email.

Recruitment strategy for interviews with program staff will be developed in collaboration local site coordinating agency and will target staff at study sites who have been employed for at least 3 months. We will work with coordinating agency at each site and send an email to all program staff introducing the study and inviting them to participate in an in-person or phone interview. Program staff who are interested in the interview study will contact researchers for screening.

In the recruitment email, it will be made clear that participation in the interview is totally voluntary. This will be particularly emphasized for program staff at each site to ensure that they do not feel coerced into participation due to a belief that they are required to do so as part of their job.

In addition, a purposeful, role-based sampling strategy will be used to recruit program staff due to their role in PrEP implementation or because other interviews identified them as having an important perspective. For program staff who were identified through this process, we will use identical recruitment procedures through an email invitation as outlined above.

Informed Consent Process

The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject, or parent/LAR if applicable, will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

We will not collect any confidential information in our interviews with clients and program staff. The only record linking their identity and the research would be the consent document, as a result, we request a waiver of written documentation of consent.

Informed consent process will take place at our international site (Yunnan, China) and will be conducted in Mandarin Chinese, the primary language of the region, by Chinese-speaking research staff. All research staff will complete required human subject training and additional training on obtaining informed consent before conducting

any consent activities. All procedures related to informed consent have been reviewed and approved by Yunnan CDC IRB (see attached approval letter). Columbia personnel may also be involved in obtaining informed consent from potential participants.

This study will use electronic consenting (“e-consenting”) for potential study participants. Given that potential participants will be recruited in person at study sites and remotely, both in person e-consent and remote e-consent will be used, with an information sheet that describes study procedures and without a signature. All e-consent process will occur online using the China-based survey platform WenJuanXing (WJX, https://www.wjx.cn/), which our team has previously used for conducting e-consent and data collection.

1. Consent process for client interview. Clients will be recruited through two ways: in-person recruitment in the waiting room, and through information on the recruitment handout.

(1) For clients who are recruited through an in-person mechanism in the waiting room, in-person e-consent will be conducted after they indicated their interest in the study and are screened eligible. Research staff will bring the potential participant to a private room. Potential participants will be given ample time to read an information sheet (see submitted document) on an electronic tablet. They will also be given a chance to ask questions and express concerns.

Additionally, research staff who have been designated to consent will discuss the specifics of the study including but not limited to the purpose of the research, procedures, time commitment, required tasks, benefits, risks, confidentiality etc. in a comprehensible (nonscientific) manner, using language readily understandable by the

participant. Participants will be told that the participation is voluntary and that, if they do not consent, they will not be penalized. The consent process will include a request for permission to audio-record the interview for transcription and analysis. The person consenting will assure the voluntariness of the consent and will assess comprehension of the informed consent form through a teach-back method.

If clients wish to be in the study and are ready to give consent, they will click an “I Agree” icon to consent to participate in the interview study. The research staff consenting will offer the participant a copy of the information sheet via email. If participants choose to receive a copy, research staff will remind participants that it is possible that the information sheet might be seen by others and therefore their confidentiality might be breached, so it is important that they properly store the copy.

(2) For clients who wish to conduct the interview via telephone, research staff will email clients a link to an information sheet describing the purpose, procedures, potential risks and benefits of participating in this interview study. The consent process will include a request for permission to audio-record the interview for transcription and analysis. The email will also include information on how questions from clients may be asked and answered from a remote location, e.g. scheduling an in-person interview with research staff who are designated to recruitment and obtaining informed consent at study site, or scheduling a time for phone calls or electronic chatting.

If clients wish to be in the study and are ready to give consent, they will click an “I Agree” icon to consent to participate in the interview study. Once the client has given the consent, they will see a reminder that asks them to print or email a copy of this information sheet for their own records. They will also be reminded that it is possible

that the information sheet might be seen by others and therefore their confidentiality might be breached, so it is very important that they properly store the copy.

2. Consent process for program staff interview. We will use identical consent procedures as listed above.

Confidentiality of study data

All data will be in electronic format and we will not have any hard copy of study data. In general, we will use Secure Sockets Layer (SSL) encryption to securely transfer the study data that are in electronic format. We will store study data on password-protected, encrypted computers, and will restrict access to the data to key study personnel.

This study will analyze data from five different sources. Here is a detailed description of how we will ensure confidentiality and safely stored data from five different sources:

1. SIC and COINS data

Description: The PrEP-SIC data includes a log of implementation activities completed by each site along with the dates of activity completion (e.g.: date written PrEP implementation plan completed, date first PrEP user retained in care for six months). The COINS tool assesses direct and indirect expenses, including the number of hours per role expected in completing each implementation activity listed in the SIC. SIC and COINS data will be collected by our Yunnan-based research coordinator through phone call and in-person site visits at two to four-week intervals and entered

into the SIC website. SIC and COINS tool measures implementation process and does NOT contain personal identifiable information (PII) or protected health information (PHI).

2. PrEP M&E data

Description: Yunnan CDC (our primary collaborator in China and a subaward recipient on this grant) is upgrading their HIV prevention monitoring and evaluation (M&E) system to incorporate PrEP service delivery indicators. We expect this PrEP M&E data system to start working in May 2020, and it will document data including routine HIV utilization, PrEP service delivery and process measures for all facilities involved in PrEP implementation across the province and including at our study site. Yunnan CDC staff will extract data and aggregated at site level (e.g. number of HIV testing done per site, percentage of MSM clients receiving sexual health needs assessment, number of PrEP initiations). Only this site-level, aggregated data will be shared with the B-HAPPY study team.

Data transfer and storage: The HIV prevention M&E system was created by Yunnan CDC in compliance with local ethical review and human subject protection regulations. Data that are extracted from the system will be saved in encrypted, password-protected database. Secure Sockets Layer (SSL) encryption will be used to securely transfer the extracted data from the system to our study team. We will store the database in password-protected, encrypted computers, and will restrict access to the data to key study personnel.

3. Client checklist

Description: To evaluate the process of HIV prevention and PrEP care delivery at each site, MSM clients at all facilities participating in PrEP implementation will be asked

to anonymously fill out a 7-question yes/no checklist at visit exit. Sample questions include: "were you aware of PrEP prior to your visit today? (Yes / No)". The checklist will be answered anonymously and will not collect any personal identifiable information (PII) or protected health information (PHI). Study sites will program the questions on an online survey platform, and use a tablet to collect this data.

Data transfer and storage: Dedicated program staff will download checklist data from the online survey platform regularly and save them in encrypted, password-protected database. Secure Sockets Layer (SSL) encryption will be used to securely transfer the data. We will store the database in password-protected, encrypted computers, and will restrict access to the data to key study personnel.

4. Client interview

Description: our study will conduct interviews with MSM clients to understand their experience accessing HIV prevention service and PrEP care at study sites, and factors associated with their decisions of PrEP use and regimen choice. See "Study procedures" section for details of the interview.

Storage: For interviews with participants who give permission to audio-record, interviews will be recorded on a device that is not connected to the Internet. After the interview, the recording will be uploaded through a Virtual Private Network (VPN) to be stored in a password-protected, encrypted computer. Dedicated research team staff will transcribe and/or conduct rapid analysis of qualitative data using memo writing or debriefing techniques. For interviews that are transcribed, audio recordings will be deleted after we review transcripts for accurate translation. Any identifying information (e.g. name, home address, date of birth) will be redacted in the transcripts. Computers

containing electronic data will be password protected with encryption software. This data will be coded and CUMC research staff will not have access to the key to link the direct identifiers.

5. Program staff interview

Description: Our team will conduct interviews with program staff at eight sites to understand their experience with PrEP implementation, discuss environmental context and resource-related issues as well as components of delivery and challenges in real time to inform the refinement of implementation process. See "Study Procedures" section for details of the interview.

Storage: Identical procedures will be used for the client interview.

Risks, Benefits & Monitoring

Potential risks

This is a study with minimal risk. Study procedures involving human subjects (i.e. in-depth interviews with clients and program staff) pose no more risk than expected in daily life. Participants (both MSM clients in PrEP implementation and study site staff who are enrolled in survey or focus groups) in this study might experience potential risks including the following:

Sensitive topics. The goal of client interview is to understand their experience accessing sexual health services, including HIV and STI prevention, at study sites. Some participants may feel slightly uncomfortable or irritated with the questions discussing their experience with sexual health services. To address this risk, participants are encouraged but not required to answer all interview questions. Participants may skip or terminate the interview at any time. For program staff, the

interview might include questions related to their organization culture, their perceptions of and roles in PrEP implementation. Some program staff may experience anxiety or discomfort caused by some of the questions. To address this risk, program staff are encouraged but not required to answer all interview questions. They may terminate the interview at any time.

Loss of confidentiality. We will not collect any personal identifiable information (e.g. name, address, place and date of birth, private health information) in our interview studies. We will make every effort to keep information confidential, but no system for protecting confidentiality can be completely secure. Given that the only record linking the subject and the research would be the consent document with their signature and the principal risk would be potential harm resulting from a breach of confidentiality, we requested a waiver of documentation of informed consent, and decided to use information sheet for consent. We will minimize risk of a breach of confidentiality by anonymizing in-depth interviews with a unique identifier, deleting audio recordings after we review transcripts for accurate transcription, and redacting any identifying information from transcripts of interviews. Participants will also have an option to decline to answer any or all questions. Study participants are encouraged but not required to answer all interview questions. They may terminate the interview at any time. More details on how we plan to ensure confidentiality of study data are described in the "Confidentiality of study data" section.

Potential Benefits

Client interview: There is no direct benefit for MSM clients to participate in the study. However, knowledge gathered in the study may help researchers better

understand PrEP implementation for MSM in China. This may help prevent HIV and might be beneficial to MSM clients in Yunnan and other places.

Program staff interview: There is no direct benefit for program staff to participate in the study. However, knowledge gathered in the study may help researchers better understand program staff's perspectives of PrEP implementation in China. This may help identify facilitators and barriers to PrEP service delivery, and might be beneficial to program staff to carry out HIV prevention services and PrEP care at their workplace.

Available alternative interventions

This is a study with minimal risk. The alternative to this study is not to participate. For MSM clients, non-participation in the study will not have a negative impact on their access to regular HIV and STI services at study sites. For site program staff, non-participation in the interviews will not negatively impact their employment nor their eligibility to participate PrEP implementation or ongoing capacity building activities.

Data and Safety Monitoring

This study entails minimal risk to study participants and does not require a Data and Safety Monitoring Board (DSMB). The PI (Dr. Meyers), study site investigators in Yunnan CDC, and other designated personnel will conduct regular internal monitoring to assure the safe and proper conduct of the protocol, following the general principles of quality management. Internal monitoring of eligibility documentation and information sheet will be conducted by the research team shortly after enrollment begins. Internal monitoring activities will be documented by logs, and meeting minutes.

Subjects

Target enrollment: 352

The proposed study will be conducted outside of the US. All sites are located in Yunnan, China. Based on race and ethnicity data of Chinese population, we expect all potential participants to be Asian, and non-Hispanic or Latino. This study will not exclude certain racial or ethnic group members from participating in the research. This study will include two types of research participants: 1.MSM clients: our study is exclusively focused on men who have sex with men (MSM) population with the goal of developing and testing a Model to Implement and Sustain PrEP Delivery for MSM in China. MSM population have been disproportionally impacted by the HIV/AIDS epidemic in China (see Background section for more details). The planned distribution of this type of study participants will be 100% male sex (at birth), Asian and non-Hispanic or Latino. 2.Program staff: we estimate the gender distribution of this type of participants will be 50% male and 50% female.

Upon completion of the interview, participants will be compensated 100 RMB (approximately USD $16) for their time. The compensation is determined based on our discussion with local collaborators and our previous experience conducting research in China.

Statistical Analysis Plan

Traditional designs—whether client-randomized or site-randomized—were not viable due to statistical power, contamination risk, and the dual focus on intervention and implementation outcomes. For instance, randomizing clients would risk contamination within sites, and randomizing sites would drastically restrict power. This

is addressed by the proposed stepped-wedge design,[25-27] with all sites participating in a baseline period (Standard Implementation), experiment period (Enhanced Implementation), and post-experiment period (Observation). Blocks of sites are randomized to the *timing* of the experiment period. Because intervention condition *changes over time*, the intervention effects reflect within-block changes (e.g., between the Enhanced and Standard periods). The design is highly flexible and maximizes power, and the proposed analyses straightforwardly accommodate different data structures for client-services outcomes (Aim 1) and implementation process outcomes (Aim 2), clients that span periods, and outcomes that are both research- and site-collected.

Data structure. For Aim 1, the *client-services outcomes* are structured with repeated visits (level-1) that are nested within clients (level-2) who are nested within periods (level-3) that are nested within sites (level-4). However, for analysis, the outcomes will reflect a single status for each client (e.g., initiation of PrEP), reducing the data to a three-level structure. For Aim 2, the *implementation process outcomes* are structured with three repeated measurements (i.e., across the baseline, enhanced, and observation periods; level-1) that are nested within sites (level-2). In each case, the small number of sites will be addressed. Of note, across aims, supplementary time-to-event analyses[28, 29] (e.g., the effect of Standard Implementation on time to client awareness) are possible by reformulating the data to client- and site-period structures. Likewise, clients will be associated with the period in which the outcome status is finalized.

Model building, estimation, and significance testing. The nested data structures will be evaluated using mixed-effects regression models, but with 8 sites, specialized methods are required to estimate and validate the effects.[29,30] Model estimation will utilize Bayesian Markov chain Monte Carlo (MCMC) methods.[27] With this approach, the results are based on a large number of replications, providing an empirically-based sampling distribution—rather than a single point estimate—for each model parameter (e.g., the effect of Enhanced Implementation). Further, the conclusions will be validated using a frequentist, fixed effects approach (i.e., dummy-coded indicators) to control for site effects.[31] To test for within-block changes across the three periods, two dummy-coded indicators will be included to differentiate the Enhanced and Observation periods from the reference Standard period. Continuous, dichotomous, and ordered categorical outcomes will be evaluated according to Gaussian, binomial, and ordinal distributions. To evaluate the magnitude and precision of effects, 95% CIs will be computed, along with odds ratios (ORs) for non-linear outcomes. The Bayesian MCMC models will be implemented in MLwiN,[27] and single-level regression models will be implemented in R.[32]

Evaluation of Specific Aim 1: To evaluate whether the addition of SIC-guided PrEP delivery (Enhanced Implementation) to standard health system PrEP delivery improves services outcomes, including: awareness, screening, offer, initiation, and continuation at 6 months. Although the outcomes are repeatedly monitored, each reflects a client-level status. The three-level mixed-effects regression model, with clients (level-1) within periods (level-2) within sites (level-3), will include control variables for client characteristics (e.g. age, partnership status, ethnicity [Han vs other], sexual identity) and site characteristics (e.g. staffing, collaboration history between VCT and

STI clinics, institutional leadership, localized epidemiology), along with indicators for study periods. Additionally, to control for temporal effects—natural improvements in PrEP implementation over time—for each client, the models will control for the time of study entry using linear and quadratic polynomials for the number of months from the start of the Standard period. With a single outcome status for each client, this controls each client's outcomes for the timing of participating during the site's PrEP implementation process. The results will indicate the average within-block change from Standard to Enhanced in the log-odds of awareness, screening, offer, initiation, and continuation. Likewise, to determine whether the effects are maintained, outcomes from the Sustainment period will be compared to the Standard and Enhanced periods.

Statistical power for Aim 1. Multilevel power analysis typically assumes interventions are at the level of individuals or groups. However, here, the intervention is time-varying. As such, power for the primary client-services level outcomes was estimated using a multi-step approach recommended by Hox[33]:

First, the *total sample* of observations was computed. For client-services level PrEP outcomes (ie, awareness, screening, offer, initiations, continuation), the sample size calculation reflects the size of the site client population and the availability of donated TDF/FTC (minimum of 1064 PrEP initiators). We anticipate ~2600 MSM clients per site per year and estimate ~133 PrEP initiators per site. However, this sample size is nested, introducing dependency and decreasing the level of statistical power.

Second, to penalize the total sample for nesting, the design effect formula is reorganized (i.e. $n_{eff} = n/[1+\{n_{clus}–1\})$ to provide the effective sample size of independent observations. Using a conservative nesting effect (i.e. =0.25 for phases/sites), the

observations provide statistical power equivalent to 32 independent observations. Despite the large number of MSM clients each year, the effective sample reaches an upper limit of 32 due to (a) the small number of sites and (b) the large cluster size per site. However, the large cluster provides high reliability for estimated level-2 effects.

Third, the effective sample size is used in a conventional power analysis. The results indicated that power is .80 to detect an effect of OR = 3.3 for the effect of Standard Implementation on client services outcomes. This is equivalent to a medium-to-large standardized effect of d=0.66, or a between-period difference in probability of 29%. For a less conservative nesting effect (=0.10), the sample is sufficient to detect OR=2.0, or a 16% between-period difference.

Evaluation of Specific Aim 2: To compare the time, costs, and resources required for Standard versus Enhanced PrEP implementation. The expected opportunity cost of implementation for sites will be modeled using an estimator that will identify the “best practice” implementation costs. The theoretical model assumes that sites attempt to minimize costs of implementation in order to maximize excess revenue subject to a standard economic production function**. This production function supports a dual cost function: where C_{it} represents the SIC-measured implementation costs for the i^{th} program in the t^{th} phase, X_{it} are characteristics of program *i* in phase *t*, is an i.i.d. error term, is a one-sided error term corresponding to the technical inefficiency for the i^{th} practice in phase, and represents the coefficients of the best practice (most efficient) cost function. We assume the best-practice cost function is of the CobbDouglas form, such that the log-linear transformation yields**.

With estimates of the model parameters, we will predict the best practice implementation costs and technical inefficiency costs for each program. We will also explore which program characteristics and contextual factors are associated with higher or lower estimated inefficiencies. We will include measures of the “best practice” implementation costs, technical cost inefficiency and intervention costs in a model predicting successful implementation. The aggregated cost variables will be added to linear probability models (because cost measures require a prediction substitution model) as covariates alongside SIC Duration and Proportion scores to predict the binary outcome of whether a program sustained a minimum of 1-year post Stage 8 of the SIC (Competency). Differences in use of resources will be examined between sites that sustain versus those that do not. The assessment and analysis of implementation costs will be critical for the government as they develop their plan for widespread scale-up.

Implementation outcomes. For Aim 2, with the focus on implementation process outcomes (rather than client services outcomes), the data are structured with three periods (level-1) within sites (level-2). The outcomes include the proportion of implementation activities completed, duration of activity completion, maximum implementation stage reached, and benchmarks on the Five-80s (3 consecutive months for implementation, 6 consecutive months for sustainment). The model will include key client and site characteristics, and dummy-coded indicators to differentiate the three periods. The results will indicate the difference between Enhanced and Standard in the level of each implementation outcome. As with Aim 1, the conclusions will be validated based on single-level models with fixed-effect control variables for site differences. Likewise, with the focus on achieving implementation process benchmarks, the model

will be extended to a time-to-event framework,[29] testing for differences between Enhanced and Standard in the time required to achieve benchmarks (adjusted for the duration of the Standard period). With the focus on implementation process outcomes, power for this aim is inherently limited. Results will focus on estimates of 95% CIs for the effect of Enhanced Implementation.

Attrition & Missing Data. Following intention-to-treat principles, sites will be retained in research measurement independently of participation in Enhanced Implementation.[34] Highly successful tracking and retention protocols will minimize missing data. However, some data will inevitably be missing. To address this, assumptions will be evaluated, and informed by the results, one of several approaches will be used[35]: i) For a small proportion of missing data with evidence of Missing at Random (MAR), the data will be analyzed using the estimation procedures described above. ii) For a non-trivial amount of missing data and evidence of MAR, multiple imputation for repeated measurements will be used.[36] iii) For a non-random missing data mechanism, pattern mixture models will be used to identify and control the effect of the non-random mechanism.[37, 38]

Data Analysis

Data analysis was informed by the Consolidated Framework for Implementation Research (CFIR). CFIR consolidates holistic factors determining the implementation and delivery of an intervention/innovation. Evidence shows that utilizing CFIR can lead to a better PrEP implementation design and a smoother PrEP service delivery to the target audience. We developed an Interview Guide and conducted initial data analysis based on the CFIR V1.0. Following updates to the CFIR in 2022, we applied CFIR V2.0

to develop an analytic matrix applied to the data to identify our key findings. We employed the Rapid Qualitative Analysis approach to analyze the data. Implementation studies show that rapid analysis can yield similar and consistent results while saving costs and resources. Data were first transcribed verbatim into Chinese and then translated verbatim to English for analysis. Four members of the research group split into teams of two, with each team reading the assigned transcripts and then summarizing the transcript into a two-page memo with a goal to reduce the data. An excel-based matrix template was developed with the CFIR domains, subdomains, constructs, and subconstructs listed in the rows and facilitators, barriers and solutions to overcoming barrier written as the column headers. After creating the matrix and arriving at consensus within the research team on the definition of each CFIR construct, text from transcripts was copied into the matrix. Teams met weekly to review matrix application and ensure consistency. Differences in application of matrix and interpretation of data were reconciled through discussion. Finally, two teams came together to discuss and name the most relevant barriers, facilitators, and solutions to overcoming barriers within each CFIR constructs.

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