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Effectiveness of Self-testing Kits Availability on Improving HIV Testing Frequency for Chinese Men Who Have Sex with Men and Their Sexual Partners: A Protocol for A Multicenter Randomised Controlled Trial

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Abstract

Introduction: HIV epidemic is increasing among men who have sex with men (MSM) in China, yet HIV testing uptake remains low. As an emerging approach, HIV self-testing (HIVST) has the potential to promote HIV testing coverage and frequency in this population. However, evidence of the effectiveness on implementation of HIVST among Chinese MSM and their sexual partners is scarce.

Methods and analysis: The randomized controlled trial will be performed in Changsha, Changde, Shaoyang, and Yiyang, Hunan province, China, recruiting 184 recent testers (men who had at least one HIV test within the past 2 years) and 26 non-recent testers (men who did not have HIV tests within 2 years or never had an HIV test). Eligible men will be randomly divided 1:1 into two groups: intervention (with free HIVST kits plus site-based HIV testing services) and control (site-based HIV testing services only). Participants in the intervention group will be provided with two free finger-prick-based HIVST kits, and can apply for two to four kits every 3 months for 1 year.

Participants in both groups will complete questionnaires via WeChat at five separate times: baseline, 3rd, 6th, 9th, and 12th month. The primary outcome is the mean number of HIV tests for MSM over the 12-month study period. The secondary outcome is the mean number of HIV tests for sexual partners of MSM over the 12-month study period. The tertiary outcomes are the self-reported proportion of consistent condom usage for anal sex, and the numbers of sexual partners during the

12-month study period.

Ethics and dissemination: The study has been approved by the Institutional Review Board of Behavioral and Nursing Research in Xiangya School of Nursing of Central South University, China (2018002). Study results will be disseminated through conferences and academic journals.

Trial registration number: Chinese Clinical Trial Registry (ChiCTR1800015584).

Strengths and limitations of this study

- No study has reported effectiveness of free HIV self-testing (HIVST) kits availability on increasing HIV testing frequency among men who have sex with men (MSM) in China.
- One major innovation of this study is to determine effectiveness of distribution of HIVST kits from MSM to their sexual partners, which will provide evidence to guide the application of HIVST to promote partner testing and improve HIV testing coverage.
- Findings from this study will have potential to help policymakers to scale up the HIVST approach to reach more high-risk individuals and could be utilized to develop contextualized HIV prevention strategies for Chinese MSM.
- In this longitudinal study, maintaining MSM for 12 months is difficult and thus loss to follow-up is possible.
- Data about sexual partners' use of HIVST kits which will be obtained indirectly

by report of MSM may be inclined to bias.

Introduction

Globally, HIV remains a major public health threat, with a total of approximately 36.7 million individuals infected at the end of 2015.[1] Despite great efforts to improve HIV prevention and treatment, the annual number of newly HIV-infected individuals remains around 2.2 million over the past 5 years.[2] Notably, the transmission rate of HIV among men who have sex with men (MSM) is alarmingly high globally, accounting for 30% of all infected individuals.[3] China has also faced a severe HIV epidemic among MSM,[4] with the HIV prevalence among MSM increasing nearly 9 times from 0.9% in 2003 to 8.0% in 2015,[5 6] and 25.5 % of newly infected individuals were attributed to MSM in 2017.[7]

In 2014, UNAIDS set up the "90-90-90" goal aiming to control the HIV epidemic by 2020, with 90% of HIV-infected individuals getting tested and diagnosed, 90% of diagnosed individuals receiving treatment, and 90% of individuals under treatment achieving viral suppression.[8] However, only 60% of HIV-positive individuals have been tested around the world,[3] far from reaching the first goal. The situation in China is similar. A recent meta-analysis showed that 62% of MSM had not taken an HIV test over the past 12 months, and nearly 50% had never been tested in their lifetime.[9] Lack of adequate HIV testing, multiple sexual partners, and frequent high-risk sexual behaviors have exacerbated HIV prevalence among MSM and may lead to further transmission to the general population via sexual contacts with female sexual

partners.[10 11] Moreover, late HIV testing and late antiretroviral treatment may increase the probability of HIV/AIDS-related deaths.[12] Thus, it is essential to promote HIV testing, especially among MSM.

As a complementary approach, HIV self-testing (HIVST) has significant potential to scale up HIV testing coverage. It can be used by individuals to collect specimens (their own blood or saliva), perform a test, and read the test results by themselves.[13] With the characteristics of convenience, privacy, and confidentiality,[14-16] HIVST may be very attractive to MSM who are impacted by HIV/AIDS-related stigma and discrimination; limited transportation; and/or reluctance to wait when taking the test at the traditional sites, such as the Center for Disease Prevention and Control [CDC], sites of voluntary counseling and testing services for AIDS, and hospitals.[17] A recent review indicated that HIVST kits had high acceptability (>67%) among MSM of the 14 included studies,[18] not specific to oral fluid based or blood based. However, the usage rate of HIVST kits was low in certain countries, with reported rates of 3.5% in France, 6.1% in China, and 11.6% in the USA.[19-21] The barriers to use included worry about a positive result, the relatively high cost of kits, and concerns about correct usage of the kits.[22]

Data released by UNAIDS (2017) underlines that reaching MSM and their partners with HIV testing services may have the potential to control the HIV epidemic.[23] In the United States, a randomized controlled trial (RCT) showed that the availability of HIVST could increase HIV testing uptake among MSM.[24] A previous RCT in Australia also indicated that HIVST could increase the HIV testing frequency

among MSM, especially in delayed testers (those who had never received HIV testing or had not been tested within 2 years).[25] Moreover, a previous US study showed that 79%-91% of MSM were willing to distribute HIVST kits to their sexual partners.[26] Serostatus disclosure to their regular or casual sexual partners after testing with HIVST kits would promote safe sexual practices if the testing results were positive.[27 28] Thus, distribution of HIVST kits from MSM to their sexual partners could be an effective way to expand HIV testing and reduce high-risk sexual behaviors among MSM.[27 28]

In accordance with this strategy, a guideline on HIVST was issued by the WHO in 2016 to promote HIV testing and partner disclosure.[13] However, in the guideline, there was only evidence from two RCTs to support the effectiveness of HIVST kits for improving HIV testing frequency among MSM.[24 25] Further research is urgently needed to determine the effects of providing free HIVST kits on MSM and their sexual partners in China.

Methods

Study objectives

This randomized controlled trial is designed to determine whether the distribution of HIVST in an intervention group compared to a control group improves the frequency of HIV testing among MSM (primary aim) and their sexual partners (male and female) (secondary aim). The study also aims to explore whether HIVST reduces high risk sexual behaviors of MSM (tertiary aim). Outcomes will be compared

between participants in the intervention and control groups who have histories of recent and non-recent HIV testing.

Study settings

This study will be conducted in four cities within Hunan Province, namely Changsha (the capital of the province), Changde, Shaoyang, and Yiyang. The settings include urban and rural areas. Delivery services of free HIVST kits are unavailable through any organizations in these cities. HIV prevalence in Hunan Province ranks 9th nationally in mainland China.[29] The number of HIV/AIDS patients in Hunan Province was about 24,000 in 2016, with 4,974 newly infected.[30] Notably, 64.8% of the new patients were infected through male-to-male sexual intercourse.[30] In our unpublished cross-sectional study, 37.7% of MSM had never tested for HIV in Hunan Province.

Participants

Two subgroups of MSM will be recruited: recent testers (men who had at least one HIV test within the last 2 years) and non-recent testers (men who did not have HIV tests within the last 2 years or never had a HIV test). Zuo An Cai Hong, a gay-friendly community-based organization (CBO) ---- with seven sub-locations in the participating settings of Hunan Province, will collaborate in this study. The CBO provides rapid HIV tests, counseling, and referral for MSM, and it conducts around 1,500-2,000 HIV tests each year. Thus, the feasibility of the study recruitment is supported.

Inclusion criteria

Individuals are eligible for participation if they meet the following criteria: (1) male anatomy; (2) 18 years of age or older; (3) reporting condomless anal or oral sex with men in the past 3 months; (4) HIV negative by rapid HIV testing at screening; (5) planning to reside in Hunan Province during the next year; (6) possessing a smartphone and adept in using WeChat; and (7) voluntarily agreeing to participate in the study and provide written informed consent.

Exclusion criteria

Individuals will be excluded if they: (1) have a serious psychiatric illness, (2) are participating in other research programs, or (3) cannot speak and/or read Chinese.

Study procedure

Study design

A multisite RCT design will be used to determine the effectiveness of HIVST on improving HIV testing frequency among Chinese MSM and their sexual partners, and to explore whether HIVST reduces high risk sexual behaviors of MSM in China. Participants will be randomly assigned to intervention and control groups, with a 1:1 ratio. The intervention group will be provided with free HIV self-testing kits and site-based HIV testing services for 1 year, and participants in the control group will have access to site-based HIV testing for 1 year (the control group will also receive the kits after the study concludes) (Fig. 1).

Recruitment

Participants will be recruited through posting of flyers (1) in the office and waiting areas of the four study locations, and (2) on Blued (a social media site for MSM), the instant online-chatting platform of QQ and WeChat (public number of Zuo An Cai Hong). CBO staff also will provide study information to MSM who are coming for testing or counseling. A WeChat account and a phone number will be established solely for study online consultation and follow-up.

MSM who express interest in this study will be contacted by the research assistant (RA) via WeChat or cellphone for purposes of scheduling an appointment at the nearby sublocation of the CBO to complete the screening procedure and receive a rapid HIV test following oral consents. Fig.1 presents the recruitment flow chart.

Figure1 Flow of recruitment and intervention.

Randomization

Securing of written informed consent will be obtained from eligible MSM prior to randomization into the intervention group and control group. Computer-generated randomized number tables developed by SPSS 18.0 will be used for this purpose. Two separate randomized number tables will be used for recent testers and non-recent testers.

Blinding

During the screening and informed consent procedure, the RAs will be blinded to

the randomization number tables, which will be sealed in opaque and sequentially numbered envelopes. After screening procedure and written informed consent, the envelope will be opened and the group assignment will be exposed to both the participants and the RAs. Throughout the project, the data analyst will be blinded to the group assignments.

Intervention group

Participants in the intervention group will have access to free HIVST kits in addition to site-based HIV testing services. They will be encouraged to perform HIV tests for themselves and their sexual partners using the HIVST kits. At enrollment, participants will be provided two HIVST kits with detailed instructions and information. Instructions and additional information will also be posted in the official account of Zuo An Cai Hong on WeChat. Participants in the intervention group will be asked to submit a photo of each test result, following which they can apply to receive new kits. A cross-sectional study in China indicated that the mean number of sexual partners of MSM was 4.79 during the past 6 months.[31] Given the repeated tests, distribution to sexual partners and the recommendation of 2-4 tests per year for high-risk MSM,[32 33] participants can apply for 2-4 kits every 3 months, and a maximum of 12 kits for 1 year. For participants' convenience, these kits can be obtained at study sites or through express delivery. With 24 hours' notice, the kits will be delivered in private packages without any information about HIV/AIDS or testing visible on the packaging. To encourage MSM to send back the photos of their results, participants will be charged a 30¥ (the equivalent of $5 USD) deposit for each kit,

which will be returned immediately after the RA receives the result photos. Each kit will be numbered sequentially on the outer packing before distribution for monitoring purposes.

The product of self-testing kits

Selection of the type of HIVST kits (oral fluids from mouth swabs versus blood samples from finger pricking) was made with consideration of research findings. Previous studies indicate that 5%-10% of participants made procedural errors,[34 35] and 10% requested additional help beyond the provided demonstration and instructions when using oral self-testing kits.[35] Thus, a finger-prick based HIVST kit, a third generation of Alere Determine HIV 1/2 rapid assay (Alere Medical Co., Ltd, Japan), approved by the US Food and Drug Administration and China's State Food and Drug Administration was selected for use in this study.[36 37] This test can detect HIV 1/2 antibodies in blood specimens after 6 weeks since being infected by HIV.[3] The specimen is obtained by pricking a finger using a disposable peripheral blood needle made by STERiLANCE in China. Blood is collected by EDTA capillary tube and dropped on a specimen reaction zone of the HIVST kit, and then Alere Determine Chase solution is added in the reaction zone.[38] The result can be read in 15-60 minutes.[38] The specificity and sensitivity of the Alere Determine HIV 1/2 are 99.68% and 100%, respectively.[39] Every kit is accompanied by instructions including testing procedure, interpretation of results, and notes. The HIVST is preliminary for screening, and a positive result requires confirmation by enzyme-linked immunoassay in the CDC laboratory.

Support hot lines

Participants will be able to contact RAs by WeChat or a 24-h telephone support line to obtain consultation on the HIVST administration and interpretation of results. Records will be maintained on the purpose of the consultation.

Follow-up of positive results

Participants testing themselves or their sexual partners positive on the HIVST results will be advised to inform the RAs by the 24-h telephone support hotline or WeChat. The RAs will provide additional consultation about positive results and treatment options for HIV positive individuals (including MSM and their sexual partners). Confirmatory laboratory testing will be advised for any positive results. Transfer services to the local CDC for further HIV testing and professional psychological counselling will be provided, as necessary.

Control group

Participants in the control group will receive usual care provided at the CDC, CBO-based rapid HIV testing sites, or local hospitals where they may receive HIV testing. After completion of the 12-month follow-up, these participants can obtain a free supply of HIVST kits for a 12-month period. The same procedure offered to the intervention group will be implemented after follow-up evaluations are completed.

Outcome measures

The primary outcome is the mean number of HIV tests received by MSM from

baseline to the 12-month evaluation. This number will be calculated based upon the total number of HIVST kits and site-based HIV tests. The secondary outcome is the mean number of HIV tests for sexual partners within 12 months reported by MSM, using the same calculations. The tertiary outcomes are the frequency of consistent condom usage for anal sex (never/sometimes/usually/always using condoms), and the numbers of reported sexual partners during the past 12 months.

Data collection

Data will be collected anonymously through online questionnaires produced by "*sojump*" (http://www.sojump.com), a professional online survey company, which has a confidential contract with the study team to encrypt the data and ensure the safety and privacy of the participants' information. An account with *sojump* will be set up, and the password will only be accessed by the RAs. Participants in the intervention and control groups will receive and complete the questionnaires via WeChat five times, at baseline and 3-, 6-, 9-, and 12-month follow-ups.

The content validity of the baseline questionnaire was obtained by expert review. Included in this questionnaire are items related to social-demographic information, HIV testing history (number of HIV tests, test results, and reasons for site-based HIV tests/self tests), partner testing history (number of tests with HIVST kits distributed by MSM and site-based HIV tests recommended by MSM, test results, and number of sexual partners' refusing to test), and high-risk sexual behavior history (number of sexual partners, number of and reasons for condomless oral or anal sex), during the

past year and last 3 months. Two previously pilot-tested items assess HIV testing self-efficacy (Cronbach's a = 0.74) with statements about confidence in HIV self-testing and confidence in regular HIV testing (every 6 months). Response choices are based on a 10-point Likert-type scale ranging from 1 = not at all confident to 10 = completely confident.

The follow-up questionnaires, to be administered at 3-month intervals, include items from the baseline measure evaluating HIV testing, partner testing, high-risk sexual behavior during the past 3 months, and self-efficacy for HIV testing. Participants who report positive or uncertain results on HIVST will be asked whether they have linked to care for confirmatory laboratory HIV testing.

At the 12-month follow-up, participants will also be asked questions about their experiences with self-testing and their willingness to use HIVST kits in the future. Compensation ($16 per person per time) will be provided to participants for their time spent filling out the questionnaires.

If any follow-up questionnaires are not been completed, we will remind participants via WeChat and/or text messages three times at intervals of 1, 2, and 3 weeks after the questionnaires being sent.

Statistical analysis plan

Analysis plan

Analyses will be conducted using SPSS 18.0. Data will be imported directly to SPSS18.0 from *sojump*, avoiding data inputting errors. Statistical results will be

reported with *p* values and 95% *CI* for the corresponding hypothesis tests. P values <0.05 are considered statistically significant. Baseline characteristics of the two groups will be compared. Analyses will be performed between the intervention and control groups for recent and non-recent testers.

The primary analysis will compare the mean number of HIV tests within 12 months by using independent sample *t*-tests. At the end of the study, generalized estimated equation models will be used to analyze the variation tendency of the mean number of HIV tests every 3 months for participants. We will also use independent sample *t*-tests to analyze the mean number of HIV tests for sexual partners of MSM.

The frequency of high-risk sexual behaviors every 3 months will be analyzed using a generalized estimated equation model. The relationship between the results of HIVST (positive, negative or uncertain) and condom use rate after the test will be explored using logistic regression analysis. The trend of HIV testing self-efficacy will be explored with generalized estimated equation models. The rate of positive self-testing results and the linkage to care will be only analyzed descriptively.

Sample size

The target sample size was calculated using G-power 3.0[40] with a one-tailed test, 80% power, and a 5% significance level. Calculations of sample size were made with consideration of previous research findings in China[41] indicating the mean number of HIV tests for recent testers was 1.35 tests per year. Guidelines recommend individuals at high-risk have 2-4 HIV tests per year,[32 33] thus an increase from 1.35 to 2 tests per

year [standard deviation: 1.61][41] is anticipated for recent testers. The mean number of HIV tests for non-recent testers is 0.2 tests per year based upon findings of past research in Australia.[25] Thus, we expect to detect an increase from 0.2 to 1 test per year [standard deviation: 0.7][25] for non-recent testers. Given a 20% missing rate, we conservatively estimate 184 recent testers and 26 non-recent testers will help detect the difference in HIV testing frequency between the two arms.

Study schedule

Two years (April 14 2018 - April 14 2019) will be needed to complete the study, including 6 months to recruit participants, 1 year for follow-up and collecting data, and 6 months to process the data and report.

Patient and public involvement

We took participants' priorities into account by conducting a interviews to explore their experience and asking their preference for delivery methods. But participants were not involved in the study design. In addition, they were not involved in the study recruitment and conduction either. Participants have right to refuse to participate in this study after accessing the burden of the intervention (including long follow-up process and time spent in completing questionnaires for five times). All participants will maintain rights to access services at the CDC or CBO. If the effectiveness of HIVST was confirmed by the study, the results will be disseminated to the study population.

Ethics and dissemination

The study has received an ethical approval from the Institutional Review Board of Behavioral and Nursing Research in Xiangya School of Nursing of Central South University, China (approval number 2018002). Moreover, the following measures will be taken to meet ethical standards: (1) written informed consent from participants will be required before enrollment and oral informed consent for rapid HIV testing at the time of screening, and (2) personal information of participants will be stored in an offline encrypted computer that can only be accessed by the research team. Results from this study will be disseminated through conferences and academic journals.

Trial registration

The study has been registered with Chinese Clinical Trial Registry [trial ID: ChiCTR1800015584, on April 9, 2018].

Discussion

The HIV epidemic is rapidly growing among MSM,[3-5] yet HIV testing uptake remains far below the recommended level in China and other countries.[3 9] Due to diverse socioeconomic status, the coverage of site-based HIV testing services differs by country and region. As a complementary approach, HIVST has the potential to expand availability of basic HIV testing services and broader HIV testing coverage.[42] However, HIVST has not been widely utilized around the world.[43] One of the main reasons is lack of enough rigorous evidence on the implementation of HIVST to promote HIV testing, which will aggravate the concerns for potential hazards of HIVST without supervision.[41]

This study is designed to explore the effectiveness of free HIVST kits availability on increasing HIV testing frequency among MSM in a resource-limited country, as previous RCTs have been performed only in developed countries.[24 25] Several types of HIVST kits have been approved by China's regulation department.[37] However, there are no relevant policies for use and regulation of the self-testing kits. China is exploring strategic approaches to integrate HIVST with site-based HIV testing services. This RCT study targets both recent testers and non-recent testers and HIV testing frequencies for the latter group are far below the recommended level. If successful, the study will provide evidence for policymakers to scale up the HIVST approach to reach more high-risk individuals. The evidence from this study could also be utilized to develop tailored and contextualized HIV prevention strategies for Chinese MSM.

A major innovation of this study is to determine the effects of distribution of HIVST kits from MSM to their sexual partners on enlarging HIV testing coverage. HIV-positive MSM who were infected through regular or casual sexual partners accounted for an increasing proportion of newly infected individuals.[23] Although partner testing (encouraging MSM to bring their partners to have HIV tests) has been recommended by WHO since 2012,[44] few data are available to assess the implementation of this policy.[45] The approach of self-testing has the potential to improve partner testing for HIV due to its convenience and privacy. However, to our best knowledge, there is no study reporting the effectiveness for partner testing with distribution of free HIVST kits among MSM in China. Evidence from this study will

help to guide the application of HIVST kits to promote partner testing and scale up HIV testing coverage.

The major challenge of this study is to maintain our participants for 12 months. Previous longitudinal studies reported about 18% of participants lost to follow up among MSM in China.[46 47] To tackle this problem, we will enlarge the sample size by 20%, and contact participants every 3 months by asking them to fill out the follow-up questionnaires. Moreover, data from the sequenced follow-up evaluations could demonstrate dynamic changes in HIV testing frequency, and high-risk sexual behavior, which may expand understanding about implementation of HIVST among MSM and their sexual partners.

This study has several limitations. First, participants must have a rapid HIV test (only HIV negative individuals will be enrolled) at recruitment settings prior to entering the study, which will exclude some MSM who live far from study settings or are concerned about stigma. Second, free HIVST kits will be provided, and thus the result cannot be generalized directly to the community, where HIVST kits are not free or may be expensive. Third, finger-prick based testing kits will be used, so the results may not apply to oral-fluid based kits. A fourth limitation is that data about sexual partners' use of HIVST kits will be obtained indirectly by report of MSM without direct verification.

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Contributors

CZ and XL initiated and designed this protocol, with DK and LG providing expertise on the methodology of the study. CZ, XL and JZ helped with the design of the questionnaires. All authors edited the protocol and agreed with the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

MSM: men who have sex with men; HIVST: HIV self-testing; CDC: Center for Disease Prevention and Control; RCT: randomised controlled trial; CBO: community based organization; RA: research assistant.

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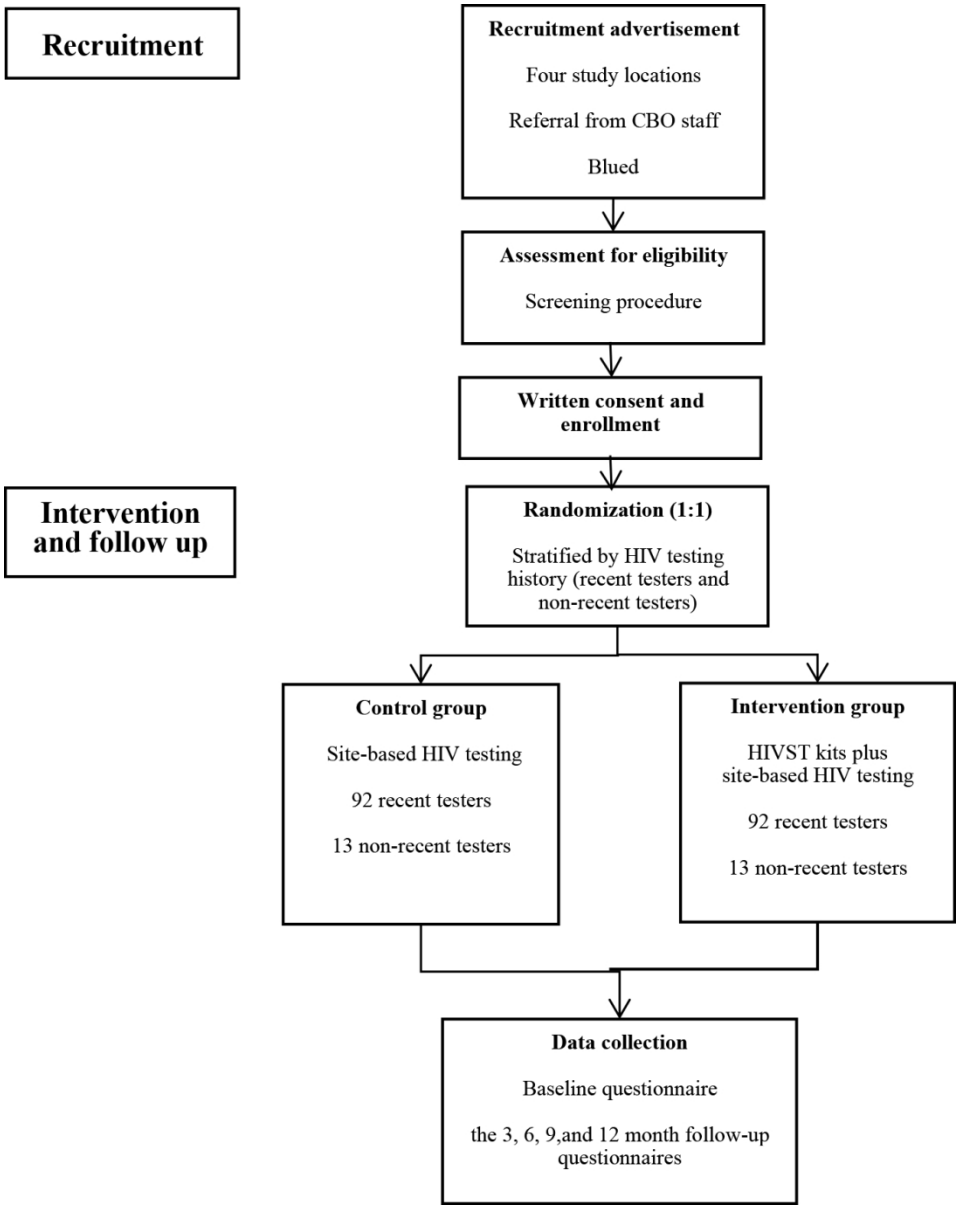

Figure1 Flow of recruitment and intervention.

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Effectiveness of Self-testing Kits Availability on Improving HIV Testing Frequency for Chinese Men Who Have Sex with Men and Their Sexual Partners: A Protocol for A Multicenter Randomised Controlled Trial

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Abstract

Introduction: HIV epidemic is increasing among men who have sex with men (MSM) in China, yet HIV testing uptake remains low. As an emerging approach, HIV self-testing (HIVST) has the potential to promote HIV testing coverage and frequency in this population. However, evidence of the effectiveness on implementation of HIVST among Chinese MSM and their sexual partners is scarce.

Methods and analysis: The randomized controlled trial will be performed in Changsha, Changde, Shaoyang, and Yiyang, Hunan province, China, recruiting 184 recent testers (men who had at least one HIV test within the past 2 years) and 26 non-recent testers (men who did not have HIV tests within 2 years or never had an HIV test). Eligible men will be randomly divided 1:1 into two groups: intervention (with free HIVST kits plus site-based HIV testing services) and control (site-based HIV testing services only). Participants in the intervention group will be provided with two free finger-prick-based HIVST kits, and can apply for two to four kits every 3 months for 1 year.

Participants in both groups will complete questionnaires via WeChat at five separate times: baseline, 3rd, 6th, 9th, and 12th month. The primary outcome is the mean number of HIV tests for MSM over the 12-month study period. The secondary outcome is the mean number of HIV tests for sexual partners of MSM over the 12-month study period. The tertiary outcomes are the self-reported proportion of consistent condom usage for anal sex, and the numbers of sexual partners during the

12-month study period.

Ethics and dissemination: The study has been approved by the Institutional Review Board of Behavioral and Nursing Research in Xiangya School of Nursing of Central South University, China (2018002). Study results will be disseminated through conferences and academic journals.

Trial registration number: Chinese Clinical Trial Registry (ChiCTR1800015584).

Strengths and limitations of this study

- No study has reported effectiveness of free HIV self-testing (HIVST) kits availability on increasing HIV testing frequency among men who have sex with men (MSM) in China.
- One major innovation of this study is to determine effectiveness of distribution of HIVST kits from MSM to their sexual partners, which will provide evidence to guide the application of HIVST to promote partner testing and improve HIV testing coverage.
- Findings from this study will have potential to help policymakers to scale up the HIVST approach to reach more high-risk individuals and could be utilized to develop contextualized HIV prevention strategies for Chinese MSM.
- In this longitudinal study, maintaining MSM for 12 months is difficult and thus loss to follow-up is possible.
- Data about sexual partners' use of HIVST kits which will be obtained indirectly

by report of MSM may be inclined to bias.

Introduction

Globally, HIV remains a major public health threat, with a total of approximately 36.7 million individuals infected at the end of 2015.[1] Despite great efforts to improve HIV prevention and treatment, the annual number of newly HIV-infected individuals remains around 2.2 million over the past 5 years.[2] Notably, the transmission rate of HIV among men who have sex with men (MSM) is alarmingly high globally, accounting for 30% of all infected individuals.[3] China has also faced a severe HIV epidemic among MSM,[4] with the HIV prevalence among MSM increasing nearly 9 times from 0.9% in 2003 to 8.0% in 2015,[5 6] and 25.5 % of new infections were attributed to MSM in 2017.[7]

In 2014, UNAIDS set up the "90-90-90" goal aiming to control the HIV epidemic by 2020, with 90% of HIV-infected individuals getting tested and diagnosed, 90% of diagnosed individuals receiving treatment, and 90% of individuals under treatment achieving viral suppression.[8] However, only 60% of HIV-positive individuals have been tested around the world,[3] far from reaching the first goal. The situation in China is similar. A recent meta-analysis showed that 62% of MSM had not taken an HIV test over the past 12 months, and nearly 50% had never been tested in their lifetime.[9] Lack of adequate HIV testing services, multiple sexual partners, and frequent high-risk sexual behaviors have exacerbated HIV prevalence among MSM and may lead to further transmission to the general population via sexual contacts with female sexual

partners.[10 11] Moreover, delayed HIV testing and delayed antiretroviral treatment may increase the probability of HIV/AIDS-related deaths.[12] Thus, it is essential to promote HIV testing, especially among MSM.

As a complementary approach, HIV self-testing (HIVST) has significant potential to scale up HIV testing coverage. It can be used by individuals to collect specimens (their own blood or saliva), perform a test, and read the test results by themselves.[13] With the characteristics of convenience, privacy, and confidentiality,[14-16] HIVST may be very attractive to MSM who are impacted by HIV/AIDS-related stigma and discrimination; limited transportation; and/or reluctance to wait when taking the test at the traditional sites, such as the Center for Disease Prevention and Control [CDC], sites of voluntary counseling and testing services for AIDS, and hospitals.[17] A recent review indicated that HIVST kits had high acceptability (>67%) among MSM of the 14 included studies,[18] not specific to oral fluid based or blood based. However, the usage rate of HIVST kits among MSM was low in certain countries, with reported rates of 3.5% in France, 6.1% in China, and 11.6% in the USA.[19-21] The barriers to use included worry about a positive result, the relatively high cost of kits, and concerns about correct usage of the kits.[22]

Data released by UNAIDS (2017) underlines that reaching MSM and their partners with HIV testing services may have the potential to control the HIV epidemic.[23] In the United States, a randomized controlled trial (RCT) showed that the availability of HIVST could increase HIV testing uptake among MSM.[24] A previous RCT in Australia also indicated that HIVST could increase the HIV testing frequency

among MSM, especially in delayed testers (those who had never received HIV testing or had not been tested within 2 years).[25] Moreover, a previous US study showed that 79%-91% of MSM were willing to distribute HIVST kits to their sexual partners.[26] Serostatus disclosure to their regular or casual sexual partners after testing with HIVST kits would promote safe sexual practices if the testing results were positive.[27 28] Thus, distribution of HIVST kits from MSM to their sexual partners could be an effective way to expand HIV testing and reduce high-risk sexual behaviors among MSM.[27 28]

In accordance with this strategy, a guideline on HIVST was issued by the WHO in 2016 to promote HIV testing and partner disclosure.[13] However, in the guideline, there was only evidence from two RCTs to support the effectiveness of HIVST kits for improving HIV testing frequency among MSM.[24 25] Further research is urgently needed to determine the effects of providing free HIVST kits to MSM and their sexual partners in China.

Methods

Study objectives

This randomized controlled trial is designed to determine whether the distribution of HIVST in an intervention group compared to a control group improves the frequency of HIV testing among MSM (primary aim) and their sexual partners (male and female) (secondary aim). The study also aims to explore whether HIVST reduces high risk sexual behaviors of MSM (tertiary aim). Outcomes will be compared

between participants in the intervention and control groups who have histories of recent and non-recent HIV testing.

Study settings

This study will be conducted in four cities within Hunan Province, namely Changsha (the capital of the province), Changde, Shaoyang, and Yiyang. The settings include urban and rural areas. Delivery services of free HIVST kits are unavailable through any organizations in these cities. HIV prevalence in Hunan Province ranks 9th nationally in mainland China.[29] The number of HIV/AIDS patients in Hunan Province was about 24,000 in 2016, with 4,974 newly infected.[30] Notably, 64.8% of the new patients were infected through male-to-male sexual intercourse.[30] In our unpublished cross-sectional study, 37.7% of MSM had never tested for HIV in Hunan Province.

Participants

Two subgroups of MSM will be recruited: recent testers (men who had at least one HIV test within the last 2 years) and non-recent testers (men who did not have HIV tests within the last 2 years or never chad a HIV test). Zuo An Cai Hong, a gay-friendly community-based organization (CBO) ---- with seven sub-locations in the participating settings of Hunan Province, will collaborate in this study. The CBO provides rapid HIV tests, counseling, and referral for MSM, and it conducts around 1,500-2,000 HIV tests each year. Thus, the feasibility of the study recruitment is supported.

Inclusion criteria

Individuals are eligible for participation if they meet the following criteria: (1) born as a male; (2) 18 years of age or older; (3) reporting condomless anal or oral sex with men in the past 3 months; (4) HIV negative by rapid HIV testing at screening; (5) planning to reside in Hunan Province during the next year; (6) possessing a smartphone and adept in using WeChat; and (7) voluntarily agreeing to participate in the study and provide written informed consent.

Exclusion criteria

Individuals will be excluded if they: (1) are participating in other research programs (2) cannot speak and/or read Chinese, or (3) score higher than 35 on the Brief Psychiatric Rating Scale.[31]

Study procedure

Study design

A multisite RCT design will be used to determine the effectiveness of HIVST on improving HIV testing frequency among Chinese MSM and their sexual partners, and to explore whether HIVST reduces high risk sexual behaviors of MSM in China. Participants will be randomly assigned to intervention and control groups, with a 1:1 ratio (by CZ). The intervention group will be provided with free HIV self-testing kits and site-based HIV testing services for 1 year, and participants in the control group will have access to site-based HIV testing for 1 year (the control group will also receive the HIVST kits after the study concludes) (Fig. 1).

Recruitment

Participants will be recruited starting from December 2017 through posting of flyers (1) in the office and waiting areas of the four study locations, and (2) on Blued (a social media site for MSM), the instant online-chatting platform of QQ and WeChat (public number of Zuo An Cai Hong). CBO staff also will provide study information to MSM who are coming for testing or counseling. A WeChat account and a phone number will be established solely for study online consultation and follow-up.

MSM who express interest in this study will be contacted by the research assistant (RA) (CZ) via WeChat or cellphone for purposes of scheduling an appointment at the nearby sublocation of the CBO to complete the screening procedure and receive a rapid HIV test following oral consents. Fig.1 presents the recruitment flow chart.

Figure1 Flow of recruitment and intervention.

Randomization

Securing of written informed consent will be obtained from eligible MSM prior to randomization into the intervention group and control group. Computer-generated randomized number tables developed by SPSS 18.0 (by JZ) will be used for this purpose. Two separate randomized number tables will be used for recent testers and non-recent testers.

Blinding

During the screening and informed consent procedure, the RAs will be blinded to the randomization number tables, which will be sealed in opaque and sequentially numbered envelopes. After screening procedure and written informed consent, the envelope will be opened and the group assignment will be exposed to both the participants and the RAs. Throughout the project, the data analysts will be blinded to code numbers representing the group assignments.

Intervention group

Participants in the intervention group will have access to free HIVST kits in addition to site-based HIV testing services. They will be encouraged to perform HIV tests for themselves and their sexual partners using the HIVST kits. At enrollment, participants will be provided two HIVST kits along with detailed instructions and information without any face-to-face training from our study. Instructions and additional information will also be posted in the official account of Zuo An Cai Hong on WeChat (https://mp.weixin.qq.com/s/vi9Nl-uLOeWnoJajvsq63Q). Participants in the intervention group will be asked to submit a photo of each test result, following which they can apply to receive new kits. A cross-sectional study in China indicated that the mean number of sexual partners of MSM was 4.79 during the past 6 months.[32] Given the repeated tests, distribution to sexual partners and the recommendation of 2-4 tests per year for high-risk MSM,[33 34] participants can apply for 2-4 kits every 3 months, and a maximum of 12 kits for 1 year. For participants' convenience, these kits can be obtained at study sites or through express delivery. With 24 hours' notice, the kits will be delivered in private packages without any information about HIV/AIDS or

testing visible on the packaging. To encourage MSM to send back the photos of their results, participants will be charged a 30¥ (the equivalent of $5 USD) deposit for each kit, which will be returned immediately after the RA receives the result photos. Each kit will be numbered sequentially on the outer packing before distribution for monitoring purposes. In addition, MSM can also purchase HIVST kits online if they need more than 4 kits every 3 months.

The product of self-testing kits

Selection of the type of HIVST kits (oral fluids from mouth swabs versus blood samples from finger pricking) was made with consideration of research findings. Previous studies indicate that 5%-10% of participants made procedural errors,[35 36] and 10% requested additional help beyond the provided demonstration and instructions when using oral self-testing kits.[36] Thus, a finger-prick based HIVST kit, a third generation of Alere Determine HIV 1/2 rapid assay (Alere Medical Co., Ltd, Japan), approved by the US Food and Drug Administration and China's State Food and Drug Administration was selected for use in this study.[37 38] This test can detect HIV 1/2 antibodies in blood specimens at six weeks post-infection.[3] The specimen is obtained by pricking a finger using a disposable peripheral blood needle made by STERiLANCE in China. Blood is collected by EDTA capillary tube and dropped on a specimen reaction zone of the HIVST kit, and then Alere Determine Chase solution is added in the reaction zone.[39] The result can be read in 15-60 minutes.[39] The specificity and sensitivity of the Alere Determine HIV 1/2 are 99.68% and 100%, respectively.[40] Every kit is accompanied by instructions including testing procedure,

interpretation of results, and notes. The HIVST is preliminary for screening, and a positive result requires confirmation by enzyme-linked immunoassay in the CDC laboratory.

Support hot lines

Participants will be able to contact RAs by WeChat or a 24-h telephone support line to obtain consultation on the HIVST administration and interpretation of results. Records will be maintained on the purpose of the consultation.

Control group

Participants in the control group will receive the usual care provided at the CDC, CBO-based rapid HIV testing sites, or local hospitals where they may receive HIV testing. Also, they can buy HIVST kits online if needed. After completion of the 12-month follow-up, these participants can obtain a free supply of HIVST kits for a 12-month period. The same procedure offered to the intervention group will be implemented for the control group after follow-up evaluations are completed.

Follow-up of positive results

Participants who have positive results for themselves or their sexual partners using HIVST kits will be advised to contact the RAs by the 24-h telephone hotline or WeChat. The RAs will provide additional consultation about the testing results and recommend them to have confirmatory laboratory tests in local CDC. Transfer services to the local CDC and professional psychological counselling institute will be provided, as necessary. If the participants are confirmed to be HIV positive, the

process of follow-up data collection will be discontinued for them.

Outcome measures

The primary outcome is the mean number of HIV tests used by MSM from baseline to the 12-month evaluation. This number will be calculated based upon the total number of HIVST kits and site-based HIV tests reported by participants. The secondary outcome is the mean number of HIV tests for sexual partners within 12 months reported by MSM, using the same calculations. The tertiary outcomes are the frequency of consistent condom usage for anal sex (never/sometimes/usually/always using condoms), and the numbers of reported sexual partners during the past 12 months.

Data collection

Data will be collected anonymously through online questionnaires produced by "*sojump*" (http://www.sojump.com), a professional online survey company, which has a confidential contract with the study team to encrypt the data and ensure the safety and privacy of the participants' information. An account with *sojump* will be set up, and the password will only be accessed by the RAs. Participants in the intervention and control groups will receive and complete the questionnaires via WeChat five times, at baseline and 3-, 6-, 9-, and 12-month follow-ups.

The content validity of the baseline questionnaire was obtained by expert review (including two experts from CDC, two experts on clinical psychology and one expert on HIV/AIDS prevention and control). Included in this questionnaire are items related

to social-demographic information, HIV testing history (number of HIV tests, test results, and reasons for site-based HIV tests/self tests), partner testing history (number of tests with HIVST kits distributed by MSM and site-based HIV tests recommended by MSM, test results, and number of sexual partners' refusing to test), and high-risk sexual behavior history (number of sexual partners, number of and reasons for condomless oral or anal sex), during the past year and last 3 months. Two previously pilot-tested items assess HIV testing self-efficacy (Cronbach's a = 0.74) with statements about confidence in HIV self-testing and confidence in regular HIV testing (every 6 months). Response choices are based on a 10-point Likert-type scale ranging from 1 = not at all confident to 10 = completely confident.

The follow-up questionnaires, to be administered at 3-month intervals, include items from the baseline measure evaluating HIV testing, partner testing, high-risk sexual behavior during the past 3 months, and self-efficacy for HIV testing. In addition, data will be collected from men in both groups about the sources of obtaining HIV self-test kits, such as from our study, online purchase or their friends. Participants who report positive or uncertain results on HIVST will be asked whether they have linked to care for confirmatory laboratory HIV test and antiretroviral treatment.

At the 12-month follow-up, participants will also be asked questions about their experiences with self-testing and their willingness to use HIVST kits in the future. Compensation ($16 per person) will be provided to participants for their time spent after filling out the questionnaires each time.

If any follow-up questionnaires are not been completed, we will remind participants via WeChat and/or text messages three times at intervals of 1, 2, and 3 weeks after the questionnaires being sent.

Statistical analysis plan

Analysis plan

Analyses will be conducted using SPSS 18.0. Data will be imported directly to SPSS18.0 from *sojump*, avoiding data inputting errors. Statistical results will be reported with *p* values and 95% *CI* for the corresponding hypothesis tests. P values <0.05 are considered statistically significant. Baseline characteristics of the two groups will be compared. Analyses will be performed between the intervention and control groups for recent and non-recent testers.

The primary analysis will compare the mean number of HIV tests within 12 months by using independent sample *t*-tests. At the end of the study, generalized estimated equation models will be used to analyze the variation tendency of the mean number of HIV tests every 3 months for participants. We will also use independent sample *t*-tests to analyze the mean number of HIV tests for sexual partners of MSM.

The frequency of high-risk sexual behaviors every 3 months will be analyzed using a generalized estimated equation model. The relationship between the results of HIVST (positive, negative or uncertain) and condom use rate after the test will be explored using logistic regression analysis. The trend of HIV testing self-efficacy will be explored with generalized estimated equation models. The rate of positive

self-testing results and the linkage to care (the rate of MSM who have confirmatory laboratory testing and initiate antiretroviral treatment in CDC) will be analyzed descriptively.

Sample size

The target sample size was calculated using G-power 3.0[41] with a one-tailed test, 80% power, and a 5% significance level. Calculations of sample size were made with consideration of previous research findings in China[42] indicating the mean number of HIV tests for recent testers was 1.35 tests per year. Guidelines recommend individuals at high-risk have 2-4 HIV tests per year,[33 34] thus an increase from 1.35 to 2 tests per year [standard deviation: 1.61][42] is anticipated for recent testers. The mean number of HIV tests for non-recent testers is 0.2 tests per year based upon findings of past research in Australia.[25] Thus, we expect to detect an increase from 0.2 to 1 test per year [standard deviation: 0.7][25] for non-recent testers. Given a 20% missing rate, we conservatively estimate 184 recent testers and 26 non-recent testers will help detect the difference in HIV testing frequency between the two arms.

Study schedule

Two years (December 14 2017 - December 13 2019) will be needed to complete the study, including 6 months to recruit participants, 1 year for follow-up and collecting data, and 6 months to process the data and report.

Patient and public involvement

We took participants' priorities into account by conducting interviews for 23

MSM to explore their experience and asking their preference for delivery methods. Results from interviews indicated that 89.5% (17/19) MSM who had HIV self-tests preferred finger-prick based testing kits, and all MSM expressed belief that express mail was a great way to receive HIVST kits if no information about AIDS or HIV showed on the package. This information helped us to design our study and choose the appropriate delivery method. But these men were not involved in the study design. In addition, they were not involved in the study recruitment and conduction either. Potential participants have the right to refuse to participate in this study after assessing the burden of the intervention (including long follow-up process and time spent in completing questionnaires for five times). All participants will maintain rights to access services at the CDC or CBO. After the study is completed, the results will be disseminated to the study population.

Ethics and dissemination

The study has received an ethical approval from the Institutional Review Board of Behavioral and Nursing Research in Xiangya School of Nursing of Central South University, China (approval number 2018002). Moreover, the following measures will be taken to meet ethical standards: (1) oral informed consent for rapid HIV testing at the time of screening and written informed consent before enrollment will be required, and (2) personal information of participants will be stored in an offline encrypted computer that can only be accessed by the research team. Results from this study will be disseminated through conferences and academic journals.

Trial registration

The study has been registered with Chinese Clinical Trial Registry [trial ID: ChiCTR1800015584, on April 9, 2018].

Discussion

The HIV epidemic is rapidly growing among MSM,[3-5] yet HIV testing uptake remains far below the recommended level in China and other countries.[3 9] Due to diverse socioeconomic status, the coverage of site-based HIV testing services differs by country and region. As a complementary approach, HIVST has the potential to expand availability of basic HIV testing services and broader HIV testing coverage.[43] However, HIVST has not been widely utilized around the world.[44] One of the main reasons is lack of enough rigorous evidence on the implementation of HIVST to promote HIV testing, which will aggravate the concerns for potential hazards of HIVST without supervision.[42]

This study is designed to explore the effectiveness of free HIVST kits availability on increasing HIV testing frequency among MSM in a resource-limited country, as previous RCTs have been performed only in developed countries.[24 25] Several types of HIVST kits have been approved by China's regulation department.[38] However, there are no relevant policies for use and regulation of the self-testing kits. China is exploring strategic approaches to integrate HIVST with site-based HIV testing services. This RCT study targets both recent testers and non-recent testers and HIV testing frequencies for the latter group are far below the recommended level. If

successful, the study will provide evidence for policymakers to scale up the HIVST approach to reach more high-risk individuals. The evidence from this study could also be utilized to develop tailored and contextualized HIV prevention strategies for Chinese MSM.

A major innovation of this study is to determine the effects of distribution of HIVST kits from MSM to their sexual partners on enlarging HIV testing coverage. HIV-positive MSM who were infected through regular or casual sexual partners accounted for an increasing proportion of newly infected individuals.[23] Although partner testing (encouraging MSM to bring their partners to have HIV tests) has been recommended by WHO since 2012,[45] few data are available to assess the implementation of this policy.[46] The approach of self-testing has the potential to improve partner testing for HIV due to its convenience and privacy. However, to our best knowledge, there is no study reporting the effectiveness for partner testing with distribution of free HIVST kits among MSM in China. Evidence from this study will help to guide the application of HIVST kits to promote partner testing and scale up HIV testing coverage.

The major challenge of this study is to maintain our participants for 12 months. Previous longitudinal studies reported about 18% of participants lost to follow up among MSM in China.[47 48] To address this problem, we will enlarge the sample size by 20%, and contact participants every 3 months by asking them to fill out the follow-up questionnaires. Moreover, data from the sequenced follow-up evaluations could demonstrate dynamic changes in HIV testing frequency, and high-risk sexual

behavior, which may expand understanding about implementation of HIVST among MSM and their sexual partners.

This study has several limitations. First, participants must have a rapid HIV test (only HIV negative individuals will be enrolled) at recruitment settings prior to entering the study, which will exclude some MSM who live far from study settings or are concerned about stigma. Second, free HIVST kits will be provided, and thus the result cannot be generalized directly to the community, where HIVST kits are not free or may be expensive. Third, finger-prick based testing kits will be used, so the results may not apply to oral-fluid based kits. A fourth limitation is that data about sexual partners' use of HIVST kits will be obtained indirectly by report of MSM without direct verification. A final limitation is that the sample of non-recent testers is small (n=26) which may limit generalizability for this group.

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Contributors

CZ and XL initiated and designed this protocol, with DK and LG providing expertise on the methodology of the study. CZ and XL helped with the design of the questionnaires. JZ provided the support of statistical analysis. All authors edited the protocol and agreed with the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

MSM: men who have sex with men; HIVST: HIV self-testing; CDC: Center for Disease Prevention and Control; RCT: randomised controlled trial; CBO: community based organization; RA: research assistant.

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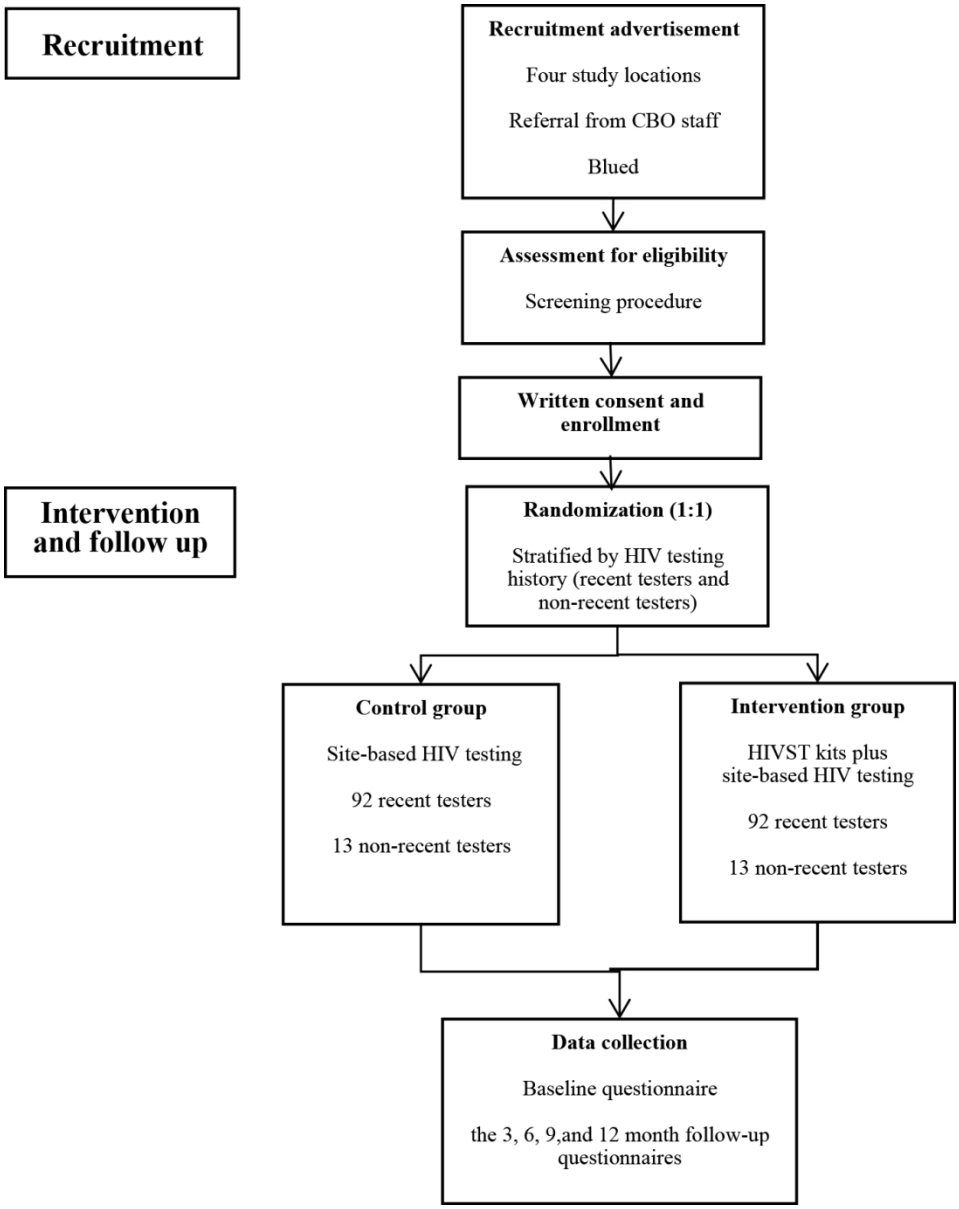

Figure1 Flow of recruitment and intervention.

117x147mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, line2-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page17,line12 &page18,line 1
	2b	All items from the World Health Organization Trial Registration Data Set	N
Protocol version	3	Date and version identifier	N
Funding	4	Sources and types of financial, material, and other support	Page21,line2-4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page20,line11-13&line18-20
	5b	Name and contact information for the trial sponsor	N
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page13,line17-21&page18, line1-2
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4, line 2-page 6, line14
	6b	Explanation for choice of comparators	N
Objectives	7	Specific objectives or hypotheses	Page 6, line17-page 7, line 2
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 8, line17-page 9, line 4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7, line4-11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 8, line1-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page10, line13-page13, line7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page13, line3-4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page15, line3-4
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page11, line10-11 &page12, line10-16 &page13, line1-7

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page13, line 6-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page16, line15-17
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page16, line 3-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 9, line6-15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 9, line20-page10, line 1-3
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page10, line 5-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 9, line1 &page9,line10 &page20,line1-3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page10, line 6-8 & line10-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page10, line 8-10

Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page13, line15-21 & page14, line1-19
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page14, line20-21 &page15, line 1-3
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page13, line17-21
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page15, line12-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page15, line17-21
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page13,line17-21&page18, line1-2
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page13, line 7

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page13, line1-7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page17, line18-20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 9, line12-20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page13, line15-21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page21, line7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page17, line20

	31b	Authorship eligibility guidelines and any intended use of professional writers	N
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	This can be accessed from Chinese Clinical Trial Registry. http://www.chictr.org.cn/edit.aspx?pid=24804&htm=4
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.