

Cluster Randomized Controlled Trial of Integrated Interventions to Reduce HIV Incidence Among MSM in China

I. Background

MSM (men who have sex with men) populations are the primary victims of the HIV epidemic. Controlling the AIDS epidemic in this population is a key focus and major challenge in global AIDS prevention and treatment. Research has demonstrated that measures such as condom use, MSM dating app interventions, pre-exposure/post-exposure prophylaxis, and prevention of synthetic drug use can effectively reduce high-risk behaviors and lower HIV infection risk. Antiretroviral therapy (ART) for AIDS can effectively reduce viral load in infected individuals and decrease transmission risk. During the "Twelfth Five-Year Plan" period, our research group conducted a community-based randomized controlled intervention study on expanded HIV testing and treatment among MSM populations in 16 cities including Beijing, Shanghai, Kunming, Wuhan, Chongqing, Nanjing, Hangzhou, and Nanning. Results showed that expanded testing and treatment measures effectively improved HIV diagnosis rates and treatment coverage among MSM populations, and successfully reduced population-level HIV viral load. However, because diagnostic and treatment coverage did not reach sufficient scale, and the various measures were not effectively integrated to form a comprehensive intervention package, the intervention failed to significantly reduce HIV incidence among MSM populations. During the "Thirteenth Five-Year Plan" period, building upon the "Twelfth Five-Year Plan" foundation, we propose to organically integrate existing evidence-based effective interventions to form an integrated intervention technology package, implementing comprehensive interventions ranging from behavioral to biomedical interventions among MSM populations to achieve the project's expected goal of significantly reducing HIV transmission.

II. Objectives

(1) To develop one integrated intervention package for reducing new HIV infections among MSM.

(2) To assess the effectiveness of developed intervention package in reducing population-level infectiousness of HIV-positive MSM, and decreasing HIV incidence of MSM.

III. Study Design

A cluster-randomized community intervention-control study design is adopted, with cities as the study units. Cities which meet inclusion criteria are match-paired and

randomized into intervention and control group. The control group receives standard services, while the intervention group receives comprehensive interventions including testing promotion activities, early diagnosis, immediate treatment upon diagnosis, MSM-specific mobile dating apps, synthetic drug use intervention, and post-exposure prophylaxis (PEP) in addition to standard services.

Baseline surveys will be conducted before intervention implementation, and final evaluation surveys will be carried out after intervention implementation as the basis for final intervention effect evaluation. The surveys adopt a cross-sectional survey method. Each city will survey 400 MSM individuals at baseline and at final evaluation, with 8,000 individuals surveyed across 20 cities for each survey. HIV-1 LAg-Avidity enzyme immunoassay (LAg-Avidity EIA) will be applied to conduct recent infection laboratory testing on HIV-positive individuals identified through cross-sectional surveys. HIV incidence rates in the intervention and control groups will then be calculated based on avidity test results.

The research technical route is shown in Figure 1 below:

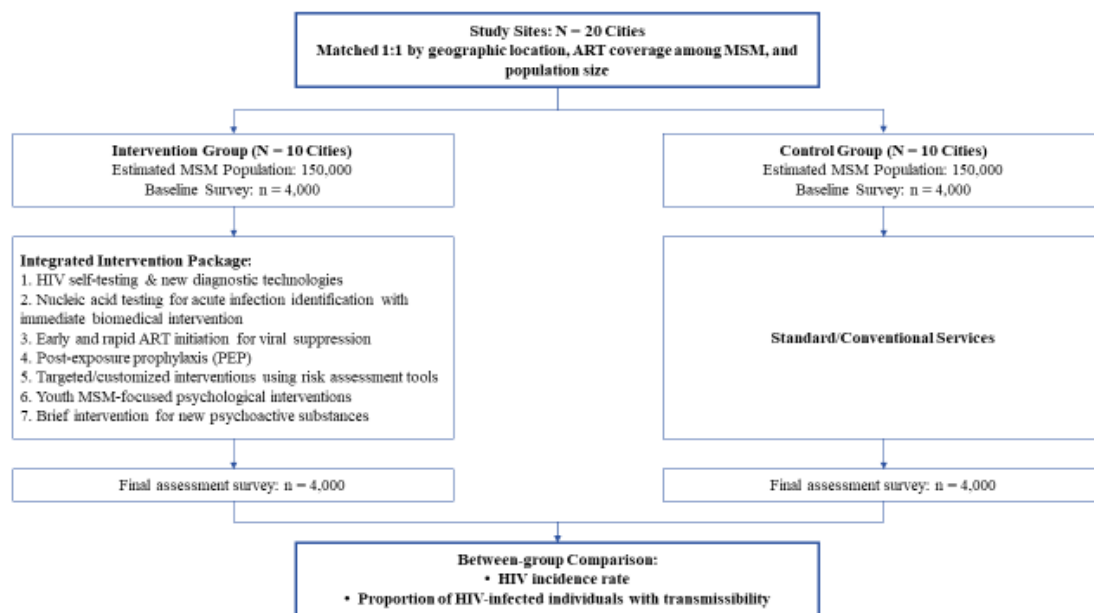


Figure 1. Overall Research Design Diagram

IV. Study Site Selection and randomization

City selection criteria are as the following: (1) urban population between 1-5 million; (2) annual number of newly reported HIV/AIDS cases among MSM exceeding 90 cases. Based on cluster-randomized study design and field work capacity, the cluster sample size is determined to be 20 cities. The 20 cities are paired 1:1 according to geographic location and treatment coverage ratio among MSM with HIV. After pairing, the two cities in each pair are randomly assigned to either the intervention or control group. Cities are enrolled and cluster randomization of these cities are as the following:

Intervention cities: Ningbo and Wenzhou in Zhejiang; Yangzhou, Xuzhou, and Wuxi in Jiangsu; Zhongshan in Guangdong; Qingdao and Jinan in Shandong; Xiamen in Fujian; Shijiazhuang in Hebei.

Control cities: Taizhou and Jinhua in Zhejiang; Changzhou, Suzhou, and Nantong in Jiangsu; Foshan in Guangdong; Yantai in Shandong; Fuzhou in Fujian; Tangshan and Baoding in Hebei. Analysis of urban population size, HIV epidemic among MSM, and treatment coverage ratios in intervention and control groups is presented in Table 1.

Table 1. Clustering, population size, and MSM HIV epidemic/ART of enrolled cities

Group	Pair	Province	City	Population size (10,000s)	HIV+ ART Coverage (%) by 2014	MSM Coverage (%) by 2014	No. of HIV+ MSM in 2014
Intervention	1	Zhejiang	Ningbo	227.6	82.3		232
Control	1	Zhejiang	Taizhou	350.8	80.5		126
Intervention	2	Zhejiang	Wenzhou	152.5	68.4		196
Control	2	Zhejiang	Jinhua	94.6	68.8		197
Intervention	3	Jiangsu	Yangzhou	230.9	73.2		105
Control	3	Jiangsu	Changzhou	322.6	68.8		140
Intervention	4	Jiangsu	Xuzhou	499.1	59.0		113
Control	4	Jiangsu	Suzhou	538.2	61.5		390
Intervention	5	Jiangsu	Wuxi	109.6	65.2		255
Control	5	Jiangsu	Nantong	437.1	66.7		214
Intervention	6	Guangdong	Zhongshan	279.3	56.6		101
Control	6	Guangdong	Foshan	150.0	58.8		113
Intervention	7	Shandong	Qingdao	471.6	58.7		197
Control	7	Shandong	Yantai	183.7	57.8		130
Intervention	8	Fujian	Xiamen	159.7	55.5		166
Control	8	Fujian	Fuzhou	302.8	51.3		167
Intervention	9	Hebei	Shijiazhuang	276.7	69.6		208
Control	9	Hebei	Tangshan	311.1	68.4		108
Intervention	10	Shandong	Jinan	433.6	54.6		212
Control	10	Hebei	Baoding	439.1	50.3		223

Note: Central urban population data are from 2013.

Table 2. Balance Analysis Between Intervention and Control Groups (Paired t-test)

Indicator	Intervention	Control	T	P
Central urban population size (2013)	284.1±138.7	313.0±139.3	-0.551	0.595
2014 proportion of newly reported cases with CD4<200	25.1±8.7	27.3±7.1	-0.601	0.563
2014 ART coverage among living HIV+ MSM (%)	64.3±9.1	63.3±9.2	1.209	0.258
2014 number of newly reported HIV+ MSM cases (current residence)	178.5±55.0	180.8±84.5	-0.067	0.948

V. Rationale of intervention package development

This study will organically integrate existing evidence-based effective intervention measures, emphasizing comprehensive integrated interventions for MSM populations.

The intervention consists of two major modules, employing an integrated intervention technology composed of seven intervention techniques.

(1) Model 1: Biomedical Intervention Model

1.Promote the implementation of multiple new diagnostic technologies including self-testing among MSM populations to diagnose and identify more infected individuals earlier.

2.Conduct HIV viral load testing on samples from MSM populations with indeterminate or negative confirmatory test results to diagnose acute-phase infected individuals early and implement biological interventions to control viral replication promptly and reduce transmission.

3.Apply rapid ART technology to suppress viral replication early and rapidly, controlling the virus to a non-transmissible level before HIV transmission occurs.

4.Provide post-exposure prophylaxis (PEP) for individuals at risk of exposure. For uninfected individuals in this population, non-occupational post-exposure prophylaxis will be implemented, enabling MSM populations with higher exposure risk to take preventive antiviral medications prophylactically to reduce infection risk, protect susceptible populations, and lower new infections.

(2) Model 2: Behavioral Intervention Model The behavioral intervention model is based on the Knowledge-Attitude-Practice (KAP) theory to promote behavioral change. Specific approaches include:

1.HIV Infection Risk Assessment and Testing Promotion through Smart APPs: The MSM community structure is complex with diverse sexual behaviors, resulting in varying HIV infection risks. Building on previous work, the research team has developed an H5-page risk assessment tool suitable for this population to differentiate risk levels among target groups. For subjects who complete risk assessment, behavioral

and social information will be integrated and visualized using Tableau and Continuity big data analysis tools. Group analysis, time series and dynamic analysis, and balance analysis methods will be applied to display overall HIV infection risk profiles. Moving average and random variation analysis will be used to predict infection risks, providing fundamental data for precise interventions.

This study will introduce information dissemination technology from news media, attempting to deliver AIDS intervention information using this technology. Mobile intelligent adaptive technology will be integrated to establish an in-platform mobile APP, combined with new media technology for interventions among MSM populations. Additionally, based on risk assessment, Global Positioning System (GPS) technology will be used to accurately push information promoting HIV testing and behavioral risk reduction. Simultaneously, a full-platform appointment testing system will be established to collect MSM testing and behavioral information for effect evaluation.

2. Psychological Intervention for Youth with High-Risk Behaviors and Infected Individuals: Through recruiting peer educators on campuses, peer education will be utilized among at-risk populations to conduct psychological protection training for preventing HIV infection and psychological stress prevention education for those already infected, as well as information on how to seek medical assistance and psychological support.

3. Brief Intervention for Synthetic Drug Use Prevention: Given the increasing number of young people using new synthetic drugs in recent years, accompanied by increased unprotected sexual behaviors and HIV infection risk, this project plans to conduct brief interventions for new synthetic drug use among youth and student populations. Through group discussions, peer education, and other methods, the project will disseminate education on skills and techniques to stay away from unsafe sexual behaviors and drugs, aiming to raise AIDS risk awareness, promote safe sexual behaviors, increase condom use rates, reduce AIDS transmission risk, and cut off transmission routes.

The specific integrated intervention package framework is shown in Figure 5 below.

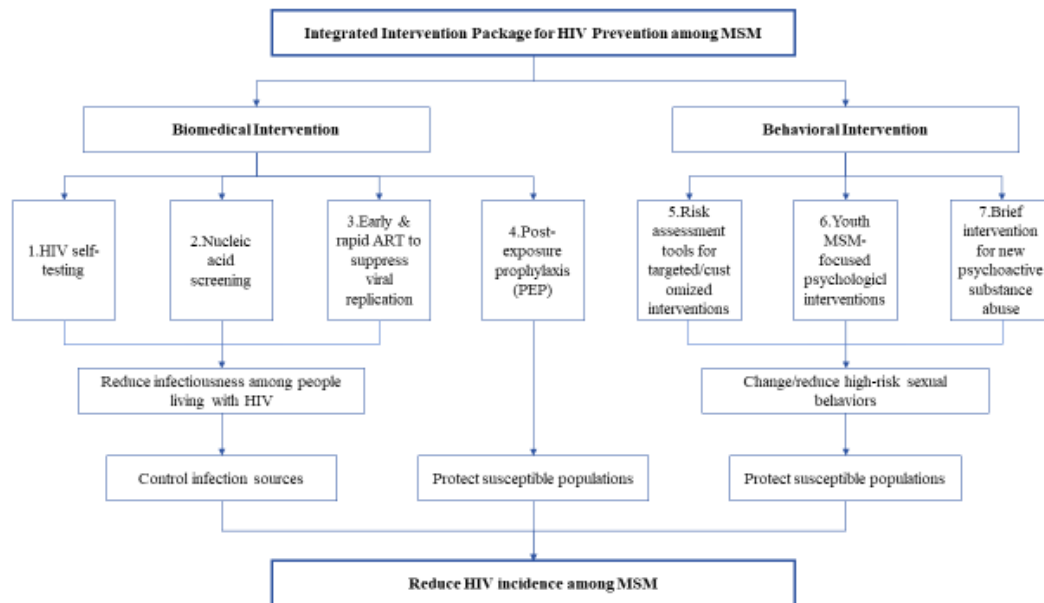


Figure 2. Intervention package Diagram

VI. Intervention Implementation

The aforementioned seven intervention measures are designated as Sub-Tasks 1-7, with intervention effectiveness evaluation as Sub-Task 8. The specific implementation process is described below.

Task 1: Implementation of Self-Testing and Multiple Testing Strategies

Promoting timely diagnosis of infected individuals is a core technical challenge in the global effort to end the AIDS epidemic. Low HIV testing coverage represents a key problem in China's MSM HIV prevention efforts. This task targets the characteristics of MSM populations by implementing a combination intervention primarily using self-testing and peer-driven testing to improve HIV diagnosis rates.

Specific Objective: Each intervention city will complete an average of 3,000 HIV tests annually among MSM populations, including 300-500 self-tests, to achieve an HIV testing coverage rate exceeding 90% by 2020.

1.create an HIV testing atmosphere through social networks. In intervention cities, utilize interpersonal networks among MSM to raise awareness and willingness to prioritize health and timely testing, thereby promoting testing behaviors.

2.implement self-testing. Building upon existing laboratory-based testing, promote self-testing among MSM through both online and offline channels to enrich current HIV testing strategies and improve accessibility and acceptability. Each city will complete 300 self-tests by the end of 2018 and no fewer than 600 by 2020.

3.implement peer-driven testing. Conduct peer-driven and informed-partner testing based on health-priority advocacy activities, using both self-testing and site-

based testing methods.

4. conduct effectiveness evaluation. The research team will design standardized evaluation tools, with project area CDCs responsible for collecting various data related to core evaluation indicators, including health fashion advocate registration information, training workshop files, testing data (self-testing kit sales volume and testing numbers, results and feedback), testing volume and results at major venues, and core information such as peer-driven testing volume and results. Supervision and evaluation will occur annually, with mid-term and final project evaluations each conducted once.

The calculation method for HIV testing coverage among MSM populations uses the estimated number of currently living HIV-infected individuals in the MSM population as the denominator, calculated at project end by collecting estimated local MSM population size and combining it with local HIV prevalence. The numerator is the number of currently living HIV-infected individuals identified in the MSM population by project end.

Task 2: Nucleic Acid Technology to Identify Acute Infections and Implement Biological Intervention

Part 1: Early Nucleic Acid Diagnosis

Current HIV diagnosis among MSM populations primarily relies on HIV antibody confirmatory testing. However, for acute-phase infected individuals and a small number of advanced-stage patients, confirmatory test results are often indeterminate or negative, causing diagnostic delays. These two patient groups have very high HIV viral loads and strong transmission capacity. This task proposes using nucleic acid testing methods for early diagnosis in the intervention group.

The specific objective is to add HIV viral load testing to all samples with indeterminate or negative confirmatory results among MSM in the 10 intervention cities (estimated average of 30 samples per city annually) to diagnose acute-phase infected individuals and a small number of advanced-stage patients who cannot be confirmed through HIV antibody testing, enabling early intervention and treatment to precisely control secondary transmission.

Activities implemented by relevant institutions:

Primary screening institutions including CDCs, hospitals, and MSM community groups will conduct primary HIV screening tests for MSM, prioritizing HIV antigen-antibody combination test kits. For individuals with positive primary screening reactions, they will promptly recollect 5ml of anticoagulated blood, complete a testing registration form, and deliver to the local HIV confirmatory testing laboratory within one day. They will timely inform test subjects of primary screening results, conduct behavioral intervention counseling for positive results, and advise those with recent high-risk behaviors to return for follow-up testing after two weeks. Institutions with disease reporting authority will conduct case reporting, follow-up, and treatment referral for confirmed positive cases according to regulations; upon receiving viral load

test reports, they will conduct case reporting and follow-up for cases meeting nucleic acid diagnosis criteria (viral load greater than 5,000 copies/ml). Monthly summaries of MSM primary screening data will be sent to confirmatory laboratories by the fifth of the following month.

Research site HIV confirmatory laboratories will process samples and separate plasma according to nucleic acid testing requirements upon receiving blood samples. One plasma tube will complete retesting and HIV antibody confirmatory testing within four days, with results fed back to the submitting unit. The second tube will be frozen at negative 80 degrees Celsius. When confirmatory results are indeterminate or negative, the laboratory will notify the third-party viral load testing institution to collect samples within two days. If the laboratory has viral load testing capacity and can obtain results within seven days, it will conduct testing locally. Monthly summaries of MSM testing data will be sent to the National CDC AIDS Center Reference Laboratory by the tenth of the following month.

Third-party HIV viral load testing laboratories will collect blood samples and complete testing and result feedback within seven days, with reports sent to the submitting unit.

The National CDC AIDS Center Reference Laboratory will develop operation manuals, provide training and technical support, and conduct monthly data summary and analysis.

For laboratory quality control, the National CDC AIDS Center Reference Laboratory will strengthen supervision of participating laboratories beyond routine quality control, with confirmatory laboratories enhancing training, quality spot checks, and document standardization for primary screening institutions. Sensitivity of blood-applicable primary screening reagents must reach 100% and specificity over 98%.

Part 2: Intervention Effectiveness Evaluation Through Laboratory Avidity Testing

HIV incidence rate is an objective indicator for evaluating AIDS prevention effectiveness. The primary laboratory method is the HIV-1 LAg-Avidity enzyme immunoassay. This task will use this method to conduct recent infection testing on HIV-positive samples identified through annual cross-sectional surveys to objectively evaluate intervention effectiveness.

The specific objective is to select primary screening institutions as project collaborators in each city, conduct cross-sectional surveys of 500 MSM subjects annually, and perform recent infection testing on identified HIV-positive samples (estimated average of 50 samples per city annually) to calculate HIV incidence rates and provide objective data for evaluating the final objective of a 30% reduction in new infections.

Activities implemented by relevant institutions:

Project collaborators including CDCs, hospitals, and MSM community groups will conduct HIV primary screening and syphilis testing for MSM (500 people annually per city) using centrally procured test kits. For positive primary screening reactions, they will recollect blood and deliver to confirmatory laboratories within one day, and conduct case reporting according to regulations. Monthly summaries of testing data will be sent to confirmatory laboratories by the fifth of the following month.

Confirmatory laboratories will process samples and separate plasma, complete retesting and confirmatory testing within four days, and preserve the second tube at negative 80 degrees. After completing annual survey sampling, samples will be centrally delivered to the National CDC AIDS Center Reference Laboratory with background information.

The National CDC AIDS Center Reference Laboratory will develop operation manuals, provide training and technical support, conduct recent infection testing on all eligible samples, calculate HIV incidence rates, and complete annual data summary and analysis.

For quality control, the National CDC AIDS Center Reference Laboratory will strengthen supervision beyond routine procedures. It will centrally procure HIV primary screening and syphilis testing reagents with sensitivity reaching 100% and specificity over 98%.

Task 3: Rapid Treatment Technology to Control Viral Transmission

Research from San Francisco found that initiating antiretroviral therapy on the day of diagnosis can shorten time to viral suppression from 4.3 months to 1.8 months and increase the six-month viral suppression success rate to 95%. Therefore, rapid antiretroviral treatment technology can significantly reduce HIV transmission. This task will adopt same-day ART initiation in the intervention group to minimize the time from diagnosis to treatment initiation, shortening the interval from an average of one month to within two weeks, increasing treatment coverage to over 90%, raising the six-month viral suppression success rate to over 90%, and reducing secondary HIV transmission.

The specific objectives are: proportion initiating ART within two weeks of antibody diagnosis greater than 90%; ART coverage in intervention population greater than 90%; ART cohort follow-up retention rate greater than 95%; ART adherence greater than 95%; six-month viral load suppression success rate greater than 90%.

1. develop standardized guidelines for rapid treatment technology. Select approximately 200 infected individuals with two positive primary screening results in Beijing who rapidly initiate ART within two weeks, document the process and technical specifications into operation guidelines for use at intervention sites.

2. implement rapid treatment technology in intervention cities. In the 10

intervention cities, obtain informed consent from 95% of newly identified infected individuals, enroll patients who rapidly initiate ART within two weeks, and maintain follow-up retention rate above 95%.

Conduct training-of-trainers for rapid treatment implementation strategies, selecting key personnel from designated hospitals, CDCs, and communities in each intervention city to participate in a trainers' workshop in Beijing, followed by stepwise training for local personnel. Train medical staff and MSM volunteer key personnel to improve communication skills and integrate the rapid treatment concept into work models. Conduct series training activities for infected individuals through unified QQ and WeChat groups managed by volunteer key personnel, organizing outreach activities and training sessions for newly identified infected individuals to improve acceptance of rapid treatment and enhance adherence and efficacy.

Hold phase supervision meetings annually in each intervention city to assess implementation difficulties and evaluate the feasibility, acceptability, safety, and effectiveness of the rapid treatment strategy, conduct data analysis, and write reports.

Conduct effectiveness evaluation at project mid-term and end by comparing ART coverage and time intervals from diagnosis to treatment initiation between intervention and control cities, using data from the China CDC AIDS Treatment and Care Data Collection System obtained quarterly.

Task 4: Promotion of Non-occupational Post-exposure Prophylaxis

MSM non-occupational post-exposure prophylaxis refers to situations where unprotected male same-sex sexual behavior occurs with HIV-infected individuals or those of unknown status. Unprotected sexual behavior carries greater HIV infection risk than needlestick injuries, particularly unprotected anal intercourse. Numerous studies demonstrate that antiviral drugs play a crucial role in blocking HIV transmission. While occupational postexposure prophylaxis has been implemented in China for years, guidelines for non-occupational exposure including sexual exposure have not been issued. In practice, increasing numbers of individuals with sexual exposure seek drug blocking services, but medical institutions lack guidelines and cannot provide medication, missing critical opportunities to block HIV transmission.

The United States, United Kingdom, Canada, and Australia have developed national nPEP guidelines and conducted numerous studies. Both animal experiments and human studies confirm that taking blocking drugs as soon as possible and continuing for 28 days after sexual contact or other non-occupational exposures reduces HIV infection likelihood. Therefore, we will attempt to promote nPEP in MSM interventions, explore implementation plans suitable for China, facilitate national nPEP guideline development, and minimize new HIV infections.

This task aims to achieve a 20 percentage point increase in nPEP acceptance among MSM in intervention cities compared to control cities, reaching 30% by study

end, with a 90% blocking success rate among nPEP recipients.

1. Determine the nPEP work plan by organizing experts to discuss strategies including risk assessment protocols, drug selection, required tests, and principles for drug sources and payment methods. Also organize experts from antiviral treatment institutions and CDCs in the 10 intervention cities to develop location-appropriate workflows.

2. Conduct publicity campaigns. Develop promotional materials including a video, cards, posters, and manuals explaining nPEP concepts, effectiveness, risk assessment, and local service contacts. Distribute these materials offline at CDCs, VCT sites, treatment sites, MSM community groups, bars, bathhouses, and testing points. Produce 100 video CDs per city for continuous playback and 2,000 sets of materials annually for three years. Train 30 key MSM volunteers annually in each city to promote nPEP knowledge in community activities, with five thematic activities covering 50 MSM each, achieving expected offline coverage of 3,000 person-times per city annually. Conduct online publicity through established QQ groups, WeChat official accounts, and MSM dating platforms, pushing nPEP knowledge monthly using various formats, achieving expected online coverage of 5,000 person-times per city annually.

3. Implement nPEP. Basic process: nPEP service sites are located at antiviral treatment medical institutions. After suspected exposure, MSM first receive rapid HIV testing. Positive results trigger confirmatory testing and counseling; negative results receive professional nPEP consultation and adherence education, with medical staff assessing eligibility. Medication is provided to eligible individuals.

Intervention targets are determined referencing WHO and US CDC guidelines through expert consultation, with established inclusion and exclusion criteria. Medication regimens are also determined referencing international guidelines through expert consultation.

Coordinate with provincial and municipal CDCs, treatment institutions, and pharmaceutical companies to stock nPEP drugs in intervention cities to ensure timely availability. MSM voluntarily accepting nPEP should purchase drugs at their own expense.

Provide relevant testing including HIV antigen-antibody testing at baseline, 4-6 weeks, and 3-month post-exposure, and blood biochemistry testing for creatinine and transaminases at baseline and 4-6 weeks.

Train medical staff at nPEP-providing institutions in intervention cities at project initiation and mid-point on nPEP knowledge, workflows, and medication regimens.

4. Conduct process evaluation. Perform qualitative interviews and questionnaire surveys among some MSM populations to understand nPEP cognition and needs and improve intervention models. Conduct regular follow-up of nPEP recipients to collect information including seroconversion, analyze factors affecting effectiveness, and explore suitable intervention models. Monthly collect data on nPEP recipients and

seroconversion in intervention cities, and every six months in control cities, using these as evaluation indicators. Assess intervention effectiveness by comparing changes in nPEP acceptance proportions between baseline and final surveys in both groups.

Task 5: HIV Infection Risk Assessment Tool for Targeted Intervention

This task explores comprehensive intervention strategies using network social software platforms among MSM populations to improve HIV testing rates and antiviral treatment coverage, promote condom use, change synthetic drug abuse behaviors, and ultimately reduce HIV incidence.

The specific objectives are: by 2020, HIV testing coverage among active MSM social software users in intervention cities reaches 90%; and the proportion of newly identified HIV-infected individuals through appointment systems who accept antiviral treatment is no less than 90%.

Intervention content and activities follow the technical route shown in Figure 6.

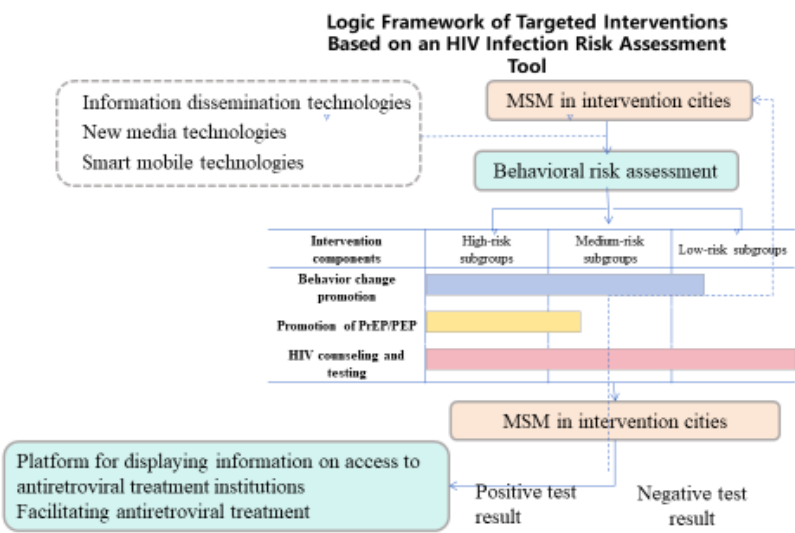


Figure 3. Task 5 Intervention Logic Framework

1. Introduce information dissemination technology to form new network intervention strategies. Use diverse information transmission functions of social software to regularly push intervention materials to MSM in intervention cities. Design and develop materials promoting HIV testing, treatment, and behavioral change in various formats, pushed monthly through MSM dating software to approximately 200,000 people across 10 cities, with expected readership exceeding 150,000.

2. Develop intelligent risk assessment tools for precise intervention. The research team has developed a risk assessment scale suitable for Chinese MSM populations based on international scales and domestic survey data. An H5-page tool for

smartphones screens local MSM by IP address and regularly pushes the assessment tool. Based on results, subjects are classified into risk-level sub-populations receiving personalized monthly intervention information on testing, treatment, behavior change, and drug reduction. Control cities receive entertainment information.

3. Combine online appointment with offline testing to build a new HIV testing model. The online-offline model uses social software platforms to establish consultation and testing appointment systems while deploying convenient offline testing sites. The open platform, temporarily named "Happy Testing," can be accessed through various portals and meets personal information security protection standards. Field visits evaluate recommended testing sites based on service skills, MSM acceptance, convenience, and laboratory standards to determine final sites whose GPS locations are imported into the appointment system for navigation.

Diverse information technology promotes testing through the platform, stimulating demand for health status awareness and improving service utilization. Subjects with appointment codes visit designated sites at appointed times for offline HIV testing.

4. Combine new media and intelligent mobile technology to expand antiviral treatment. The platform promotes treatment acceptance among infected individuals identified through testing. With informed consent, infected individuals are included in a treatment institution information platform containing details on treatment facilities in the 10 intervention cities. Monthly internal messages push treatment-related materials to promote early treatment and improve adherence among those already receiving treatment. Communication groups managed by senior MSM infected individual care volunteers encourage voluntary participation.

5. Combine new media with traditional intervention to promote behavior change. Intervention strategies start with knowledge transmission and risk awareness enhancement through four sequential themes: core MSM knowledge, infection proportion and transmission risk, necessity of safe sexual behaviors, and testing necessity. An annual synthetic drug hazard publicity month concentrates on drug dangers. Based on the foot-in-the-door effect theory, audiences are encouraged to start with small, easy behavior changes to promote more sustained and difficult risk behavior changes. The project leverages different information transmission functions of MSM dating software with appropriate materials for multi-angle HIV internet intervention. Two volunteers per city are trained to conduct monthly HIV-related discussions in communication groups, with professional training ensuring management and operation capacity.

Evaluation indicators and methods include network intervention metrics (push volume, read volume, click volume, conversion rates), testing behavior indicators (appointment system usage, testing completion, positivity rates, treatment numbers), baseline/mid-term/final surveys, and open cohort evaluation. In mid-2018, internal messages through social software platforms will recruit 500 local MSM per city for

network baseline surveys covering demographics, behaviors, drug use, infection status, and treatment. Post-survey subjects are referred to other sub-tasks' offline surveys. Mid-term evaluation in July-August 2019 and final surveys in April-June 2020 assess behavioral changes, prioritizing baseline participants. Comparisons between intervention and control cities and between final and baseline results evaluate effectiveness.

Open cohort evaluation uses the appointment testing system with phone numbers and unique codes to establish a natural open cohort. Analysis of subjects completing at least two tests provides important data including new infection rates. Comparison between intervention and control cities evaluates comprehensive intervention effectiveness, coordinated with Sub-Task 8.

Task 6: Psychological Intervention for young MSM

Young MSM is defined as those aged 18-24 years. Surveys show HIV infection rising rapidly in this group, with over 58% having two or more male sexual partners in the past six months and only 57.5% using condoms at last same-sex encounter. Poor mental health including depression and anxiety are important risk factors and barriers to HIV testing. This task uses MSM dating platforms to push customized mental health intervention information to young MSM in intervention cities to solve mental health problems, promote changes in unprotected sexual behaviors and HIV testing, and ultimately reduce HIV incidence.

The specific objectives are: increase past-year HIV testing proportion among young MSM in intervention cities by 30% compared to control cities; and reduce unprotected sexual behavior proportion by 30% compared to control cities.

Intervention content is delivered to local MSM aged 18-24 screened by IP address, including mental health intervention, HIV infection risk factor education, and safe sex negotiation ability improvement.

Intervention activities cover approximately 40,000 young MSM across intervention and control cities. In the intervention group, column articles introduce mental health problems and their relationship with HIV infection every three months. Psychological problem self-assessment scales are pushed via links with referral recommendations. Network psychological intervention consultation accounts provide free counseling. HIV infection risk factor knowledge maps are pushed every three months, with cartoon animation programs every six months. Column articles on improving condom negotiation abilities are pushed every three months, with interview voice programs featuring community opinion leaders every six months.

Effectiveness evaluation conducts four annual random sampling surveys to assess impact on young MSM behaviors. Using PASS 15.0 software and cluster randomized controlled design, each city needs 24 young MSM (240 per group total) to detect a reduction in unprotected sexual behavior from 40% to 28% with 90% power at $\alpha=0.05$. Evaluation indicators include past-year HIV testing proportion and past-six-month

unprotected sexual behavior proportion, observed through 240-person samples in each group.

Task 7: Intervention for New Synthetic Drugs and High-Risk Sexual Behavior

According to strict international definitions, new synthetic drug use among Chinese MSM reaches 40%. Drug proliferation boosts HIV epidemic spread. By the end of 2014, there were 247 million drug abusers worldwide, with only about 29.5 million (12%) being heavy abusers, meaning 80-90% were general or mild abusers. Research shows brief interventions effectively reduce drug use frequency, dosage, and methods among these users. Brief intervention uses motivational interviewing based on behavior change theory to help drug users recognize their behavior and hazards and promote change, typically lasting 3-15 minutes. This study treats MSM in 10 cities as potential drug users, using brief intervention to reduce synthetic drug use, decrease AIDS-related high-risk sexual behaviors, and ultimately reduce HIV incidence.

Specific objectives are: reduce the proportion of drug use in the past year (past three months, past one month) in the intervention group by 10% at final survey; and reduce drug use frequency by 10% at final survey.

1. Develop a new synthetic drug brief intervention manual. Before official implementation, experts will draft manual content based on domestic and international literature and Chinese MSM conditions, including implementation steps, content, key points, and duration. An expert seminar will revise the draft, followed by pilot testing with about 20 MSM in a non-research city for final refinement. The AIDS Center will uniformly print the manual for use by trained MSM peer educators.

2. Train peer educators. Brief interventions are primarily implemented by MSM peer educators in intervention cities, with each responsible for about 80-100 local MSM. Each intervention city needs to select about 8-10 peer educators with good communication skills and peer education experience. Training ensures independent intervention implementation. Considering population mobility and effectiveness, each city will organize about four training workshops during the two-year intervention period, training 8-10 peer educators each time (about 400 total over two years).

3. Implement brief intervention activities. Peer educators begin local implementation after training. These should be integrated into ongoing monthly prevention work rather than conducted separately. Before activities, peer educators assess subjects' drug use status and implement different brief interventions based on results. They must keep records for each activity, with cities reporting progress every three months. Management personnel conduct irregular supervision to ensure quality.

Intervention methods include group or one-on-one sessions. Frequency requires each peer educator to intervene with about 80-100 people, completing one round every four months, three times annually, or about 20-25 people monthly. Each subject receives intervention for 24 months from enrollment.

4. Conduct propaganda and education on reducing or resisting synthetic drugs.

While developing the manual, extract content to produce targeted, acceptable educational materials for network intervention and offline education. Online peer education cooperates with Blued to regularly push graphic information. Offline materials are distributed during brief interventions in cities not covered by network intervention to raise awareness of synthetic drug hazards.

5. Conduct process evaluation. Baseline and final surveys at project start and end compare levels to evaluate effectiveness. Indicators include past-year drug use proportion, frequency, and methods. Process indicators come from three-month progress reports including intervention person-times and completion ratios (calculated as intervention person-times divided by 4,800, the expected total per city over two years: 800 persons $\times$ 3 times/year $\times$ 2 years).

Task 8: Evaluation of Intervention

The seven intervention strategies above implement comprehensive measures to reduce HIV incidence among MSM populations from different dimensions. This task comprehensively evaluates the overall effectiveness of these integrated interventions.

The most intuitive indicator for measuring preventive intervention effectiveness is changes in new HIV infections. However, due to AIDS' particularities, this cannot be obtained by counting new reported cases like other infectious diseases. HIV's long incubation period means newly diagnosed individuals have typically been infected for many years. No simple diagnostic method exists to determine recent infection. Recent experimental diagnostic developments enable avidity testing to distinguish recent (within about 180 days) from long-term infections, allowing incidence calculation using biostatistical formulas. Additionally, internet technology and electronic identification enable establishment of open cohorts for multi-site tested MSM, with those changing from uninfected to infected representing new infections for incidence calculation. Furthermore, since AIDS transmission depends on infectious source numbers and proportions, and infected individuals on treatment with undetectable viral loads are non-infectious, measuring community viral load is an important objective indicator for transmission risk and intervention effectiveness. Evaluation research will focus on several core indicators using multiple technical solutions.

Primary evaluation indicator: HIV incidence rate among MSM populations.

Secondary evaluation indicators include biomedical intervention indicators (community viral load among MSM infected individuals, HIV testing coverage, treatment coverage, major intervention service utilization proportion) and behavioral indicators (condom use rate, synthetic drug use rate).

Evaluation methods consist of three parts.

1. HIV incidence calculation based on MSM population cohort: using identifiable dating software identity codes, establish an appointment testing platform natural cohort and compare incidence rates during different implementation periods. This coordinates with Task 5.

2.HIV incidence calculation based on HIV-1 LAg-Avidity enzyme immunoassay: survey 500 MSM per city annually, apply avidity testing to all Western blot-confirmed positive samples to diagnose recent infections, then calculate incidence at baseline, mid-term, and final stages using the avidity formula. This coordinates with Task 2.

3.HIV transmission efficiency evaluation based on community viral load: randomly select 110 MSM infected individuals from each of the 20 cities in 2018 and 2020 for baseline and final community viral load testing, comparing levels between intervention and control cities.

Survey subjects include natural cohort participants (aged 18+ using dating software with recent male same-sex behavior, providing informed consent), avidity testing participants (aged 18+ using dating software with recent male same-sex behavior, voluntarily testing at designated sites during April-June 2018-2020), and community viral load participants (randomly selected MSM infected individuals from the AIDS information system during 2018-2020).

Sample size estimation: natural cohort sample size is determined by actual platform usage, estimated at about 100,000 based on recent testing participation.

$$\frac{(Z_{\alpha/2} + Z_{\beta})^2 * [P_1 * (1 - P_1) + P_2 * (1 - P_2)] * [1 + (m - 1)\rho]}{(P_1 - P_2)^2}$$

Avidity testing sample size uses group-randomized controlled study formulas with $\alpha=0.05$, $\beta=0.2$, $P_1=0.05$, $P_2=0.03$, and intra-cluster correlation coefficient of 0.002, requiring at least 10 cities per group with no fewer than 500 cases per city. Three rounds of surveys during April-June 2018-2020 will survey 30,000 MSM total, with 3,000 avidity tests. Viral load testing sample size uses paired design formulas with $\alpha=0.05$, $\beta=0.1$, $P_1=0.85$, $P_2=0.70$, and inter-pair variance of 0.007, requiring minimum 50 samples per city, with 110 sampled for improved efficiency.

Survey implementation includes establishing a geographically positioned appointment testing platform on dating software where MSM can search for nearest testing sites. Researchers track detection numbers and positives through backend data, establishing an open natural cohort using fixed identity recognition to calculate incidence during different periods.

Avidity testing combines appointment platform information to conduct centralized surveys during April-June 2018-2020 at 5-15 testing sites per city, completing tasks when each round reaches 500 surveyed and 50 avidity tests. Implementation steps include: determining survey sites at local CDCs or community offices with reception, consultation, and rapid testing areas; conducting concentrated surveys during specified periods; recruiting eligible participants; having subjects complete electronic questionnaires on mobile phones covering demographics, AIDS knowledge, sexual behaviors, drug use, and testing; performing on-site rapid HIV and syphilis testing with

venous blood collection for positives; and conducting avidity testing on all Western blot-confirmed infections (estimated 50 per city).

$$1: \quad k = (Z_{\alpha} + Z_{\beta})^2 \times \frac{\text{Var}(d)}{(\mu_d^2)}$$

$$2: \quad \text{Var}(d) = \frac{P_1(1-P_1)+P_2(1-P_2)}{M} + 2\delta^2$$

Community viral load testing randomly selects 110 MSM infected individuals from each city before end of April 2018 and 2020, with local staff contacting selected individuals for sampling after obtaining informed consent. Sampling, delivery, and testing follow current viral load procedures, with all testing completed before end of June each year and results summarized and uploaded.

Data management includes cross-sectional survey data (avidity testing and community viral load) entered and verified by survey sites within one month and reported to the research team. Cohort survey data management uses the appointment testing system to establish an open cohort identified by phone numbers and single codes, stored on cloud servers with real-time backup and hierarchical management based on researcher responsibilities and permissions.

Laboratory testing methods are implemented by Task 2, with details in Task 2's intervention effectiveness evaluation section.

VIII. Quality Control

1.Site quality control.

The project leader organizes regular supervision to provide on-site guidance for each sub-task and research site, twice annually per project area. Supervision content includes work plan development and implementation status, problems occurring during implementation, and timely communication and consultation with sub-task responsible units and researchers to negotiate solutions. Each research site regularly holds coordination meetings between sub-tasks to report research progress and existing problems, propose solutions for coordination and connection between tasks, and ensure each research task is implemented on schedule and with quality.

2.Data information management.

When implementing the project, the research team will follow scientific research information management and national regulations on personal information security protection. First, all project researchers must study policies on scientific research information management and personal information security protection. Second, all research populations must sign confidentiality agreements. Third, scientific research data will implement classified management; data information without network media participation will not be shared with network information institutions. Fourth, two-way confidentiality management will be implemented for two types of data information involved in network media participation in project research: one is user registration personal information already possessed by network media institutions; the other is

research data generated from research activities. When involving registration personal information of high-risk populations on network media platforms, the research team will promise information providers that obtained research subject data will only be used for major special scientific research purposes, will not publish any results related to personal identification information, and will not use relevant information for profit or commercial purposes. Scientific research data information generated on network platforms during project implementation will undergo electronic confidentiality technology processing, meaning data transmission and storage will follow national cyberspace administration third-level security protection requirements. Before data analysis, information providers will delete all personally identifiable information before providing it to the research team for data analysis. Fifth, the project leader organizes relevant experts to conduct regular supervision and inspection of data information security, promptly improving any identified hidden dangers.