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Real-time digital intervention on oral pre-exposure prophylaxis adherence among MSM: randomized controlled trial

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Oral pre-exposure prophylaxis (PrEP) effectively prevents HIV among men who have sex with men, but its adherence faces significant hindrances. We evaluated the effectiveness of real-time digital intervention in promoting oral PrEP adherence through a randomized controlled trial using electronic medication monitors. The trial was registered on the Chinese Clinical Trial Registry (ChiCTR1900025604) and randomized 442 MSM to intervention (247) or control group (195). At the 6-month follow-up, the intervention group exhibited significantly higher oral PrEP adherence than the control (83.1% vs. 59.8%; adjusted net difference: 21.0%, 95% confidence interval: 12.9–29.2%, $p < 0.001$), while no differences were detected in the number of male sexual partners, condomless anal intercourse prevalence, or substance use disorder, with consistent results across both daily and event-driven oral PrEP regimens. Therefore, digital intervention significantly increased oral PrEP adherence over 6 months in the daily and event-driven subgroups but demonstrated no effect on high-risk behaviors.

Oral pre-exposure prophylaxis (PrEP), either daily or event-driven regimen[1,2], is an evidence-based HIV prevention strategy for high-risk populations, including men who have sex with men (MSM)[3]. However, low adherence to oral PrEP directly undermines its efficacy[4]. The protection diminishes at below 40% adherence[5], leading to increased risks of HIV transmission and drug resistance[6]. Prior researches have demonstrated that suboptimal adherence to oral PrEP regimens is associated with multifactorial determinants, including non-adherence due to forgetfulness, safety concerns regarding pharmacological agents, inadequate health literacy, socioeconomic constraints, and psychosocial challenges[7,8]. Therefore, optimizing oral PrEP adherence is critical for its implementation.

The COVID-19 pandemic and the Mpox outbreak highlighted the need for digital health solutions[9,10]. Digital adherence technologies, including short message service (SMS) reminders, geosocial health platforms, and dose-confirmation monitoring systems, show clinically validated efficacy in optimizing therapeutic compliance among individuals with HIV/AIDS or chronic conditions[11,12]. These interventions mediate adherence improvements through multiple mechanisms: mitigating dose-timing inaccuracies, delivering tailored therapeutic education, and implementing reinforcement learning frameworks. However, previous studies on SMS-based oral PrEP adherence interventions yielded inconsistent results. A study in Chicago showed that an interactive text-messaging intervention improved PrEP adherence among young MSM[13]. Conversely, SMS-based interventions did not improve PrEP adherence among black MSM and transgender women in New York[14], vulnerable young people in Los Angeles and New Orleans[15], young women in Kenya[16], MSM in China[17], or male sex workers in the US Northeast[18]. Thus, SMS reminders alone may not

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adequately engage participants[19], necessitating updated, multifaceted digital interventions to improve oral PrEP adherence.

Despite heterogeneous behavioral trends observed across various studies, high-risk sexual behaviors, e.g., condomless anal intercourse (CAI) and multiple partners, persist among PrEP users, significantly hindering HIV/STI prevention. Seattle PrEP users reported a 46% increase in condomless sex after 12 months[20], whereas a Dutch AMPrEP trial documented declining CAI with casual partners[21]. Digital interventions may enhance PrEP use[15] or reduce HIV risk behaviors[22] through real-time monitoring and algorithm-driven behavioral nudges. Emerging evidence suggests anonymized peer networks mitigate stigma-related barriers[23], while simulated clinical engagement extends intervention effects to sexual health decision-making[24]. However, rigorous quantification of direct behavioral impacts (e.g., partner concurrency, condomless acts) remains lacking.

While oral PrEP effectively prevents HIV, challenges in uptake, persistence, and adherence persist. Long-acting PrEP may enhance adherence and provide more stable protection[25,26]. However, cost, availability, and provider training barriers impede the widespread implementation of long-acting PrEP. Thus, interventions are required to enhance adherence to oral PrEP, a less demanding and lower-cost option to foster better health outcomes. Most studies on digital interventions focused on daily oral PrEP in high-income countries[3,14,27], with limited data on event-driven oral PrEP or low- and middle-income countries. Therefore, we conducted a randomized controlled trial (RCT) in China to evaluate the efficacy of digital intervention for real-time enhancement of oral PrEP adherence (DIRECT-PrEP) over 6 months and assess their impacts on high-risk behaviors.

Results

Participant characteristics

Participants were recruited from Sept. 20, 2019, to Jul. 31, 2020. Follow-ups were completed on Nov. 27, 2020. Of the 516 invited individuals on PrEP, 442 (85.7%) were included and randomly assigned to the intervention (247) or control (195) group. The intervention and control groups included comparable proportions of daily (150 vs. 105, respectively) and event-driven (97 vs. 90, respectively) PrEP users, respectively. The follow-up completion rate was 88.2% (390/442) at 3 months and 96.6% (427/442) at 6 months, with higher rates in the intervention group (94.7% and 98.4%) than in the control group (80.0% and 94.4%) at both time points (Fig. 1).

Baseline characteristics showed that 53.8% (238/443) of the participants were under 30 years old, and 81.7% (361/443) held a college or higher degree (Table 1). Of the 1659 missed doses detected, 81.9% (1358/1659) were effectively monitored, and 18.1% (301/1659) in the event-driven PrEP subgroup were excluded due to lack of sexual activity. Among the monitored missed doses, 99.1% (1346/1358) were in the daily PrEP subgroup, 39.4% of which (530/1346) were remedied by system interventions and 20.4% (275/1346) by research assistants, while 39.8% (541/1346) remained as missed doses. Among the 12 monitored missed doses in the event-driven PrEP subgroup, 10 were remedied by system interventions (Supplementary Table 1). All smart pillbox issues experienced by 34 participants were resolved (e.g., changing reminders from sound to vibration and adjusting volume settings).

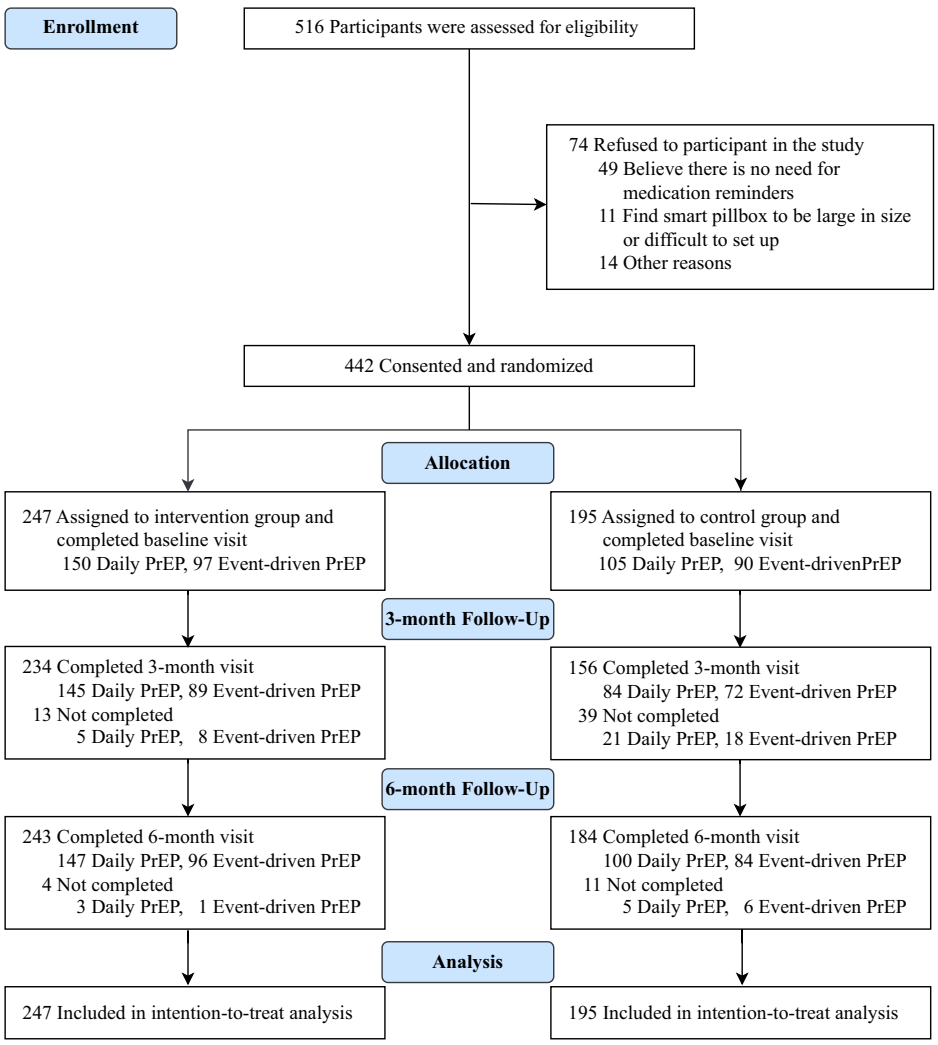

Fig. 1 | Study flowchart. Not completed signifies that no data were gathered due to the complete absence of the visit, primarily because participants were unable to travel amid the COVID-19 pandemic. While some individuals missed a visit, they eventually resumed participation in subsequent visits. PrEP pre-exposure prophylaxis.

Table 1 | Baseline characteristics of participants

Characteristics	Overall *n* (col%)	Intervention *n* (col %)	Control *n* (col %)	*p* value
Total, *n*	442 (100.0)	247 (100.0)	195 (100.0)	
Age, year				0.124
<30	238 (53.8)	125 (50.6)	113 (57.9)	
≥30	204 (46.2)	122 (49.4)	82 (42.1)	
Ethnicity				0.310
Han	395 (89.4)	224 (90.7)	171 (87.7)	
Others	47 (10.6)	23 (9.3)	24 (12.3)	
Education				0.856
College or above	361 (81.7)	201 (81.4)	160 (82.1)	
High school or below	81 (18.3)	46 (18.6)	35 (17.9)	
Marital status				0.546
Single	231 (52.3)	131 (53.0)	100 (51.3)	
Cohabitating with male partners	176 (39.8)	94 (38.1)	82 (42.1)	
Married or cohabiting with a female partner	25 (5.7)	17 (6.9)	8 (4.1)	
Separated, divorced, or widowed	10 (2.3)	5 (2.0)	5 (2.6)	
Income, US $ per month				0.122
<580	165 (37.3)	82 (33.2)	83 (42.6)	
580–1159	147 (33.3)	89 (36.0)	58 (29.7)	
>1159	130 (29.4)	76 (30.8)	54 (27.7)	
PrEP regimen				0.146
Daily PrEP	255 (57.7)	150 (60.7)	105 (53.8)	
Event-driven PrEP	187 (42.3)	97 (39.3)	90 (46.2)	
Daily PrEP baseline adherence	224 (87.8)	135 (90.0)	89 (84.8)	0.208
Event-driven PrEP baseline adherence	124 (66.3)	68 (70.1)	56 (62.2)	0.255
Sexual orientation				0.272
Homosexual	344 (77.8)	197 (79.8)	147 (75.4)	
Bisexual, straight, or other	98 (22.2)	50 (20.2)	48 (24.6)	
Sexual role with man				0.795
Top	171 (38.7)	99 (40.1)	72 (36.9)	
Bottom	123 (27.8)	67 (27.1)	56 (28.7)	
Versatile	148 (33.5)	81 (32.8)	67 (34.4)	
Venue for seeking sex				0.709
Online (Gay dating application)	265 (60.0)	150 (60.7)	115 (59.0)	
Offline (Park/ public bath/bar)	177 (40.0)	97 (39.3)	80 (41.0)	
Sexual behaviors in the past 3 months				
Has regular partner(s)	311 (70.4)	181 (73.3)	130 (66.7)	0.131
Has CAI with regular partner(s)	179 (40.5)	101 (40.9)	78 (40.0)	0.850
Has casual partner(s)	204 (46.2)	105 (42.5)	99 (50.8)	0.084
Has CAI with casual partner(s)	97 (21.9)	56 (22.7)	41 (21.0)	0.678
Substance use disorder[a]	188 (42.5)	104 (42.1)	84 (43.1)	0.837
Active syphilis infection	38 (8.6)	21 (8.5)	17 (8.7)	0.936

Categorical variables were compared between groups using the chi-square test.
PrEP pre-exposure prophylaxis, *CAI* condomless anal intercourse, *col* column.
[a]Substance includes rush (poppers or alkyl nitrites), MDMA (3,4-methylenedioxymethamphetamine; ecstasy), ice, amphetamines, tramadol hydrochloride, or ketamine hydrochloride. Participants with active syphilis infection were seropositive for both *Treponema pallidum* particle agglutination and rapid plasma reagin tests.

Primary and secondary outcomes

During follow-ups at 3 and 6 months, the intervention group demonstrated significantly higher PrEP adherence (83.3% and 83.1%) than the control group (60.9% and 59.8%), with adjusted net differences of 21.1% (95% CI: 12.5% to 29.7%) and 21.0% (95% CI: 12.9% to 29.2%; $p < 0.001$ for both). At the 3-month follow-up, both the daily PrEP and event-driven PrEP subgroups in the intervention group demonstrated significantly higher adherence (86.9% and 77.5%) compared to the control group (64.3% and 56.9%), with adjusted net differences of 21.1% (95% CI: 10.4% to 31.9%) and 17.5% (95% CI: 3.1% to 31.8%; $p < 0.05$ for both). Consistent trends were observed in the daily and event-driven PrEP subgroups at the 6-month follow-up. No significant between-group differences (all $p > 0.05$) were detected in the number of male sexual partners, CAI prevalence, or substance use disorder over 3 and 6 months (Table 2).

Post-intervention adherence and behavior trends

Figure 2 displays the adherence and sexual behavior trends. Over 6 months, the event-driven PrEP subgroup in the intervention group exhibited a notably increased adherence from 70.1% to 82.3% ($p = 0.042$). In contrast, the adherence in the control group declined from 74.4% to 59.8% ($p = 0.030$), particularly in the daily PrEP subgroup (decreasing from 84.8% to 58.0%; $p < 0.001$). No statistically significant changes in the number of male sexual partners (from 4.4 to 3.3), the proportion of CAI (from 53.8% to 45.7%), and the proportion of substance use disorder (from 42.1% to 35.0%) were observed in the intervention group (all $p > 0.05$). According to stratified analyses by PrEP regimen, the intervention and control groups showed no statistically significant differences in sexual behaviors (number of partners and CAI) and substance use disorder at either time point (all $p > 0.05$) (Supplementary Table 2), nor did the trends over time (Supplementary Fig. 1).

Sensitivity analysis

Sensitivity analysis showed consistent intervention efficacy on primary and secondary outcomes between pre- and post-imputation data. At the 3- and 6-month follow-ups, the intervention group also demonstrated significantly higher PrEP adherence (83.8% and 83.4%, respectively) compared to the control group (64.6% and 61.0%; $p < 0.05$ for both time points). These effects were robust across both the daily PrEP and event-driven PrEP subgroups. However, no significant intervention effects were observed on high-risk behaviors or substance use disorder (Supplementary Table 3). Sensitivity analyses of the trends in PrEP adherence, high-risk behaviors, and substance use disorder are detailed in Supplementary Fig. 2.

Discussion

To the best of our knowledge, this is the first assessment of the impact of combined telemonitoring and timely interventions on oral PrEP adherence and risk behaviors among MSM in low- and middle-income countries. The results suggested that this combination enhanced oral PrEP adherence without affecting high-risk behaviors or substance use disorder. This real-time intervention strategy fills a research gap in oral PrEP adherence and addresses barriers such as forgetfulness and irregular dosing through real-time reminders, dose tracking, and automated alerts. Smart pillbox holds significant public health value, particularly for high-risk populations, by maximizing the preventive efficacy of PrEP and reducing HIV transmission.

This study demonstrates that combining telemonitoring and timely intervention improves adherence to both oral PrEP regimens (daily and event-driven) among MSM. A study in Thailand indicated that enhanced risk recognition can affect PrEP adherence among young MSM[28]. Real-time monitoring of oral PrEP adherence can potentially improve risk awareness and daily medication habits among MSM. Furthermore, electronic medication monitors identified suboptimal adherence, thereby enabling precise interventions. However, SMS reminders derived from electronic medication monitors failed to improve oral PrEP adherence due to potential message overload[16]. Thus, research assistants provided more individualized

Table 2 | Effectiveness of telemonitoring and timely interventions on oral PrEP adherence among 442 MSM

	Proportion/No. (95% CI)		Net difference (95% CI)	*p* value	Adjusted net difference[a] (95% CI)	*p* value
	Intervention	Control				
Primary outcome						
PrEP adherence at 3 Month	83.3 (78.5–88.1)	60.9 (53.2–68.6)	22.4 (13.8–31.0)	<0.001	21.1 (12.5–29.7)	<0.001
PrEP adherence at 6 Month	83.1 (78.4–87.9)	59.8 (52.6–66.9)	23.3 (15.1–31.6)	<0.001	21.0 (12.9–29.2)	<0.001
Secondary outcomes						
Daily PrEP adherence at 3 Month	86.9 (81.3–92.5)	64.3 (53.8–74.8)	22.6 (11.9–33.3)	<0.001	21.1 (10.4–31.9)	<0.001
Daily PrEP adherence at 6 Month	83.7 (77.6–89.7)	58.0 (48.2–67.8)	25.7 (14.8–36.5)	<0.001	24.5 (13.8–35.2)	<0.001
Event-driven PrEP adherence at 3 Month	77.5 (68.7–86.4)	56.9 (45.2–68.7)	20.6 (6.3–34.9)	0.005	17.5 (3.1–31.8)	0.017
Event-driven PrEP adherence at 6 Month	82.3 (74.5–90.1)	61.9 (51.3–72.5)	20.4 (7.5–33.2)	0.002	15.6 (2.8–28.4)	0.018
No. of male sex partners at 3 Month	4.4 (3.3–5.4)	3.0 (2.2–3.8)	1.3 (−0.1–2.8)	0.069	1.3 (−0.2–2.7)[b]	0.806
No. of male sex partners at 6 Month	3.3 (2.5–4.2)	2.7 (2.0–3.4)	0.6 (−0.5–1.7)	0.296	0.5 (−0.6–1.6)[b]	0.355
CAI at 3 Month	50.0 (43.6–56.5)	51.9 (44.0–59.9)	−1.9 (−12.1–8.3)	0.711	−1.1 (−9.2–6.9)[b]	0.779
CAI at 6 Month	45.7 (39.4–52.0)	42.9 (35.7–50.2)	2.7 (−6.8–12.3)	0.573	2.5 (−5.4–10.3)[b]	0.540
Substance use disorder at 3 Month	41.0 (34.3–46.9)	41.7 (33.8–49.5)	−1.1 (−11.1–9.0)	0.834	−1.5 (−9.0–6.1)[b]	0.701
Substance use disorder at 6 Month	35.0 (28.9–41.0)	35.9 (28.9–42.7)	−0.9 (−10.1–8.3)	0.849	−0.8 (−7.5–5.9)[b]	0.820

PrEP pre-exposure prophylaxis, *MSM* men who have sex with men, *CI* confidence interval, *CAI* condomless anal intercourse.
[a]A mixed linear model adjusted for age, education and income at baseline, site, and dosing regimen (daily PrEP vs. event-driven PrEP, except in daily PrEP and event- driven PrEP adherence outcomes).
[b]The mixed linear model also adjusted for the number of male sex partners, CAI and substance use disorder at baseline.

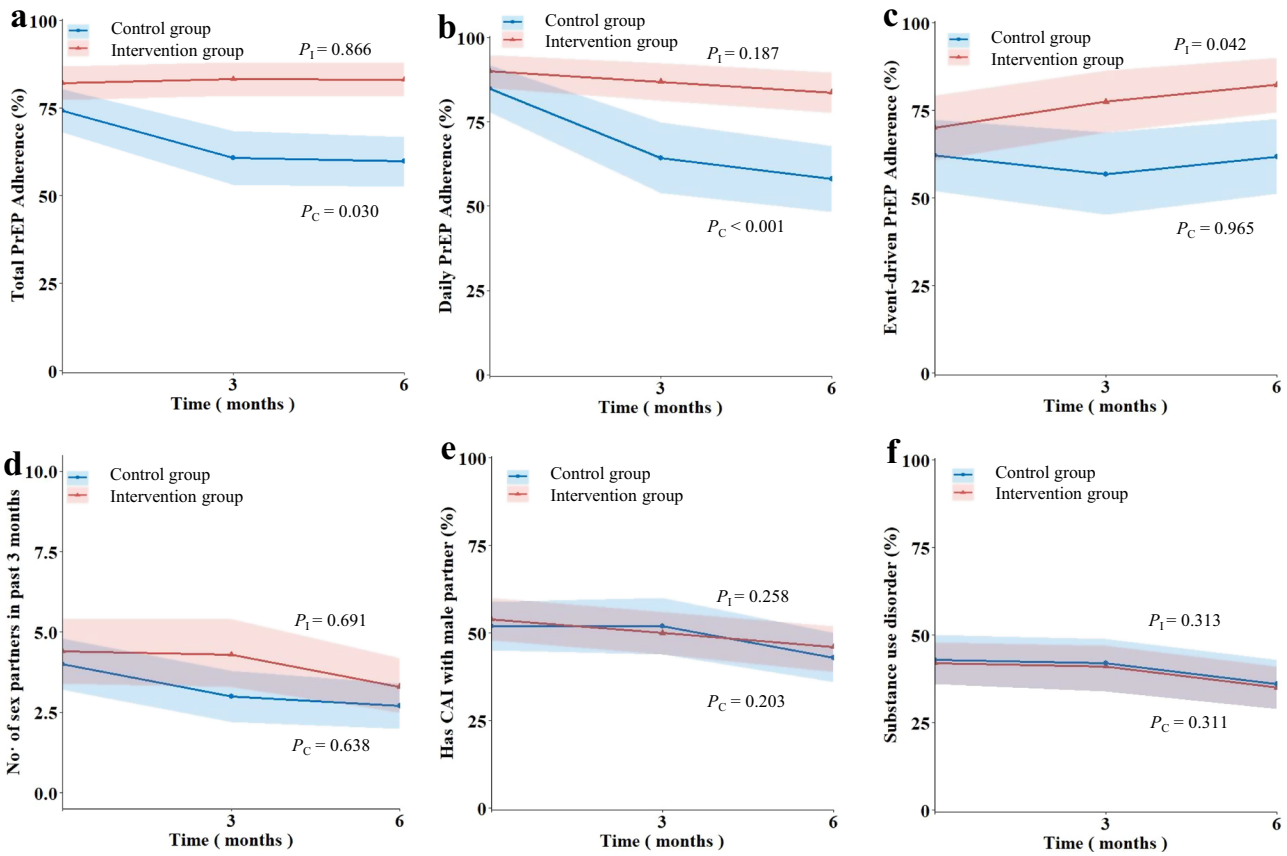

Fig. 2 | Cochran–Armitage test for trend of PrEP adherence and high-risk behaviors. Cochran–Armitage test of the trend of total PrEP adherence rate (**a**); Daily PrEP adherence rate (**b**); Event-driven PrEP adherence rate (**c**); the no. of sex partners in the past 3 months (**d**); the proportion of CAI with male partners (**e**); the proportion of substance use disorder (**f**). substance includes rush (poppers or alkyl nitrites), MDMA (3,4-methylenedioxymethamphetamine; ecstasy), ice, amphetamines, tramadol hydrochloride, or ketamine hydrochloride. p_I the *p* value derives from the trend analysis in the intervention group, p_C, the *p* value derives from the trend analysis in the control group, PrEP pre-exposure prophylaxis, CAI condomless anal intercourse.

interventions via WeChat or phone calls in the case of text message intervention failures.

In the early stages of this study, both groups showed high adherence. However, adherence declined in the control group while remaining stable or improving in the intervention group, a pattern consistent with previous PrEP studies. For instance, a study in America targeting young MSM across 12 cities revealed that most participants adhered to four or more tablets weekly during the initial 12 weeks, but adherence fell to 34% by week 48[29]. Similar decreases were observed among black MSM and transgender women in New York[14] and young women in Kenya[20]. These findings highlight the role of digital remote interventions in maintaining oral PrEP adherence, as system reminders and healthcare provider support foster a supportive environment for sustained adherence.

In addition, this study demonstrated fundamentally distinct adherence trajectories between daily PrEP in the control and event-driven PrEP in the intervention group, shaped by their unique behavioral engagement patterns. The progressive decline in daily PrEP use reflects challenges in sustaining preventive behaviors for infrequent risk exposures[29,30], while event-driven PrEP's improvement stems from its natural synchronization with sexual activity patterns[31]. Notably, digital adherence tools showed regimen-specific effectiveness, performing best when their design complemented the intrinsic motivation structure of each approach. This evidence underscores the need for differentiated implementation strategies that account for these behavioral determinants, moving beyond one-size-fits-all approaches in HIV prevention.

Despite electronic medication monitors and research assistants' interventions, missed doses persist, underlining the multifaceted influence on adherence. Thus, a holistic approach that considers social support, economic status, and education level is required to promote oral PrEP adherence[32]. Such a comprehensive approach combining monitoring, timely feedback, and a collective analysis of adherence barriers can motivate behavior change. In Kenya, community outreach and partner engagement enhanced oral PrEP adherence[33]. Telemonitoring and timely intervention may appeal more to those facing obstacles to oral PrEP adherence, particularly those with occupational constraints requiring irregular schedules or extended work hours. It is also vital to examine the characteristics of PrEP users receiving no benefit from real-time interventions. Future research will analyze non-recipient characteristics to guide PrEP implementation.

Although interventions using electronic medication monitors, high-risk behaviors among MSM using PrEP remained unchanged in this study. No statistically significant differences were detected in daily or event-driven subgroups. Researches on changes in sexual behavior post-PrEP use are inconsistent. A previous study found no effect of PrEP on the number of sexual partners, or sexual activity frequency[20], while a PrEP study from Belgium reported decreased condom use with casual partners but increased with partners of unknown HIV status[34]. Current PrEP programs and adherence interventions do not focus on reducing high-risk sexual behavior or substance use disorder. Future strategies should consider integrating behavioral interventions with oral PrEP dispensation.

While long-acting medications represent a promising advancement in HIV treatment and prevention[25,26], they are not the sole option. Meanwhile, future anti-HIV strategies may consider various mechanisms, treatment stages, and clinical scenarios. Thus, long-acting PrEP alone cannot eliminate AIDS despite its potential, and the needs of diverse populations necessitate innovative, people-centered approaches. Providing high-risk individuals with poor oral PrEP adherence with multiple options, including long-acting formulations, is crucial. Due to their user-centric, personalized, and adaptable features, low-cost, reminder-based daily oral PrEP options and event-driven oral PrEP can serve as essential alternatives. Accordingly, effectively combining various preventive strategies for different populations is critical, demanding stakeholder collaboration.

While smart pillboxes offer substantial public health potential, their implementation faces real-world challenges[35–37]: limited user acceptability due to privacy concerns and technical complexity, particularly among older or technologically inexperienced individuals; sustainability constraints stemming from waning engagement without behavioral reinforcement; structural barriers including cost and healthcare infrastructure limitations; and imperfect data accuracy from manual overrides or device errors. To maximize impact, future interventions should combine these technologies with behavioral support strategies while prioritizing user-centered design, ensuring both effectiveness and scalability across diverse populations.

This study has several limitations. Firstly, it confirmed that telemonitoring and timely interventions enhance adherence among MSM, but their efficacy in other high-risk groups warrants further investigation. Secondly, free electronic medication monitors may not reflect real-world scenarios where purchasing is more often. Thirdly, though most variables exhibited no significant differences between the China Real-World Oral Intake of PrEP (CROPrEP) participants and non-participants (Supplementary Table 4), COVID-19 restrictions did limit recruitment. Furthermore, the baseline PrEP adherence varied between the intervention and control groups, regardless of whether they were assigned to the daily PrEP or event-driven PrEP subgroup. Accordingly, we adjusted for the PrEP regimen variable in both primary and secondary outcomes. Additionally, the evident non-adherence among MSM who prefer nocturnal activities indicates a need for alternatives to manual reminders, such as smart pillboxes or potentially AI-driven 24/7 reminders[38]. Large language models could promote anonymous discussions about adherence challenges. However, evaluating the effectiveness of AI interventions requires larger samples and rigorous designs.

In conclusion, this trial found that telemonitoring and timely interventions enhance oral PrEP adherence among MSM, thus addressing prevention failures across medication modalities. However, these interventions exhibited no effect on high-risk behaviors or substance use disorder. Until long-acting PrEP is affordable and accessible, digital technologies like smart pillboxes, a key component of the people-centered HIV intervention strategy, can be leveraged for personalized support.

Methods

Study design and participants

The CROPrEP prospective interventional study assessed HIV prevention efficacy of emtricitabine-tenofovir disoproxil fumarate (F/TDF) among MSM in Shenyang, Beijing, Chongqing, and Shenzhen[39]. Participants were assigned to the PrEP users group (daily PrEP or event-driven PrEP group) and PrEP non-users groups depending on their personal decision at the baseline of CROPrEP. For the daily PrEP group, participants took one tablet (F/TDF) per day. The event-driven PrEP group followed the "2-1-1" dosing regimen. The "2-1-1" regimen involves taking 2 tablets 2 to 24 h before sex, followed by taking 1 tablet 24 and 48 h after the first dose. In case of additional sex within 48 h, participants switch to 1 tablet/day until 48 h after the final act. In case of the next sex occurring <7 days after that, the 1 tablet/day regimen continues. Otherwise, the "2-1-1" regimen restarts. Within follow-up, participants in the PrEP users groups could switch between daily and event-driven PrEP groups.

This study was a multicenter, non-blinded, two-arm RCT. MSM community opinion leaders and volunteers at the CROPrEP sites in Shenyang, Beijing, Chongqing, and Shenzhen promoted the free use of smart pillboxes among participants of CROPrEP via WeChat. MSM who volunteered for this study were randomly assigned to intervention and control groups. Eligible participants were included based on the following criteria: assigned male at birth, aged 18 to 65, engaged in anal sex with males, self-reported at least one high-risk behavior in the past 6 months (CAI with male partners, two or more male sexual partners), any STI diagnosis, history of post-exposure prophylaxis but not in the previous month, HIV-1 negative, participated in the CROPrEP project, and capable of understanding the study procedures and willing to provide written consent. The trial protocol is provided in Supplementary (Supplementary Protocol). The first participant was enrolled on Sept. 20, 2019, and the final participant completed the study on Nov. 27, 2020.

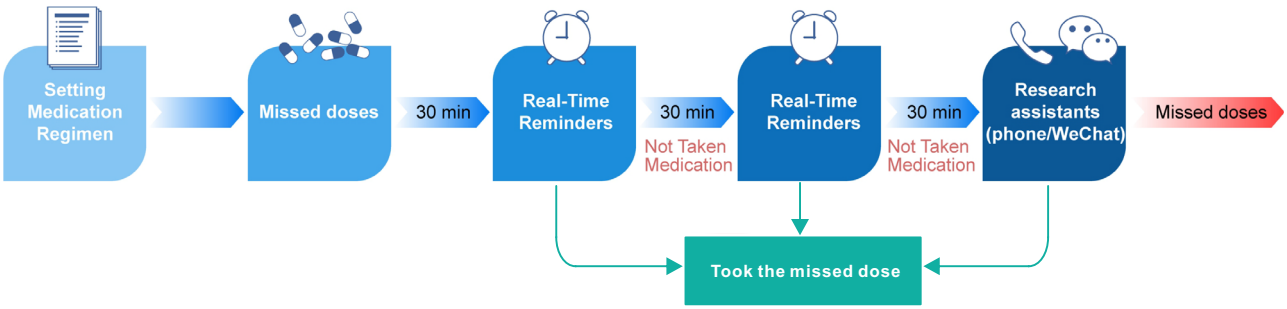

Fig. 3 | The telemonitoring and timely intervention process diagram. Setting Medication Regimen: participants configured medication reminders in the smart pillbox according to their prescribed dosing schedule. Missed doses (initial occurrence): a missed dose event was recorded if the participant failed to take the medication at the scheduled time. Real-Time Reminders: the smart pillbox would automatically trigger a reminder 30 min after the scheduled time if a missed dose was detected, and again after 60 min if the initial reminder was ignored. Took the missed dose: the participant took the missed dose following the reminder from the smart pillbox. Research assistant intervention (phone/WeChat): if the participant did not respond to the pillbox's secondary reminder, research assistants contacted them via phone or WeChat to deliver an adherence prompt. Missed doses (final determination): a missed dose was logged as missed if the participant failed to take the medication after two consecutive smart pillbox reminders and one research assistant intervention.

Randomization and masking

Following baseline screening, participants of this trial were stratified based on their medication regimens and randomly assigned to either the intervention group or the control group (1:1) using envelopes containing random numbers. The researchers devised the randomization protocol, and the research assistants implemented the grouping at each site. Participant blinding was not feasible due to the nature of the distinct interventions.

Procedures

After randomization, participants attended follow-up visits at 3 and 6 months (plus or minus 7 days). At baseline and follow-ups at 3 and 6 months, participants provided blood samples for HIV (antibodies and pooling RNA) and active syphilis infection (*Trepeonema pallidum* particle assay and rapid plasma reagin) testing and completed an online questionnaire (https://jinshuju.net/home). The questionnaire included sociodemographic information (age, ethnicity, education level, marital status, monthly income, etc.) and sexual behavior characteristics (venues for seeking sex, types of sexual partners, sexual roles, number of sexual partners in the past 3 months, condom usage, substance use disorder, etc.).

Both groups received standard care at each follow-up, including tablet counts, medication supplementation, personalized adherence education, and face-to-face counseling on PrEP adherence. Meanwhile, participants discussed adverse events with experienced physicians.

The intervention group received smart pillboxes (Supplementary Fig. 3) from Shanghai Magnesium Health Technology Co., Ltd., which utilized narrowband IoT (NB-IoT) technology for medication real-time monitoring. The device integrates multimodal reminders (auditory, vibration, light, and WeChat push notifications) triggered by preset dosing schedules, with automatic cloud-based logging of box-opening events accessible via a WeChat Mini Program interface. The rechargeable 600 mAh lithium battery provides 45 days of runtime on a single 2-h charge (via Micro-USB). In case of a missed dose, the smart pillbox emits a reminder via vibration, sound, and light. If the missed dose is not rectified, the system sends real-time reminders to the participant's mobile phone every 30 min (up to twice) and notifies research assistants. Upon notification, research assistants could review missed doses via a management platform, contact participants, and document information (Fig. 3). Doses missed before 22:00 were addressed immediately, while those after 22:00 were handled by 10:00 the next day. Repeated pillbox opening without medication intake triggers system alerts to research assistants for follow-up.

To ensure proper functioning, the smart pillbox was tested by five staff members and ten PrEP users during the design phase. Based on feedback, training materials were improved. Custom videos were created for daily PrEP and event-driven PrEP. Prior to participant recruitment, on-site staff and research assistants underwent standardized training on the smart pillbox protocol. During implementation, researchers provided participants with detailed instructional materials, including customized demonstration videos, to facilitate personalized device setup. To ensure continuous adherence monitoring, real-time technical support was made available throughout the study period. Upon study completion, all participants were required to return the smart pillboxes as per the predefined protocol.

Outcomes

The primary outcome was overall PrEP adherence, measured by tablet counts during follow-ups at 3 and 6 months. Secondary outcomes included changes in adherence over the 3 and 6 months for both daily PrEP and event-driven PrEP subgroups. Additionally, the intervention's impact on high-risk behaviors, such as the number of sexual partners, condom use, and substance use disorder, was evaluated over the 3 and 6 months.

Statistical analysis

Based on a previous study[13], we hypothesized that 72% of the intervention group and 57% of the control group would achieve expected adherence. The sample size was calculated in PASS 15.0 (NCSS, LLC, Kaysville, Utah, USA), with each group requiring 156 participants to detect adherence differences (power = 80%, two-sided $\alpha = 0.05$). Considering a 15% dropout rate, 184 participants per group (368 in total) were required.

Adherence was calculated as the ratio of tablets taken to the expected number and was deemed good if ≥90%[40]. The expected tablets number for the event-driven PrEP group ("2-1-1" dosing regimen) was calculated based on sexual activity dates, which were collected through WeChat-based online questionnaires and weekly messages. Sexual activity and medication intake data were obtained from participant-maintained weekly logs, with staff cross-verifying self-reports against pharmacy dispensing records and tablet counts during routine follow-up visits to ensure data reliability[39].

Chi-square tests were conducted to compare baseline sociodemographic characteristics and high-risk behaviors. An intention-to-treat analysis was conducted, comparing outcomes based on randomization. Covariance analysis assessed the differences in average outcome changes, adjusting for age, education, income, and dosing regimen, as well as controls at baseline (number of male sex partners, CAI, and substance use disorder). Mixed linear models evaluated the effects of telemonitoring and timely intervention on PrEP adherence at 3- and 6-month follow-ups and the impacts on high-risk behaviors and substance use disorder. The Cochran-Armitage trend test was adopted to analyze the trends in high-risk behaviors and substance use disorder. Missing data during follow-ups were addressed via multiple imputations using the 'mice' package in R, applying the random forest method across 10 imputations and 50 iterations. Sensitivity analyses were performed by comparing results from complete-case analyses with MI-derived estimates to verify the robustness of our findings. A two-tailed p value < 0.05 indicated

significance. IBM SPSS V26.0 (Armonk, NY, USA) and R 4.3.2 (R Foundation, https://www.r-project.org/) were used for the analyses.

Ethics

This study was approved by the Medical Science Research Ethics Committee of the First Hospital of China Medical University (No. 2019-253-3) and adhered to the CONSORT 2010 guidelines(Supplementary Table 5). The trial was registered before commencement (registration date: 2 September 2019; registration name: Real-time monitoring and just-in-time intervention for adherence to pre-exposure prophylaxis among men who have sex with men in China: a multicentre RCT study; registration number: ChiCTR1900025604; https://www.chictr.org.cn/showproj.html?proj=42628). The research protocol has been published[41]. Prior to the questionnaire survey, smart pillbox distribution, and specimen collection, all participants provided written informed consent and were informed of their right to withdraw without affecting their interests and privacy.

Data availability

The original data supporting the conclusions of this article and other related documents can be obtained upon reasonable request from the corresponding author.

Code availability

The code used for the analysis in this study was implemented using standard functions within the statistical computing environment R (version 4.3.1). No mathematical algorithms or original code are used. The code can be obtained upon reasonable request from the corresponding author.

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References

1. Molina, J.-M. et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N. Engl. J. Med.* **373**, 2237–2246 (2015).
2. Laurent, C. et al. Human immunodeficiency virus seroconversion among men who have sex with men who use event-driven or daily oral pre-exposure prophylaxis (CohMSM-PrEP): a multi-country demonstration study from West Africa. *Clin. Infect. Dis.* **77**, 606–614 (2023).
3. Chou, R. et al. Preexposure prophylaxis for the prevention of HIV: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* **330**, 746–763 (2023).
4. Veloso, V. G. et al. Same-day initiation of oral pre-exposure prophylaxis among gay, bisexual, and other cisgender men who have sex with men and transgender women in Brazil, Mexico, and Peru (ImPrEP): a prospective, single-arm, open-label, multicentre implementation study. *Lancet HIV* **10**, e84–e96 (2023).
5. Van Damme, L. et al. Preexposure prophylaxis for HIV infection among African Women. *N. Engl. J. Med.* **367**, 411–422 (2012).
6. Shen, M., Xiao, Y., Rong, L., Meyers, L. A. & Bellan, S. E. The cost-effectiveness of oral HIV pre-exposure prophylaxis and early antiretroviral therapy in the presence of drug resistance among men who have sex with men in San Francisco. *BMC Med.* **16**, 58 (2018).
7. Sidebottom, D., Ekström, A. M. & Strömdahl, S. A systematic review of adherence to oral pre-exposure prophylaxis for HIV—how can we improve uptake and adherence?. *BMC Infect. Dis.* **18**, 581 (2018).
8. Yigit, I. et al. Associations between PrEP stigma, PrEP confidence, and PrEP adherence: conditional indirect effects of anticipated HIV stigma. *J. Acquir. Immune Defic. Syndr.* **97**, 99 (2024).
9. Huang, Y. L. A. et al. Impact of COVID-19 on HIV preexposure prophylaxis prescriptions in the United States—a time series analysis. *Clin. Infect. Dis.* **75**, ciac038 (2022).
10. Ogaz, D. et al. Mpox diagnosis, behavioral risk modification, and vaccination uptake among gay, bisexual, and other men who have sex with men, United Kingdom, 2022. *Emerg. Infect. Dis.* **30**, 916–925 (2024).
11. Campbell, J. I. et al. Ugandan study participants experience electronic monitoring of antiretroviral therapy adherence as welcomed pressure to adhere. *AIDS Behav.* **22**, 3363–3372 (2018).
12. Siopis, G. et al. Effectiveness, reach, uptake, and feasibility of digital health interventions for adults with hypertension: a systematic review and meta-analysis of randomised controlled trials. *Lancet Digit. Health* **5**, e144–e159 (2023).
13. Liu, A. Y. et al. Randomized controlled trial of a mobile health intervention to promote retention and adherence to preexposure prophylaxis among young people at risk for human immunodeficiency virus: the EPIC study. *Clin. Infect. Dis.* **68**, 2010–2017 (2019).
14. Colson, P. W. et al. Adherence to pre-exposure prophylaxis in Black men who have sex with men and transgender women in a community setting in Harlem, NY. *AIDS Behav.* **24**, 3436–3455 (2020).
15. Swendeman, D. et al. Optimal strategies to improve uptake of and adherence to HIV prevention among young people at risk for HIV acquisition in the USA (ATN 149): a randomised, controlled, factorial trial. *Lancet Digit. Health* **6**, e187–e200 (2024).
16. Haberer, J. E. et al. Effect of SMS reminders on PrEP adherence in young Kenyan women (MPYA study): a randomised controlled trial. *Lancet HIV* **8**, e130–e137 (2021).
17. Lin, B. et al. Effect of a reminder system on pre-exposure prophylaxis adherence in men who have sex with men: prospective cohort study based on WeChat intervention. *J. Med. Internet Res.* **24**, e37936 (2022).
18. Biello, K. B. et al. PrEPare for work: a pilot randomized controlled trial of an intervention to optimize HIV PrEP outcomes among male sex workers. *AIDS Behav.* **27**, 3294–3305 (2023).
19. Haberer, J. E., Mujugira, A. & Mayer, K. H. The future of HIV pre-exposure prophylaxis adherence: reducing barriers and increasing opportunities. *Lancet HIV* **10**, e404–e411 (2023).
20. Montaño, M. A. et al. Changes in sexual behavior and STI diagnoses among MSM initiating PrEP in a clinic setting. *AIDS Behav.* **23**, 548–555 (2019).
21. van den Elshout, M. A. M. et al. Sexual behaviour and incidence of sexually transmitted infections among men who have sex with men (MSM) using daily and event-driven pre-exposure prophylaxis (PrEP): four-year follow-up of the Amsterdam PrEP (AMPrEP) demonstration project cohort. *PLoS Med.* **21**, e1004328 (2024).
22. Reback, C. J., Fletcher, J. B., Swendeman, D. A. & Metzner, M. Theory-based text-messaging to reduce methamphetamine use and HIV sexual risk behaviors among men who have sex with men: automated unidirectional delivery outperforms bidirectional peer interactive delivery. *AIDS Behav.* **23**, 37–47 (2019).
23. Free, C. et al. Effectiveness of a behavioural intervention delivered by text messages (safetxt) on sexually transmitted reinfections in people aged 16–24 years: randomised controlled trial. *BMJ* **378**, e070351 (2022).
24. Ware, N. C. et al. The Meanings in the messages: how SMS reminders and real-time adherence monitoring improve antiretroviral therapy adherence in rural Uganda. *AIDS* **30**, 1287–1294 (2016).
25. Bekker, L.-G. et al. Twice-yearly lenacapavir or daily F/TAF for HIV prevention in cisgender women. *N. Engl. J. Med*. 1–13 https://doi.org/10.1056/NEJMoa2407001 (2024).
26. Landovitz, R. J. et al. Cabotegravir for HIV prevention in cisgender men and transgender women. *N. Engl. J. Med.* **385**, 595–608 (2021).
27. Buchbinder, S. P. et al. Randomized controlled trial of automated directly observed therapy for measurement and support of PrEP adherence among young men who have sex with men. *AIDS Behav.* **27**, 719–732 (2023).
28. Kawichai, S. et al. A mobile phone app to support adherence to daily HIV pre-exposure prophylaxis engagement among young men who have sex with men and transgender women aged 15 to 19 years in Thailand: pilot randomized controlled trial. *JMIR MHealth UHealth* **10**, e25561 (2022).

29. Hosek, S. et al. An HIV pre-exposure prophylaxis (PrEP) demonstration project and safety study for young MSM. *J. Acquir. Immune Defic. Syndr.* **74**, 21–29 (2017).
30. Haberer, J. E. et al. Alignment of adherence and risk for HIV acquisition in a demonstration project of pre-exposure prophylaxis among HIV serodiscordant couples in Kenya and Uganda: a prospective analysis of prevention-effective adherence. *J. Int. AIDS Soc.* **20**, 21842 (2017).
31. Vuylsteke, B. et al. Daily and event-driven pre-exposure prophylaxis for men who have sex with men in Belgium: results of a prospective cohort measuring adherence, sexual behaviour and STI incidence. *J. Int. AIDS Soc.* **22**, e25407 (2019).
32. Mannheimer, S. et al. Factors associated with sex-related pre-exposure prophylaxis adherence among men who have sex with men in New York City in HPTN 067. *J. Acquir. Immune Defic. Syndr.* **80**, 551–558 (2019).
33. Hartmann, M. et al. Tu'Washindi na PrEP: working with young women and service providers to design an intervention for PrEP uptake and adherence in the context of gender-based violence. *AIDS Educ. Prev.* **33**, 103–119 (2021).
34. Reyniers, T. et al. The impact of PrEP on the sex lives of MSM at high risk for HIV infection: results of a Belgian cohort. *AIDS Behav.* **25**, 532–541 (2021).
35. Stringer, K. L. et al. Feasibility and acceptability of real-time antiretroviral adherence monitoring among depressed women living with HIV in the Deep South of the US. *AIDS Behav.* **23**, 1306–1314 (2019).
36. Endebu, T., Deksisa, A., Dugasa, W., Mulu, E. & Bogale, T. Acceptability and feasibility of short message service to improve ART medication adherence among people living with HIV/AIDS receiving antiretroviral treatment at Adama hospital medical college, Central Ethiopia. *BMC Public Health* **19**, 1315 (2019).
37. Kebede, M., Zeleke, A., Asemahagn, M. & Fritz, F. Willingness to receive text message medication reminders among patients on antiretroviral treatment in North West Ethiopia: a cross-sectional study. *BMC Med. Inform. Decis. Mak.* **15**, 65 (2015).
38. Liu, A. Y. et al. DOT diary: developing a novel mobile app using artificial intelligence and an electronic sexual diary to measure and support PrEP adherence among young men who have sex with men. *AIDS Behav.* **25**, 1001–1012 (2021).
39. Wang, H. et al. Association of HIV preexposure prophylaxis use with HIV incidence among men who have sex with men in China. *JAMA Netw. Open* **5**, e2148782 (2022).
40. Grant, R. M. et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N. Engl. J. Med.* **363**, 2587–2599 (2010).
41. Jin, X. et al. Real-time monitoring and just-in-time intervention for adherence to pre-exposure prophylaxis among men who have sex with men in China: a multicentre RCT study protocol. *BMC Public Health* **20**, 1160 (2020).

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Author contributions

H.S. and Q.H.H. had the idea & designed the study. Z.X.C., X.J., X.J.H., H.W., and Y.K.C. recruited participants and collected the data. Z.X.C., Z.H.Y., Y.Y.Z., and X.J. analyzed and interpreted the data. Y.J.A., Y.J.J., and Z.H.W. had a check for the analysis. Z.X.C., Y.Y.Z. and Z.H.Y. wrote the first draft of the article. H.S. and Q.H.H. revised the manuscript. All authors had unrestricted access to the data and participated in data interpretation. All the authors contributed to subsequent drafts and agreed to submit the article for publication.

Competing interests

The authors declare no competing interests.

Additional information

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