Low rate of pre-exposure prophylaxis and post-exposure prophylaxis uptake and high prevalence of transmitted drug resistance among newly diagnosed primary HIV infections in Shenzhen, China: a real-world retrospective study

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Abstract

Background: Understanding the characteristics of newly diagnosed primary human deficiency virus-1 (HIV-1) infection in the context of the post-antiretroviral therapy era and HIV drug prophylaxis is essential for achieving the new target of 95-95-95-95 by 2025. This study reported the characteristics of newly diagnosed primary HIV-1 infection in Shenzhen.

Methods: This is a real-world retrospective study. Eighty-seven newly diagnosed primary HIV-1-infected patients were recruited from January 2021 to March 2022 at the Third People's Hospital of Shenzhen. Demographic, epidemiological, diagnostic, drug resistance, and medical data were described and analyzed.

Results: Overall, 96.6% (84/87) of the newly identified primary HIV-1-infected patients were male, including 88.5% (77/87) men have sex with men (MSM), with a median age of 29.0 years (Q_1–Q_3: 24.0–34.0 years); of these, 85.1% (74/87) reported high-risk sexual behaviors with casual partners. The rate of condom usage was only 28.7% (25/87). The overall rate of pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) was 8.0% (7/87, including 4 PrEP and 3 PEP cases) around the potential exposure, although 41.4% of the patients had prior awareness of such interventions. Moreover, only 19.5% (17/87) had previously used PrEP or PEP. Of those, 58.8% (10/17) of the patients obtained drugs from the internet, and only 35.3% (6/17) reported good compliance. A total of 54.0% (47/87) of subjects were diagnosed by the HIV nucleic acid test. Acute retroviral syndrome appeared in 54.0% (47/87) of patients. The prevalence of transmitted drug resistance (TDR) mutation was 33.9% (19/56), including 6 (10.7%) against nucleoside reverse transcriptase inhibitor (NRTI) plus non-nucleoside reverse transcriptase inhibitor (NNRTI), 8 (14.3%) against NNRTI, and 5 (8.9%) against protease inhibitor (PI) only.

Conclusions: Owing to the low utilization rate and incorrect usage of PrEP and PEP, massive efforts are needed to promote HIV-preventive strategies in the MSM population. The extremely high prevalence of TDR mutation in this population implies the need for future pretreatment drug resistance surveillance.

Keywords: Antiretroviral therapy; Drug resistance; Human immunodeficiency virus-1; Post-exposure prophylaxis; Pre-exposure prophylaxis

Introduction

Human deficiency virus (HIV) infection remains a global public health problem, with 37.7 million people living with HIV (PLWH) by the end of 2020.[1] To curb the global HIV epidemic, the Joint United Nations Program on HIV and Acquired Immunodeficiency Syndrome (AIDS) (UNAIDS) advocated the 90-90-90 targets in 2014.[2] Correspondingly, comprehensive prevention methods such as treatment as prevention,[3] pre-exposure

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prophylaxis (PrEP) and post-exposure prophylaxis (PEP),[4] public education, behavior interventions, and physical blockade have been promoted. However, 1.5 million new infections were still reported per year worldwide.[1] In 2020, estimates for the 90-90-90 target indicators stood at 84% (67% to >98%), 87% (67% to >98%), and 90% (70% to > 98%), globally,[1] while these values in China were reported to be 68.9% (61.5%–78.3%), 83.4%, and 94.2% in 2018, respectively.[5] This indicates that the failure of pursuit for the first target of 90% of HIV-infected individuals being diagnosed lags behind the second and third 90% targets for 90% being on antiretroviral therapy (ART) and 90% achieving sustained virologic suppression, providing the greatest obstacle to achieving the global goal of ending AIDS by 2030 and reaching the recently proposed "95-95-95-95" target by 2025.[6] Sexual transmission is the main route of HIV acquisition in China and worldwide.[1,7] Patients with primary HIV infection are estimated to be 10 to 26 times more infectious than those with chronic HIV infection, accounting for 38% to 50% of all HIV transmissions.[8,9] Thus, the basic principles of primary human deficiency virus-1 (HIV-1) infection, clinical and diagnostic markers, and approaches to management are essential for achieving this "95-95-95-95" target.

In the context of the post-ART era accompanied by the scaling up of PrEP and PEP, patients diagnosed with primary HIV infection may exhibit different demographic, epidemiological, virological, and drug resistance features. Pre- and post-exposure HIV prophylaxis have been expanded in China since 2019, and understanding the real-world practice of PrEP and PEP will be critical for epidemic control. This article reports the characteristics of newly diagnosed primary HIV-1 infection in Shenzhen, which is one of the first-tier megacities and a typical representative resource-rich region in China, with a focus on HIV drug prophylaxis and the transmitted drug resistance repertoire.

Methods

Ethical approval

This study was approved by the Ethics Review Board of the Third People's Hospital of Shenzhen (No. 2021-0120). Written informed consent was obtained from all study participants.

Study design and participants

A retrospective study was conducted at the AIDS Clinic of the Third People's Hospital of Shenzhen, the main designated hospital providing ART and long-term follow-up for HIV-infected patients in Shenzhen, China. All primary HIV-1-infected patients were randomly recruited from January 2021 to March 2022 at the clinic. In accordance with previous guidelines,[10-12] primary HIV infection was defined by the following criteria: confirmed seroconversion determined by Western blot (WB) with or without positive HIV ribonucleic acid (RNA) test; a positive fourth-generation HIV antigen/antibody (Ag/Ab) test or undetermined WB results plus HIV RNA ≥ 5000 copies/mL; two positive HIV RNA tests with a negative HIV-Ab test (1 individual); and at least one of the aforementioned criteria preceded by at least one documented or self-reported HIV-Ab negative test and a clear potential high-risk exposure history within 6 months. Patients with documented or self-reported positive HIV-Ab tests and confirmed HIV-1 WB beyond 6 months or who could not report a clear time of high-risk exposure and confirm a negative HIV-Ab test history within 6 months were excluded. After patient recruitment, case records were analyzed by an experienced clinician. The five main data categories are given as follows: (1) demographic features such as sex, age, marital status, and highest level of education; (2) epidemiological data such as potential transmission route, HIV status of the partner, possible high-risk exposure and time, and condom use; (3) diagnostic information including latest time of a negative HIV test, and data and interval from HIV-Ag/Ab screening, WB, and HIV RNA test to potential high-risk exposure; (4) PrEP and PEP drug use information including prior knowledge, experience of PrEP/PEP use, sources for obtaining drugs, use of PrEP and PEP around the time of potential exposure, and adherence; and (5) immuno-virological parameters such as cluster of differentiation 4 positive ($CD4^+$) and $CD8^+$ T-cell counts as well as $CD4^+/CD8^+$ T-cell ratio, and HIV RNA at baseline before ART and at week 12 after ART. A total of 87 eligible subjects were enrolled.

HIV genotypic drug resistance test (GRT)

HIV genotypic drug resistance assays were performed as previously reported.[13] This was a routine and optional test for clinical patients. There were a total of 56 sequences available for analysis. Briefly, after peripheral blood collection, plasma was separated and stored at −80°C. HIV viral RNA was extracted and reverse-transcribed into complementary DNA (cDNA). The pol gene fragment with a size of around 1059 bp including the protease gene and the first 254 codons of the reverse-transcriptase gene was amplified using nested polymerase chain reaction (PCR) and then sequenced. Finally, sequencing data of HIV gene fragments from DNA sequencing were submitted to the Stanford University HIV Drug Resistance Database for the generation of antiretroviral resistance profiles and HIV subtype information.[13]

Statistical analysis

Statistical analysis was performed with GraphPad Prism v8. (GraphPad Software Inc., San Diego, CA, USA). Paired *t* test was used for paired comparisons. For between-group comparison of categorical values, two-sided chi-squared test, or Fisher's exact test was used. Data normality was assessed by the Kolmogorov-Smirnov test. Quantitative data with a normal distribution were expressed as mean ± standard deviation. Skewed quantitative data were expressed as median (Q_1–Q_3). A $P < 0.05$ was considered statistically significant.

Results

Basic characteristics of newly diagnosed primary HIV-1 infections

From January 2021 to March 2022, 87 eligible newly diagnosed primary HIV-1-infected patients were recruited

in accordance with current guidelines.[10-12] The median age of the study population was 29.0 (Q_1–Q_3: 24.0–34.0) years, including 54.0% (47/87) and 32.2% (28/87) cases in the 20 to 29 and 30 to 39 age-groups, respectively. The majority of them were male (96.6%, 84/87) and single, divorced or widow (69/87, 79.3%), and 39.1% (34/87) and 28.7% (25/87) of patients had the highest educational level of senior high school/technical secondary school and undergraduate, respectively. Of these, 88.5% (77/87) of cases involved transmission through homosexual contact, with only one (1.1%) patient being exposed via intravenous drug injection. Only 15 of 87 patients (17.2%) reported fixed sexual partners, among whom 60.0% (9/15) were HIV-positive with a known HIV status and 33.3% (5/15) had an unknown HIV status. Up to 85.1% (74/87) of subjects were exposed to casual sex partners during the most likely high-risk behavior, including 82.4% (61/74) involving strangers. Overall, 13.1% (11/84) were infected during their first men having sex with men (MSM) experience, including two cases of rape. Only 28.7% (25/87) self-reported condom use during high-risk exposure [Table 1]. A total of 11 of 87 (12.6%) reported continuing unprotected homosexual behavior with others after a high-risk exposure. Overall, these data indicated that single young MSM with relatively high educational levels were more prone to contracting HIV infection, probably due to changing sex partners while having unprotected sexual contact.

Table 1: Sociodemographic and epidemiological characteristics of newly diagnosed primary HIV-1 infections (n = 87).

Characteristics	Values
Age (years)	29.0 (24.0–34.0)
<20	3 (3.4)
20–29	47 (54.0)
30–39	28 (32.2)
40–49	4 (4.6)
≥50	5 (5.7)
Male	84 (96.6)
Marital status	
Married	13 (14.9)
Single or divorced or widow	69 (79.3)
Not available	5 (5.7)
Highest degree of education	
Illiteracy	1 (1.1)
Primary and junior school level	12 (13.8)
Senior high school or technical secondary school	34 (39.1)
Undergraduate	25 (28.7)
Graduate	8 (9.2)
Not available	7 (8.0)
Transmission route	
Homosexual	77 (88.5)
Heterosexual	9 (10.3)
IDU	1 (1.1)
Having fixed sexual partner before HIV acquisition	
Yes	15 (17.2)
No	72 (82.8)
High-risk exposure to casual sex partners	
Yes	74 (85.1)
No	13 (14.9)
With condom use while having high-risk sex behavior	
Yes	25 (28.7)
No	54 (62.1)
Not available	8 (9.2)

Data are presented as n (%) or median (Q_1–Q_3). HIV: Human deficiency virus; HIV-1: Human deficiency virus-1; IDU: Intravenous drug user.

Clinical manifestations and diagnostic features of newly diagnosed primary HIV-1 infections

Among this population, 54.0% (47/87) reported acute retroviral syndrome (ARS). The median interval between the potential high-risk exposure and ARS occurrence was 12.0 (Q_1–Q_3: 10.0–20.0) days. Common signs and symptoms included fever (39/87, 44.8%), rash (12/87, 13.8%), sore throat (11/87, 12.6%), enlarged lymph nodes (11/87, 12.6%), diarrhea (7/87, 8.0%), and fatigue (6/87, 6.9%). One case of reflux esophagitis, 1 of rhabdomyolysis, 1 of myocarditis, and 2 of acute kidney injury were also identified in this population. Regarding the specific way in which the infection was first detected, 56.3% (49/87) performed rapid HIV tests at home with self-test kits acquired from the internet, 29.9% (26/87) underwent screening at a hospital visit, and in the remaining 13.8% (12/87), infection was detected due to notification of an HIV-positive status from their partners. In total, 40.2% (35/87) had not previously undergone an HIV-Ab screening test before arriving at our clinic. Primary HIV-1 infection was confirmed in 54.0% (47/87) of the patients by a positive HIV RNA test, 32.2% (28/87) by definitive WB, and only 13.8% (12/87) by unclear WB plus a positive HIV RNA test. For the 70 available WB tests, 18.6% (13/70) cases reported negative results, 50.0% (35/70) were determined as positive, and 31.4% (22/70) remained undetermined. Overall, 30.0% (21/70) of individuals showed a p31 band, indicating the completion of HIV antibody conversion. Moreover, the median HIV RNA level of this cohort at diagnosis was 376,000 (Q_1–Q_3: 62,200–2,350,000) copies/mL. The median intervals between potential high-risk exposure and initial positive screening, WB, and HIV RNA test were 30.0 (Q_1–Q_3: 16.1–44.8), 35.5 (Q_1–Q_3: 23.3–50.0), and 42.5 (Q_1–Q_3: 23.5–60.3) days, respectively [Table 2]. Taking these findings together, earlier recognition of ARS, the rapid HIV-Ab self-test, and the rollout of HIV RNA confirmation would be helpful for the early diagnosis of primary HIV-1 infection.

Real-world implementation of HIV drug prophylaxis in newly diagnosed primary HIV-1 infections

One of the most effective preventive strategies against HIV is drug prophylaxis, which consists of the administration of antiretroviral drugs pre- and post-exposure. Fully understanding the real-world practice of PrEP and PEP is significant for their effective implementation in key populations. Among the population in this study, only four (4.6%) and 3 (3.4%) patients reported PrEP and PEP drug use around the time of potential high-risk

Table 2: Diagnostic and clinical information of newly diagnosed primary HIV-1 infections ($n = 87$).

Characteristics	Values
Signs/symptoms and diseases	
Having symptoms in acute infection	
Yes	47 (54.0)
No	40 (46.0)
Median intervals between high-risk behavior and the start of signs and symptoms (days)	12.0 (10.0–20.0)
Frequency of signs/symptoms and diseases in acute stage	
Fever	39 (44.8)
Rash	12 (13.8)
Enlarged lymph nodes	11 (12.6)
Sore throat	11 (12.6)
Diarrhea	7 (8.0)
Fatigue	6 (6.9)
Acute kidney injury	2 (2.3)
Body weight loss	1 (1.1)
Night sweats	1 (1.1)
Cough	1 (1.1)
Reflux esophagitis	1 (1.1)
Enlarged tonsils	1 (1.1)
Rhabdomyolysis	1 (1.1)
Pneumonia	1 (1.1)
Myocarditis	1 (1.1)
HIV-1 diagnostic information	
Specified reason for HIV-Ab screening	
Self-screen at home	49 (56.3)
Screened at a hospital visit	26 (29.9)
Screened due to the notification of HIV-positive partners	12 (13.8)
Median intervals between high-risk exposure and HIV-Ab screening (days)	30.0 (16.1–44.8)
Methods used for HIV diagnosis	
WB	28 (32.2)
HIV RNA	47 (54.0)
WB plus HIV RNA	12 (13.8)
Median intervals between high-risk exposure and WB (days)	35.5 (23.3–50.0)
WB results interpretation	
Determined	35 (40.2)
Undetermined	22 (25.3)
Negative	13 (14.9)
Not available	17 (19.5)
Median intervals between high-risk exposure and HIV RNA test (days)	42.5 (23.5–60.3)
Median HIV RNA (copies/mL)	376,000 (62,200–2,350,000)

Data are presented as n (%) or median (Q_1–Q_3). HIV: Human deficiency virus; HIV-Ab: HIV antibodies; RNA: Ribonucleic acid; WB: Western blot.

exposure, respectively; 4 of the 7 cases underwent HIV-Ab tests before prophylaxis; 1 used dolutagravir (DTG) as PEP and then tenofovir/emtricitabine (TDF/FTC) as PrEP very casually; and only two took PrEP/PEP in line with the administration guidance. In addition, only

Table 3: Practice of HIV drug prophylaxis in newly diagnosed primary HIV-1 infections ($n = 87$).

Characteristics	Values
PrEP use prior to high-risk exposure, n (%)	
Yes	4 (4.6)
No	83 (95.4)
PEP use after high-risk exposure, n (%)	
Yes	3 (3.4)
No	84 (96.6)
Previous use of PrEP/PEP, n (%)	
Yes	17 (19.5)
No	70 (80.5)
Taking PrEP/PEP according to guidance (in 17 individuals), n (%)	
Yes	6 (35.3)
No	11 (64.7)
Previous awareness of PrEP/PEP before infection, n (%)	
Yes	36 (41.4)
No	38 (43.7)
Unavailable	13 (14.9)
Sources for PrEP/PEP acquisition (in 17 individuals), n (%)	
Hospital	3 (17.6)
E-commerce	10 (58.8)
Hospital + E-commerce	3 (17.6)
Friends + Hospital + E-commerce	1 (5.9)

HIV: Human deficiency virus; HIV-1: human deficiency virus-1; PEP: Post-exposure prophylaxis; PrEP: Pre-exposure prophylaxis.

17 (19.5%) reported previous use of PrEP and PEP. Strikingly, only six of them (6/17, 35.3%) took medicines which complied with the doctor's recommendation. Moreover, the rate of prior awareness of PrEP and PEP was only 41.4% (36/87) [Table 3]. There were no significant differences in terms of the knowledge and usage of PrEP and PEP among different age, sex, and CD4-level subgroups [Supplementary Table 1, http://links.lww.com/CM9/B375]. The most common source for acquiring PrEP and PEP was E-commerce, while hospitals ranked second. Overall, these findings imply the low uptake rate and incorrect usage of HIV drug prophylaxis in the key population.

Treatment and transmitted HIV drug resistance mutation patterns in newly diagnosed primary HIV-1 infections

With the scaling up of ART, monitoring of transmitted HIV drug resistance is also critical for effective treatment initiation. In this study, the HIV GRT was available in 56 patients. In total, 6 (6/56, 10.7%) of them showed nucleoside reverse transcriptase inhibitor (NRTI) mutations, including 4 M184 V, 1 M184 V/I, and 1 L210W. As many as 25% (14/56) had non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations, including 9 V179E, 1 V179D, 1 V179VDE, 1 V106I, 1 K103N, and 1 V179E plus Y181C. In total, 8.9% (5/56) of the patients displayed single PI-related mutations, including 4 L10I and 1 L33F. Moreover, 6 of 56 (10.7%) showed NRTI and NNRTI mutations simultaneously.

None of the 25 available GRT results for integrase inhibitors showed integrase strand transfer inhibitor (INSTI) mutations. The overall prevalence of transmitted HIV drug resistance was 33.9% (19/56). Of the 17 patients who previously used PrEP and PEP, four had mutations, including two with L10I and two with both M184V and V179D/E. However, there were no significant differences in the incidence of transmitted drug resistance (TDR) mutations between the sexes, or among CD4-level and PrEP/PEP-use subgroups, except for a slightly higher incidence of drug resistance in the younger age-group ($\chi^2 = 3.903$, $P = 0.048$) [Supplementary Table 2, http://links.lww.com/CM9/B375]. HIV subtype analysis indicated BC as the dominant circulating subtype (26/56, 46.4%), followed by CRF01_AE (12/56, 21.4%) and then A (7/56, 12.5%). Within a median of 45.0 (Q_1–Q_3: 30.0–66.5) days after high-risk exposure, all of the recruited primary HIV-1-infected patients started ART with a single tablet regimen (STR) (32 with tenofovir alafenamide [TAF]+ emtricitabine [FTC] + bictegravir [BIC] and 18 with TAF + FTC + elvitegravir/cobicistat [EVG/c], 57.5%) as the main initial ART regimen. After 12-week treatment, only seven of the patients did not reach viral suppression (defined by HIV RNA > 500 copies/mL) (four with 2NRTI plus NNRTI, two with 2NRTI plus kaletra [KLZ], and one with TAF + FTC + EVG/c) [Table 4]. Compared with the baseline levels before ART, the $CD4^+$ T-cell count increased significantly at 12 weeks after ART initiation (355.4 ± 139.9 cells/μL *vs.* 537.9 ± 186.8 cells/μL, $P < 0.0001$), while the $CD8^+$ T-cell count decreased dramatically (1861.0 ± 1321.0 cells/μL *vs.* 995.0 ± 458.8 cells/μL, $P < 0.0001$), with a substantially reverse shift of the CD4/CD8 ratio (0.33 ± 0.26 *vs.* 0.85 ± 0.67, $P < 0.0001$) [Figure 1]. Taking these findings together, a high prevalence of transmitted HIV drug resistance was observed in this population, suggesting the importance of pretreatment drug resistance monitoring.

Table 4: ART and drug resistant patterns in newly diagnosed primary HIV-1 infections.

Characteristics	Values
Available HIV GRT	56
Frequency of drug resistance mutations	
NRTI	6 (10.7)
NNRTI	14 (25.0)
PI	5 (8.9)
Available HIV subtype	56
Frequency of HIV subtypes	
BC	26 (46.4)
CRF01_AE	12 (21.4)
A	7 (12.5)
B + CRF01_AE	4 (7.1)
CRF55_01B	3 (5.4)
B	2 (3.6)
CRF07_BC	2 (3.6)
Median intervals between high-risk exposure and the start of ART (days)	45.0 (30.0–66.5)
Number of patients receiving ART	
Yes	87 (100.0)
No	0 (0)
Regimen of ART	
2NRTI + INSTI	58 (66. 7)
2NRTI + NNRTI	16 (18. 4)
2NRTI + PI	13 (15.0)
HIV RNA at week 12 after ART initiation	
<20 copies/mL	18 (20.7)
<250 copies/mL	26 (29.9)
<500 copies/mL	36 (41.4)
>500 copies/mL	7 (8.0)

Data are presented as *n*, *n* (%) or median (Q_1–Q_3). ART: Antiretroviral therapy; GRT: Genotypic drug resistance test; HIV: Human deficiency virus; INSTI: Integrase strand transfer inhibitor; NRTI: Nucleoside reverse transcriptase inhibitor; NNRTI: Non-nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor; RNA: Ribonucleic acid.

Discussion

In this real-world retrospective study, we determined demographic, epidemiological, immuno-virological, and TDR parameters in newly diagnosed primary HIV-1 infection cases in a resource-rich region of China. First, our results implied that the collection of a detailed medical history, including events of high-risk exposure and ARS signs or symptoms, would be helpful for identifying the key population. Second, the promotion of rapid HIV-Ab tests with self-test kits and HIV RNA tests in healthcare facilities would improve the detection and confirmation of primary HIV-1 infection. Third, the low rate and incorrect use of PrEP and PEP in this study highlight the urgent need for massive efforts to expand PrEP and PEP services to high-risk populations in China. Finally, the high prevalence of transmitted HIV drug resistance may challenge the current free first-line ART therapy, making a NNRTI-sparing regimen the preferred initial regimen. These findings show the importance of implementing pretreatment drug resistance monitoring.

With the universal rollout of "treatment as prevention," "early treatment," "test and treat," and "comprehensive response" strategies, huge progress has been made with dramatical reductions of HIV/AIDS incidence, mortality, and mobility. Nevertheless, a significant gap remains in efforts to end AIDS by 2030. The achievement of the first and second 95% (95% combination prevention, 95% detection) is the foundation for controlling the AIDS epidemic. Condom and HIV drug prophylaxis are two of

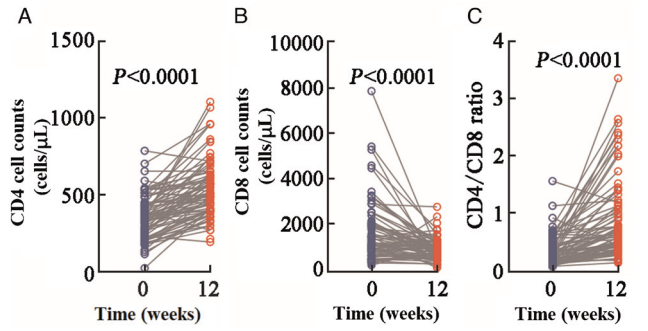

Figure 1: Changes of immunological markers at week 12 after ART initiation. Absolute $CD4^+$ (A) and $CD8^+$ (B) T-cell counts and CD4/CD8 ratio (C) before (W0) and 12 weeks after ART initiation (W12). Paired *t* test was used for between-group comparisons in A–C. *P* values are shown. ART: Antiretroviral therapy; CD: Cluster of differentiation.

the most important and effective preventive measures. However, the current study showed a low rate for the real-world practice of these interventions, revealing an urgent need to expand these measures. Although PrEP and PEP started to be promoted in China in 2019, such as the approval of Truvada® for PrEP and the issuance of Technical Guidelines for PrEP and PEP,[14,15] the rate of awareness of PrEP remains relatively low, ranging from 3% to 33% among MSM.[16-18] Only around 1% of MSM have ever initiated PrEP.[16,19,20] Moreover, only 2.82% of participants self-reported PEP use among five key populations.[16] Despite the higher rates of awareness and usage of PrEP and PEP in the current cohort than in previous reports, misuse without the right guidance and the lack of HIV-Ab monitoring before use are worrisome. The diagnosis of primary HIV infection in seven patients who used PrEP and PEP was probably due to pre-existing undiagnosed infection at PrEP/PEP initiation, instead of failed prophylaxis. In the case of good adherence, PrEP effectively prevents HIV infection, with a reduction of 62.2% to 92% in the incidence of HIV infection.[21-26] Low efficacy is driven mainly by poor compliance.[27,28] In addition, HIV breakthrough infection could occur, albeit infrequently, due to the acquisition of a drug-resistant transmitting founder.[29] Notably, delayed HIV seroconversion has been observed in PrEP users, making the diagnosis challenging, and could lead to the development of HIV drug resistance due to persistent PrEP exposure.[29-31] Many challenges are speculated to limit the scaling up of PrEP and PEP, including limited prescription of PrEP and PEP due to unfavorable attitudes among healthcare professionals, restricted access to PrEP and PEP medications due to underdeveloped healthcare services, and low engagement of community participation, public support, and media promotion.[32] Therefore, more efforts, including appropriate policy guidance and promotion, innovative and applicable PrEP and PEP service delivery models, and awareness-raising among key populations and healthcare providers,[20] should be made to guarantee the effective implementation of PrEP and PEP.

To make 95% of all PLWH aware of their HIV status, screening and detecting all individuals with suspected infection is essential. Timely detection and treatment of primary HIV-1 infection is the most important factor. However, owing to the "window period" when there is an absence of antibody seroconversion, routine HIV-Ab tests may miss some infections, resulting in false-negatives. Fourth-generation HIV-Ab/Ag assays could shorten this period to 2 weeks,[33] but may still neglect Fiebig I stage patients.[34] However, HIV RNA detection could confirm acute infection as early as 7 to 10 days after exposure. Consistent with this, the diagnostic information collected in this study also showed that 54.0% of cases were initially confirmed by the HIV RNA test. The high sensitivity of the HIV RNA test makes it a promising active screening method for certain populations such as MSM, sex workers, intravenous drug users, blood donors, and recipients of HIV drug prophylaxis. Besides, up to 56.3% of subjects in this study performed the initial HIV-Ab screening by themselves, suggesting that self-test kits are a convenient and feasible way to increase HIV testing coverage and case identification among key populations, especially MSM.[35] Shenzhen is an economically developed Chinese megacity, with a large "non-local" floating population. The findings in this study indicated that single, young MSM with casual sex partners were at high risk of HIV infection, which is in agreement with previous reports.[36] More than 97% of newly identified cases occur through sexual transmission, with male-to-male sexual contact accounting for over one-quarter[20]; moreover, MSM in developed provinces accounted for more than 50% of all new HIV infections. Up to 88.5% of newly diagnosed acute HIV infections in this study involved MSM, with 11.6% reporting continuing unprotected sex with others during a very short but contagious time after probable infection, underscoring the extremely urgent need to intensify prevention measures in this key population to reduce new infections. Successful prevention of HIV among the MSM population remains key to achieving the targets proposed by UNAIDS within China and globally.

TDR is another determinant that may impact the achievement of the last 95% target. Intriguingly, extremely high rates of TDR were found in this study, which were substantially higher than those in previous reports.[5,37] Previous studies showed a wide range (2.0%–15.0%)[38,39] of prevalence of TDR in China and significantly higher levels in developed countries (8.3%–17.2%),[40-44] which differs according to the study population, time interval, and definition of TDR. The high prevalence of drug resistance against NNRTI would pose a great threat to NNRTI-containing regimens in resource-limited regions in future. Moreover, most drug-resistant mutations such as V179D/E/V or L10I and L33I only cause low-level resistance to current ART drugs, which could explain the remaining effect of ART in this study. Nevertheless, long-term failure due to accumulative mutations remains a concern. Notably, TDR was observed in four PrEP- and PEP-experienced patients. The concurrent existence of L10I and V179D/E indicated that TDR was transmitted from sex partners. Consequently, an upward trend of drug resistance could be expected in future with the scaling up of HIV drug prophylaxis.

Despite the strengths of this work, this study also had some limitations. Owing to the small sample size, some of the results may not accurately represent the trends in the population at large. In addition, not all HIV GRTs were available for all patients. Surveillance of TDR to integrase inhibitors should be strengthened in future with the scaling up of the use of these drugs. Nonetheless, overall our findings may provide useful evidence for future prevention and treatment of HIV.

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Conflicts of interest

None.

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