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MAJOR ARTICLE

Disparity of HIV-1 Pretreatment Drug Resistance in Men Who Have Sex With Men and the Heterosexual Population in Guangxi, China

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Background. The prevalence of human immunodeficiency type 1 (HIV-1) pretreatment drug resistance (PDR) in men who have sex with men (MSM) in Guangxi remains unclear, and its effect on antiretroviral therapy (ART) needs to be further studied.

Methods. Individuals newly diagnosed with HIV in Guangxi from 2016 to 2020, which mainly included MSM and the heterosexual (HES) population, were recruited in this study. Pol sequences were sequenced to analyze PDR and construct a genetic network. The risk factors for PDR and the effect on ART were respectively analyzed.

Results. The PDR of MSM in Guangxi was 4.7% (34/716), consisting of nonnucleoside reverse transcriptase inhibitors (3.5%), protease inhibitors (0.8%), integrase strand transfer inhibitors (0.7%), and nucleoside reverse transcriptase inhibitors (0.4%), and lower than that of HES (9.3% [77/827]). The subtype was associated with PDR, and MSM was lower than HES (CRF01_AE: 3.0% vs 8.0%; CRF07_BC: 4.1% vs 7.2%). CRF55_01B (adjusted odds ratio [aOR], 3.35) was a risk factor for PDR in MSM, while CRF08_BC (aOR, 2.34) and older (aOR, 2.75) were risk factors for PDR in HES. Six of 18 (33.3%) PDR of MSM in the network connected to each other, lower than that of HES (61.1% [22/36]). CRF55_01B (aOR, 5.69) was a risk factor for PDR transmission in MSM, while CRF08_BC (aOR, 4.08) was a risk factor in HES. Pretreatment $CD4^+$ T-cell count, age, infection route, and subtype were associated with recovery of $CD4^+$ count and suppression of viral load.

Conclusions. The prevalence of PDR was different between MSM and HES, which may be associated with subtype. Thus, the monitoring of subtype and PDR should be strengthened.

Keywords. HIV-1; antiretroviral therapy; men who have sex with men; mutation; pretreatment drug resistance; transmission network.

Men who have sex with men (MSM) are at risk of human immunodeficiency virus (HIV) infection due to multiple partners, unsafe sex, and other factors [1]. Studies in Western Europe and North America have shown that MSM are one of the high-risk populations for HIV drug resistance [2, 3]. The characteristics of low condom utilization rate, multiple partners, and bisexuality are also found in MSM in China [4, 5], making MSM a bridge for HIV transmission to the general population. Studies have shown that drug-resistant strains can spread among different individuals and result in pretreatment drug resistance (PDR) in newly infected individuals, leading to an increase in the failure rate of antiretroviral therapy (ART) [6, 7].

According to drug resistance reports from the World Health Organization (WHO) in 2017 and 2019, the global prevalence of PDR demonstrated an increasing trend [8, 9], especially in countries and regions with limited medical resources. The PDR is also remarkably high in developed countries; for example, 11.2% in the United States [10], 14.7% in Romania [11], and 9.9% in Spain [12]. ART could substantially reduce the incidence and mortality of AIDS-related patients but could also accelerate the prevalence of PDR [13, 14]. At present, the overall prevalence of PDR in China is low but is continuously

Received 17 October 2022; editorial decision 09 January 2023; accepted 13 January 2023; published online 16 January 2023

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https://doi.org/10.1093/ofid/ofad016

increasing, with the rate exceeding 10% in some areas [15, 16]. The prevalence of PDR is of importance to the first-line ART options, the development of effective ART, and the reduction of drug resistance [17]. Meanwhile, China has adopted a strategy of immediate ART since 2016 [18]. The PDR rate of HIV is a key indicator for assessing ART strategies and tracking sources of HIV incidence. A previous study showed that a 2.1% transmitted drug resistance rate of HIV among a small sample of students in Beijing [19]. The low rate was interpreted as a result of the limited social network of students. However, in recent years, the wide use of geosocial networking apps among MSM has expanded sexual networks and HIV transmission [20]. Study of the PDR rate among MSM is urgently needed.

More importantly, MSM have higher PDR compared with other populations [2]. A systematic review of 212 studies revealed that the PDR in MSM in high-income countries was 10.9%–12.6% from 1999 to 2013, which was significantly higher than that in people who inject drugs (PWID) (5.2%–8.3%) and HES (6.4%–9.0%) [2]. In the United Kingdom, the PDR in MSM was higher than that in HES (8.7% vs 6.4%) [21]. PDR had significantly increased in high-risk populations in low- and middle-income countries: The PDR from 2004 to 2008 and that from 2009 to 2013 were, respectively, 4.2% and 7.8% in MSM, 2.6% and 4.1% in HES, and 2.4% and 4.8% in PWID; thus, the PDR in MSM was significantly higher than that in HES and PWID [2]. The overall prevalence of PDR in China is currently low; a report from 2000 to 2016 showed that the PDR was 3.56% in MSM and 7.34% in HES transmission [22]. However, the prevalence of PDR in MSM continues to increase in China [23], and the proportion of MSM in the new HIV-infection population increased from 2.5% in 2006 to 26.9% in 2016 [24]. Guangxi, a southwestern province of China, is one of the provinces with the highest HIV prevalence [25]. The prevalence of PDR in MSM in Guangxi had rarely been reported despite an increase in MSM infected with HIV [23].

MSM and HES newly diagnosed with HIV and untreated in Guangxi from 2016 to 2020 were included in this study for analysis. First, the PDR was characterized, and the risk factors for PDR in MSM and HES in Guangxi were analyzed. Second, the PDR between MSM and HES was compared. Third, the PDR transmission in MSM and HES was explored. Finally, the effect of PDR on HIV ART was confirmed.

METHODS

Study Population

Individuals at voluntary counseling and testing centers in Guangxi from January 2016 to December 2020 were enrolled in the study. These individuals must meet the following requirements: (1) newly diagnosed with HIV-1; (2) had not received ART; (3) followed the informed consent of participants. Peripheral blood samples and epidemiological data were also collected. Plasma was separated within 12 hours of blood collection and stored at −80°C until further use. $CD4^+$ T-cell count and viral load are the main indicators of treatment effect in the study. Blood samples were collected for $CD4^+$ T-cell counts and viral load before ART. After treatment, the doctor told patients to come back for follow-up visits: every 6 months for $CD4^+$ T-cell count detection, and every year for viral load detection, until December 2021.

According to the previous studies, the rate of drug resistance among patients on ART in Guangxi was about 4.5%–7.5%. In this study, the rate of PDR was estimated to be 4%–10%, the standard error was 0.05, and the confidence level was 0.95. According to the equation $n = \frac{z_{\alpha/2}p(1-p)}{\delta^2}$, the sample size was between 279 and 593. Considering that the sequencing failure was about 10%, 323 to 653 samples were required.

Patient Consent Statement

This study was approved by the Ethics Review Board of the Guangxi Center for Disease Control and Prevention (certificate number GXIRB2016–0047–1). All participants provided their written informed consent to participate in the study, allowing the use of demographic information and clinical records in future epidemiological studies. No additional informed consent was sought and all clinical records were de-identified before analysis. We signed a confidentiality agreement and were authorized to use the database for this study.

Testing and Sequencing

The protocols were performed in accordance with a previous study [26]. Viral RNA was extracted from the plasma samples using the QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The target fragment of 1316 bp in the *pol* gene (HXB2: 2147–3462, encoding the protease and the first 299 residues of reverse transcriptase), which spans the reverse transcriptase and protease-encoding regions, was amplified using nested polymerase chain reaction (PCR). The PCR products were sent to the company for Sanger sequencing.

Subtyping and Genotypic Resistance Analysis

All sequences were edited with Sequencher v5.1 software (Genecodes, Ann Arbor, Michigan) and aligned using BioEdit 7.1 software (Ibis Biosciences, Carlsbad, California) [26]. Reference sequences were downloaded from the Los Alamos HIV database, which included all major HIV-1 subtypes and circulating recombinant forms (CRFs), to identify the subtype of the virus gene. One hundred seventeen reference sequences were included, which covered all subtypes in China. The neighbor-joining method was used to generate the phylogenetic tree based on the Kimura 2-parameter model with 1000 bootstrap replicates using the MEGA 11.0 software (http://www.megasoftware.net) [27]. Genotypic resistance was

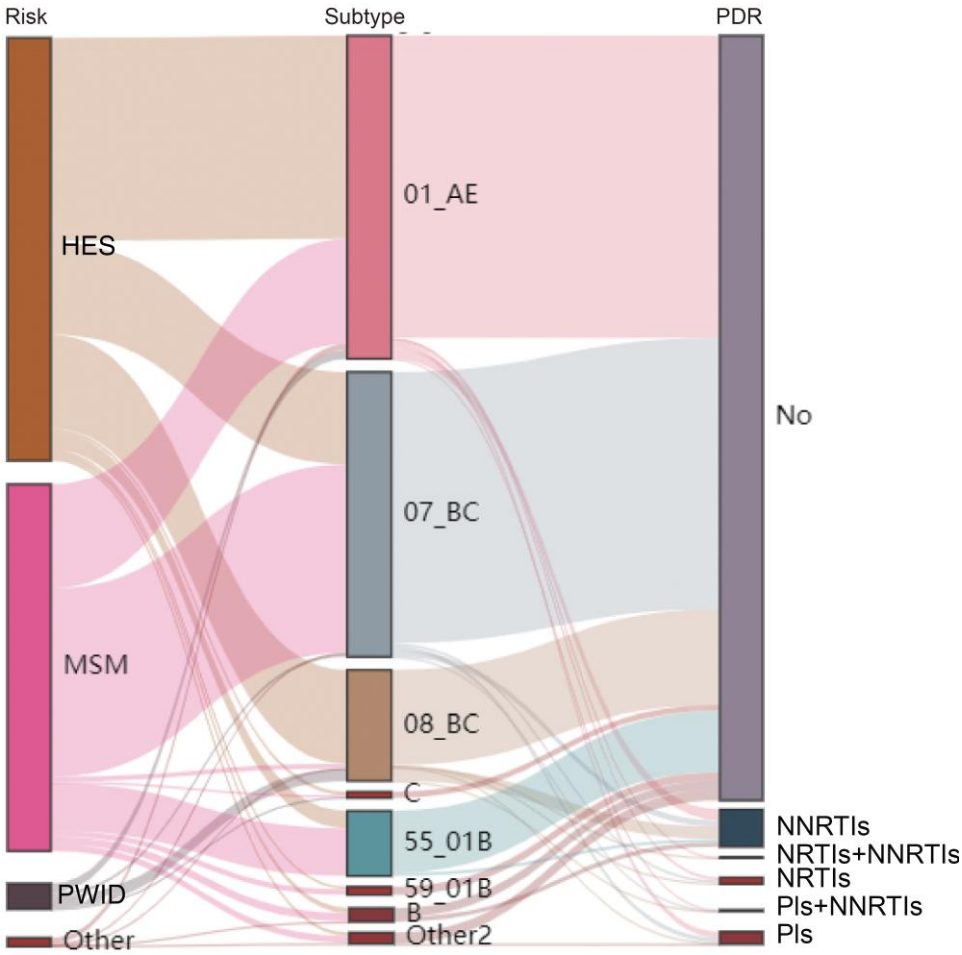

Figure 1. Proportion of infection route, subtype, and pretreatment drug resistance in people with human immunodeficiency virus type 1 infection. The mulberry figure was created with Python 3.10.1. Abbreviations: HES, heterosexual population; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PDR, pretreatment drug resistance; PI, protease inhibitor; PWID, people who inject drugs.

analyzed using the Stanford University HIV Drug Resistance Database Genotypic Resistance Interpretation Algorithm (version 8.8) and the International Antiviral Society Drug Resistance Mutation list [16]. The resistances included nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors (INSTIs). The resistance level to each antiretroviral drug was categorized as susceptible, potential low-level resistance, low-level resistance, intermediate resistance, or high-level resistance.

Genetic Network Analysis

These aligned sequences were entered into the HyPhy software to calculate their genetic distances, and Tamura-Nei93 pairwise genetic distances were calculated for all pairs of sequences. Two sequences showing a genetic distance of ≤1.5% were identified as potential transmission partners. The network was visualized using Cytoscape v3.5.1 software. The characteristics of the network, including nodes, edges, and numbers of clusters, were determined.

Statistical Analysis

Univariate and multivariate logistic regression was used in this study to analyze the risk factors associated with PDR production and transmission in MSM and HES. The *t* test was used to compare the frequency of PDR between PIs, NRTIs, NNRTIs, and INSTIs. The χ^2 test was utilized to compare the effect of PDR on ART between patients with and without PDR. The variables included gender, age, marital status, educational level, ethnicity, CD4 cell counts, HIV subtype, and year of diagnosis. Gender, age, marital status, educational level, and ethnicity were used to adjust the odds ratio (OR) in the multivariate logistic regressions. *P* values <.05 indicate statistical significance. All statistical analyses were performed using SPSS 21.0 software (IBM, Chicago, Illinois).

RESULTS

Prevalence and the Factors Associated With PDR

A total of 1653 samples, including 716 MSM, 827 HES, 50 PWID, and 15 others, were successfully sequenced. The main subtypes in

Table 1. Demographic Characteristics and Factors Associated With Pretreatment Drug Resistance in Patients With Newly Diagnosed HIV-1 Infection

Variables	No. (%)	PDR, No. (%)		OR (95% CI)	aOR (95% CI)
		With PDR	Without PDR		
Gender					
Female	258	23	235	Ref	…
Male	1285	88	1197	0.74 (.46–1.2)	…
Age, y					
<30	615	26	589	Ref	Ref
30–50	563	51	512	2.21 (1.36–3.61)**	1.78 (1.03–3.08)*
>50	365	34	331	2.32 (1.37–3.93)**	1.76 (.90–3.45)
Marital status					
Married	555	44	511	Ref	…
Unmarried	828	53	775	1.47 (.94–2.31)	…
Divorced/widowed	160	14	146	1.43 (.78–2.61)	…
Educational level					
College and above	568	32	536	Ref	Ref
High school or technical school	294	17	277	1.03 (.56–1.88)	0.82 (.44–1.55)
Junior high school/below	681	62	619	1.64 (1.06–2.57)*	0.84 (.47–1.48)
Ethnicity					
Han	816	50	766	Ref	…
Zhuang	638	43	595	0.93 (.62–1.39)	…
Other	89	8	81	1.27 (.59–2.75)	…
Infection route					
MSM	716	34	682	Ref	Ref
HES	827	77	750	2.13 (1.40–3.24)***	1.57 (1.2–2.50)
Pretreatment $CD4^+$ T-cell count, cells/μL					
<200	427	38	389	Ref	…
200–350	438	27	411	0.67 (.40–1.12)	…
>350	678	46	632	0.73 (.46–1.14)	…
Subtype					
CRF01_AE	603	38	565	Ref	Ref
CRF07_BC	550	28	522	0.77 (.46–1.28)	0.98 (.56–1.71)
CRF08_BC	192	30	154	2.74 (1.64–4.55)***	2.47 (1.44–4.23)**
CRF55_01B	126	7	105	0.74 (.31–1.78)	1.01 (.40–2.54)
Other	72	8	64	2.19 (1.01–4.75)*	2.71 (1.22–6.02)*

Univariate logistic regression and multivariate logistic regression were used to analyze the risk factors associated with PDR.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HES, heterosexual; MSM, men who have sex with men; OR, odds ratio; PDR, pretreatment drug resistance; Ref, reference group.
*$P < .05$; **$P < .01$; ***$P < .001$.

MSM were CRF07_BC (50.0%), CRF01_AE (27.6%), and CRF55_01B (12.6%) (Figure 1). In HES, the main subtypes included CRF01_AE (47.5%), CRF08_BC (21.8%), and CRF07_BC (21.5%) (Figure 1). For all populations, the age, subtype, risk factors of PDR, and prevalence of PDR differed between MSM and HES (Table 1). Logistic regression showed that the CRF55_01B subtype (adjusted OR [aOR], 3.35; $P < .05$) was the risk factor for PDR in MSM, but no significant statistical difference was observed for other factors. The PDR of CRF01_AE, CRF07_BC, CRF55_01B, and other was 3.0%, 4.1%, 6.5%, and 13.7%, respectively (Supplementary Table 1). Age >30 years (aOR, 2.75–2.82; $P < .05$) and CRF08_BC subtype (aOR, 2.34; $P < .05$) were the risk factors for PDR in HES. The PDR of CRF01_AE, CRF07_BC, CRF08_BC, and other subtypes was 8.0%, 7.2%, 16.3%, and 3.2%, respectively, and CRF08_BC had the highest PDR (Supplementary Table 2).

Characteristics of the PDR Mutation in MSM

Protease inhibitors, INSTIs, NTRIs, and NNRTIs between MSM and HES were compared. The PDR of PIs, NTRIs, and NNTRIs in MSM was lower than that in HES from 2016 to 2020 (Figure 2*A*–*C*). The PDR in MSM increased from 5.9% in 2016 to 7.0% in 2020, while that in HES varied from 9.7% in 2016 to 9.6% in 2020. The overall PDR in MSM (4.7%) was lower than that in HES (9.3%), and the difference was statistically significant (Figure 2*D*). The main PDR in MSM was NNRTIs (3.5%), followed by PIs (0.8%), INSTIs (0.7%), NRTIs (0.4%), and multiple mutations (0.2%). PIs mostly had moderate- and low-level resistance, NRTIs mainly harbored low-level resistance, and NNRTIs were mainly characterized by high- and low-level resistance (Figure 3*A*). The mutations of PIs were M46I (0.4%), M46L (0.1%), L10LFIV (0.1%), and Q58E (0.1%) and distributed in CRF01_AE (0.3%) and

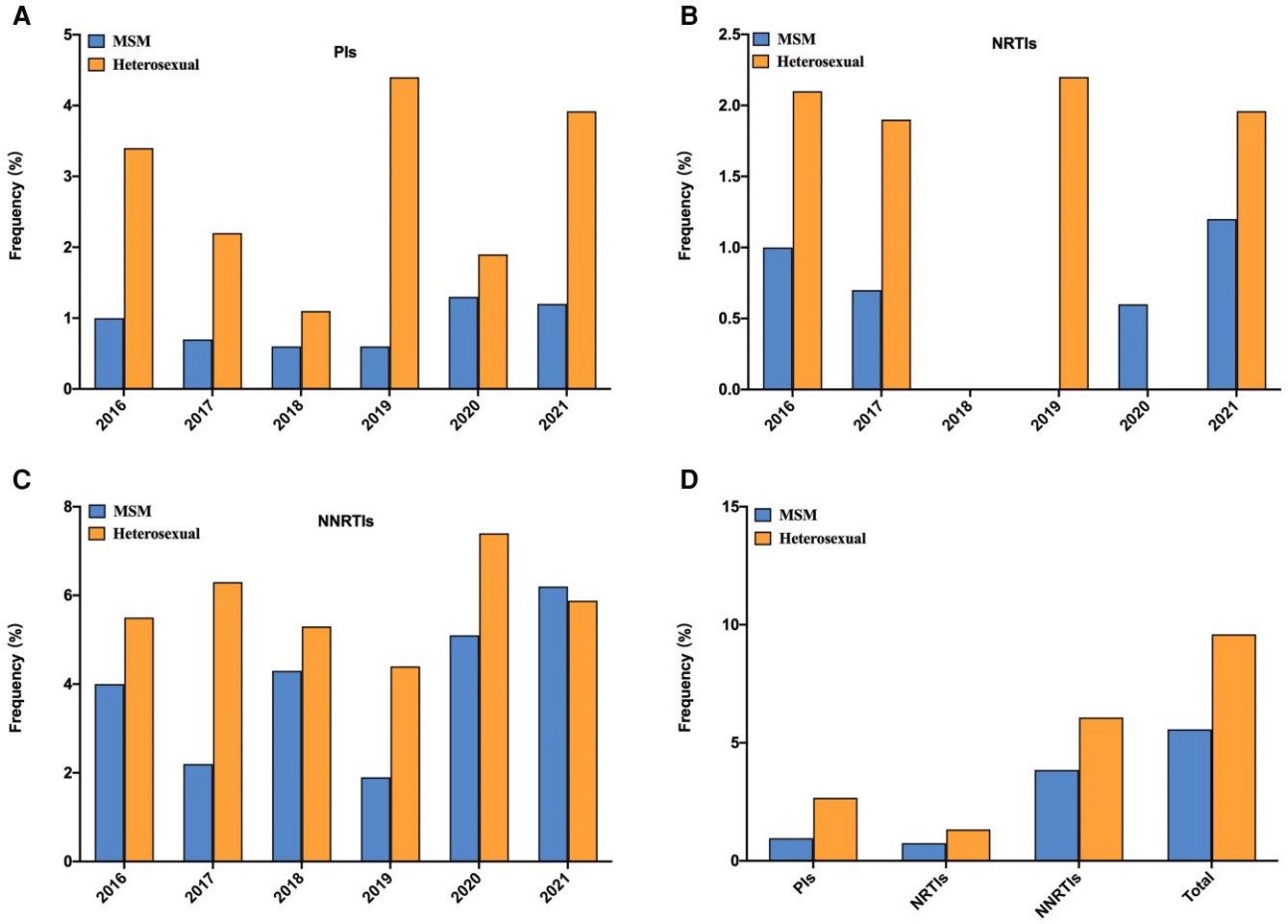

Figure 2. Comparison of protease inhibitor (PI), nucleoside reverse transcriptase inhibitor (NRTI), and nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance between men who have sex with men (MSM) and heterosexuals (HES) from 2016 to 2020. (*A*) PI resistance in MSM and HES. (*B*) NRTI resistance in MSM and HES. (*C*) NNRTI resistance in MSM and HES. (*D*) Comparison of overall pretreatment drug resistance between MSM and HES.

CRF07_BC (0.3%) subtypes. The mutations in NRTIs were T215TI (0.1%), D67G/T69L_P (0.1%), and T215TA (0.1%) and distributed in the CRF01_AE (0.1%) and CRF08_BC (0.3%) subtypes. K103N (1.3%), E138EG/V179E (0.6%), and V106I (0.6%) were the mutations for NNRTIs and were distributed in CRF01_AE (0.4%), CRF07_BC (1.4%), CRF55_01B (0.8%), and B (0.8%) subtypes (Figure 3*B*). The resistance to PIs included fosamprenavir, nelfinavir, and tipranavir; abacavir, zidovudine, stavudine, emtricitabine, lamivudine (3TC), and tenofovir disoproxil fumarate (TDF) for NRTIs; doravirine (DOR), efavirenz (EFV), etravirine, nevirapine (NVP), and rilpivirine for NNRTIs; and bictegravir, dolutegravir, elvitegravir, and raltegravir for INSTIs (Figure 3*C*). The mutation of PIs for MSM and HES mainly involved single-drug resistance, while that of NRTIs was mainly double-drug resistance. The mutation of NNRTI was mainly single-, double-, and quadruple-drug resistance in MSM, while that in HES was mainly single-drug resistance (Figure 3*D*).

PDR Transmission Within the Genetic Network

Pol sequences were used to explore the transmission of PDR among MSM and HES and construct the genetic networks. A total of 62 clusters were distributed in CRF01_AE (32/62), CRF07_BC (13/62), CRF55_01B (7/62), and other subtypes (10/62) in the MSM network, with mean edges of 2.28, 5.07, 3.27, and 1.2, respectively. A total of 31 PDRs were included in the genetic network, 18 from MSM and 13 from HES, which were distributed in CRF01_AE (5/31), CRF07_BC (14/31), CRF55_01B (7/31), and other subtypes (5/31). A total of 32.3% (10/31) of PDRs demonstrated a transmission relationship with each other (Figure 4*A*–*D*). A total of 96 clusters harbored 36 PDRs in the heterosexual network, and 61.1% (22/36) demonstrated a transmission relationship with each other (Figure 4*E*–*H*). The type of PDR was mainly NNTRIs in the network. K103N was the major mutation in the network, accounting for 39.1%, followed by E138EG, accounting for 26.1%.

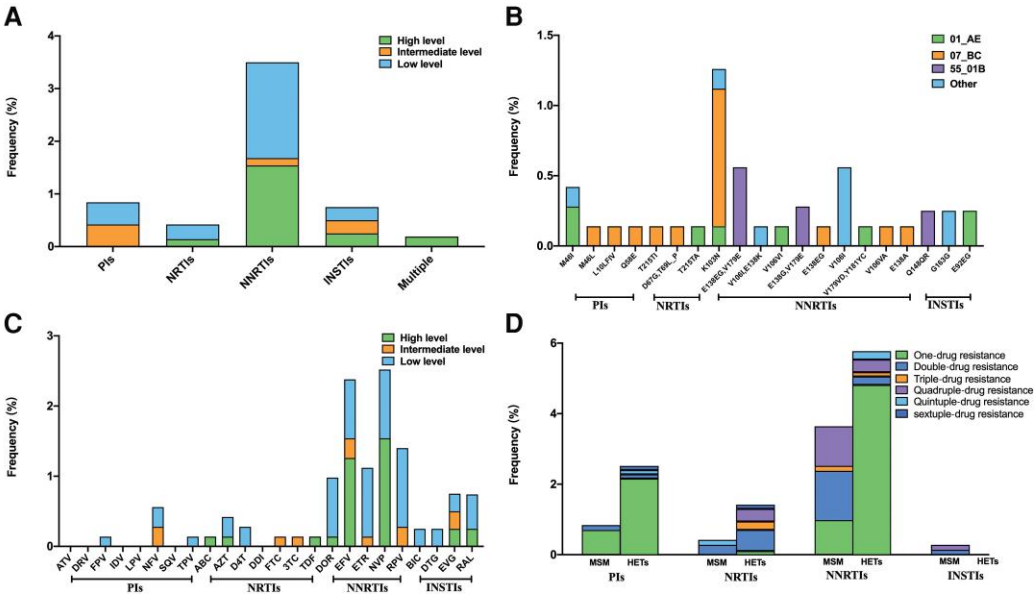

Figure 3. Characteristics of the pretreatment drug resistance mutation in men who have sex with men (MSM). (*A*) Different levels of resistance among protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and integrase strand transfer inhibitors (INSTIs). (*B*) Mutations among PIs, NRTIs, NNRTIs, and INSTIs. (*C*) Sensitive drugs to resistance. (*D*) Analysis of multiple drug resistance induced by mutations of PIs, NRTIs, NNRTIs, and INSTIs between MSM and heterosexuals (HES). Drug abbreviations: 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; BIC, bictegravir; D4T, stavudine; DDI, didanosine; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; FPV, fosamprenavir; FTC, emtricitabine; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; SQV, saquinavir; TDF, tenofovir disoproxil fumarate; TPV, tipranavir.

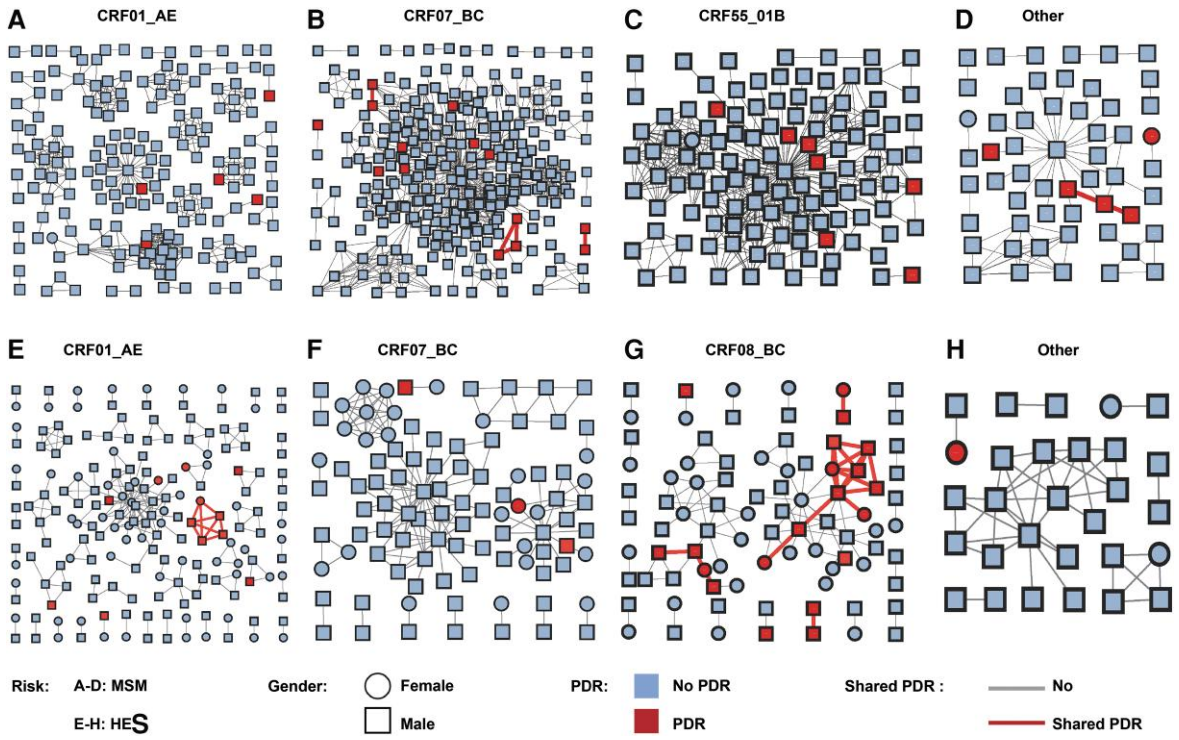

Figure 4. Transmission network of pretreatment drug resistance (PDR) in men who have sex with men (MSM) and heterosexuals (HES). (*A–D*) Transmission network of PDR among CRF01_AE, CRF07_BC, CRF55_01B, and other in MSM. (*E–H*) Transmission network of PDR among CRF01_AE, CRF07_BC, CRF08_BC, and other in HES.

Table 2. Factors Associated With Transmission of Pretreatment Drug Resistance in Men Who Have Sex With Men

Variable	No. (%)	No. in Cluster (%)	PDR in Cluster (%)	Shared PDR (%)	OR (95% CI)	aOR (95% CI)
Age, y						
<30	469 (65.5)	335 (68.0)	11 (61.1)	3 (50.0)	Ref	…
30–50	218 (30.4)	139 (28.2)	6 (33.3)	2 (33.3)	1.33 (.48–3.67)	…
>50	29 (4.1)	18 (3.6)	1 (5.5)	1 (16.6)	1.73 (.21–14.21)	…
Marital status						
Married	584 (81.6)	414 (84.1)	15 (83.3)	6 (100.0)	Ref	…
Unmarried	90 (12.6)	51 (10.3)	2 (11.1)	0 (0.0)	1.09 (.24–4.89)	…
Divorced/widowed	42 (5.9)	27 (5.4)	1 (5.5)	0 (0.0)	1.02 (.13–8.05)	…
Educational level						
College and above	424 (59.2)	295 (59.9)	11 (61.1)	4 (66.6)	Ref	…
High school or technical school	170 (23.7)	118 (23.9)	4 (22.2)	1 (16.6)	0.91 (.28–2.9)	…
Junior high school/below	122 (17.0)	79 (16.0)	3 (16.6)	1 (16.6)	1.02 (.28–3.75)	…
Ethnicity						
Han	416 (58.1)	289 (58.7)	14 (77.7)	4 (66.6)	Ref	…
Zhuang	261 (36.5)	175 (35.5)	3 (16.6)	1 (16.6)	0.34 (.1–1.21)	…
Other	39 (5.4)	28 (5.6)	1 (5.5)	1 (16.6)	0.73 (.09–5.75)	…
Pretreatment $CD4^+$ T-cell count, cells/μL						
<200	117 (16.3)	82 (16.6)	4 (22.2)	0 (0.0)	Ref	…
200–350	226 (31.6)	161 (32.7)	3 (16.6)	1 (16.6)	0.37 (.08–1.7)	…
>350	373 (52.1)	249 (50.6)	11 (61.1)	5 (83.3)	0.9 (.28–2.91)	…
Subtype						
CRF01_AE	203 (28.4)	114 (23.1)	2 (11.1)	0 (0.0)	Ref	
CRF07_BC	369 (51.5)	285 (57.9)	10 (55.5)	5 (83.3)	2.04 (.44–9.44)	2.24 (.46–10.85)
CRF55_01B	93 (13.0)	71 (14.4)	5 (27.7)	0 (0.0)	4.31 (.81–22.84)*	5.69 (1–32.57)*
Other	51 (7.1)	22 (4.4)	1 (5.5)	1 (16.6)	2.55 (.22–29.31)	2.85 (.23–36)
Diagnosed year						
2016	101 (14.1)	69 (14.0)	2 (11.1)	0 (0.0)	Ref	…
2017	137 (19.1)	99 (20.1)	2 (11.1)	0 (0.0)	0.69 (.1–5.03)	…
2018	161 (22.5)	112 (22.7)	4 (22.2)	2 (33.3)	1.24 (.22–6.96)	…
2019	159 (22.2)	106 (21.5)	3 (16.6)	1 (16.6)	0.98 (.16–6)	…
2020	158 (22.1)	106 (21.5)	7 (38.8)	3 (50.0)	2.37 (.48–11.75)	…

Univariate logistic regression and multivariate logistic regression were used to analyze the risk factors associated with transmission of PDR.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; PDR, pretreatment drug resistance; Ref, reference group.

*$P < .05$.

CRF55_01B (aOR, 5.69; $P = .05$) in MSM may be associated with the spread of PDR, but no statistical difference was observed for other factors (Table 2). Univariate logistic regression showed that age (30–50 years: OR, 7.7, $P = .05$; >50 years: OR, 7.77, $P = .048$) and CRF08_BC (OR, 4.27, $P < .001$) were associated with the spread of PDR in HES, but multivariate logistic regression showed that only CRF08_BC (OR, 4.08, $P = .001$) was associated with the spread of PDR in HES (Supplementary Table 3).

Effect of Factors on HIV ART

The $CD4^+$ T-cell counts and viral load from patients were collected from 2016 to 2022 after HIV ART. Nontreatment and treatment <6 months were excluded for further analysis. The $CD4^+$ T-cell count and viral load were selected as an indicator to evaluate the efficacy of treatment. The $CD4^+$ T-cell count was divided into 2 groups (<200, ≥200), and viral load was also divided into 2 groups (<1000, ≥1000). These age, gender, ethnic, infection routes, subtypes, and pretreatment $CD4^+$ T-cell count and viral load variables were included in the analysis. The result showed that the pretreatment $CD4^+$ T-cell counts (≥200), age (<30), MSM, and subtype CRF07_BC were conducive to $CD4^+$ T-cell count recovery than other factors (Table 3). For viral load suppression, the pretreatment $CD4^+$ T-cell counts (≥200), MSM, and subtype CRF07_BC were more likely to suppress viral load than other factors (Table 4).

DISCUSSION

The WHO HIV drug resistance classification [28] indicated that the prevalence of PDR in MSM (4.7%) in Guangxi was low (0–5%) but the PDR in HES (9.3%) was moderate (5%–15%). This finding was different from that in other countries, which was >10.0% and higher than PWID and HES [2]. The PDR in low- and middle-income countries significantly increased in all high-risk groups, and the PDR in MSM was significantly higher than that in HES and PWID [2]. Reports from 2000 to 2016 in China showed that the PDR in MSM was 3.6% and that in heterosexual transmission was 7.3% [22]. In other provinces,

Table 3. Effect of Factor on CD4⁺ T-Cell Counts After Combination Antiretroviral Therapy

Variables	CD4 T-Cell Count, Cells/μL		χ^2 *P* Value	OR (95% CI)	aOR (95% CI)
	<200	≥200			
Pretreatment CD4⁺ T-cell count, cells/μL			<.0001		
<200	147 (0.77)	185 (0.14)		Ref	Ref
≥200	43 (0.23)	1096 (0.86)		20.25 (13.94–29.43)***	15.38 (10.33–22.89)***
Pretreatment viral load, copies/mL			.005		
<1000	1 (0.01)	7 (0.01)		Ref	…
≥1000	43 (0.23)	442 (0.35)		1.47 (.18–12.22)	…
Unknown	146 (0.77)	832 (0.65)		0.82 (.1–6.67)	…
Age, y			<.0001		
<30	33 (0.17)	603 (0.47)		Ref	Ref
30–50	96 (0.51)	462 (0.36)		0.26 (.17–.40)***	0.56 (.33–.95)*
>50	61 (0.32)	216 (0.17)		0.19 (.12–.30)***	0.53 (.29–.98)*
Gender					
Male	157 (0.83)	1066 (0.83)		Ref	…
Female	33 (0.17)	215 (0.17)		0.96 (.64–1.44)	…
Ethnicity			.747		
Han	107 (0.56)	685 (0.53)		Ref	…
Zhuang	73 (0.38)	529 (0.41)		1.13 (.82–1.56)	…
Other	10 (0.05)	67 (0.05)		1.05 (.52–2.10)	…
Infection route			<.0001		
MSM	43 (0.23)	750 (0.59)		Ref	Ref
HES	139 (0.73)	498 (0.39)		0.21 (.14–.30)***	0.41 (.24–.68)**
PWID	8 (0.04)	33 (0.03)		0.24 (.10–.54)**	0.30 (.10–.86)*
Subtype			<.0001		
CRF01_AE	109 (0.57)	418 (0.33)		Ref	Ref
CRF07_BC	24 (0.13)	520 (0.41)		5.56 (3.57–8.95)***	2.63 (1.54–4.48)***
Other	57 (0.3)	343 (0.27)		1.57 (1.11–2.23)*	1.12 (.73–1.71)
Drug resistance			.47		
With PDR	15 (0.08)	83 (0.06)		Ref	…
Without PDR	175 (0.92)	1198 (0.94)		0.81 (.46–1.43)	…

χ^2 test, univariate logistic regression and multivariate logistic regression.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HES, heterosexual; MSM, men who have sex with men; OR, odds ratio; PDR, pretreatment drug resistance; PWID, people who inject drugs; Ref, reference group.

*P < .05; **P < .01; ***P < .001.

the PDR was 6.1% in Beijing [29] and 3.0% in Anhui [30]. Therefore, the overall prevalence of PDR in MSM in Guangxi was consistent with that in China. Many factors, including antiviral use, medication compliance, human genetic background, and HIV subtypes, could influence PDR. The current study identified the relationship between subtype and PDR, which was consistent with a previous study [26]. CRF55_01B and B subtype preferred drug resistance in MSM. However, the proportion of CRF55_01B (12.9%) and B (2.2%) subtypes in MSM was low, which may lead to the low PDR level in MSM in Guangxi. Moreover, this proportion increased from 10.9% in 2016 to 13.3% in 2020, which may contribute to the prevalence of PDR.

Simultaneously, the complexity and diversity of HIV genotypes may be attributed to population flow and the spread of resistant strains [31]. In the genetic network, MSM had a more concentrated network than HES; 32.3% (10/31) of PDR demonstrated a transmission relationship with each other, and CRF55_01B subtype was the risk factor for PDR transmission. In HES, 61.1% (22/36) of PDRs were related, and older and CRF08_BC subtypes were risk factors for PDR transmission. A previous study revealed the association of subtype and HIV transmission [32]. Surveillance of HIV genetic diversity and PDR in the region must be conducted, and the emergence and spread of drug-resistant strains must be prevented.

The main PDR in MSM in Guangxi was NNRTIs (3.5%), followed by PIs (0.8%) and NRTIs (0.4%). The result was inconsistent with the national surveillance report, demonstrating 1.4% for NRTIs, 1.5% for NNRTIs, and 1.9% for PIs [22], and different from the studies on 26 European countries characterized by NRTIs (4.5%), NNRTIs (2.9%), and PIs (2.0%) [33]. The WHO report revealed that the increase in global PDR was mainly due to NNRTI [8, 9]. Therefore, the high percentage of NNRTI in Guangxi could lead to PDR prevalence. In MSM in Guangxi, the main mutation in NNRTI was K103N (36.0%), followed by E138EG/V179E (16.0%) and V106I (16.0%). The K103N

Table 4. Effect of Factor on Viral Load After Combination Antiretroviral Therapy

Variables	Viral Load, Copies/mL		χ^2 *P* Value	OR (95% CI)	aOR (95% CI)
	<1000	≥1000			
Pretreatment CD4+ T-cell count, cells/μL			.011		
<200	286 (0.23)	15 (0.41)		Ref	Ref
≥200	979 (0.77)	22 (0.59)		0.43 (.22–.84)*	0.43 (.21–.88)*
Pretreatment viral load, copies/mL			.67		
<1000	4 (0)	0 (0)		Ref	…
≥1000	422 (0.33)	10 (0.27)		…	…
Unknown	837 (0.66)	27 (0.73)		…	…
Age, y			.58		
<30	551 (0.44)	19 (0.51)		Ref	…
30–50	477 (0.38)	13 (0.35)		0.79 (.39–1.62)	…
>50	237 (0.19)	5 (0.14)		0.61 (.23–1.66)	…
Gender			.349		
Male	1055 (0.83)	33 (0.89)		Ref	…
Female	210 (0.17)	4 (0.11)		0.61 (.21–1.74)	…
Ethnicity			.69		
Han	660 (0.52)	19 (0.51)		Ref	…
Zhuang	542 (0.43)	15 (0.41)		0.96 (.48–1.91)	…
Other	63 (0.05)	3 (0.08)		1.65 (.48–5.74)	…
Infection route			.025		
MSM	700 (0.55)	20 (0.54)		Ref	Ref
HES	542 (0.43)	14 (0.38)		0.90 (.45–1.81)	0.93 (.37–2.33)
PWID	23 (0.02)	3 (0.08)		4.57 (1.27–16.46)*	6.03 (1.32–27.61)*
Subtype			.028		
CRF01_AE	455 (0.36)	19 (0.51)		Ref	Ref
CRF07_BC	473 (0.37)	6 (0.16)		0.30 (.12–.77)*	0.29 (.11–.77)*
Other	337 (0.27)	12 (0.32)		0.85 (.41–1.78)	0.82 (.38–1.77)
Drug resistance			.343		
With PDR	86 (0.07)	4 (0.11)		Ref	…
Without PDR	1179 (0.93)	33 (0.89)		1.66 (.58–4.80)	…

χ^2 test, univariate logistic regression and multivariate logistic regression.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HES, heterosexual; MSM, men who have sex with men; OR, odds ratio; PDR, pretreatment drug resistance; PWID, people who inject drugs; Ref, reference group.

*$P < 0.05$.

usually caused high levels of drug resistance to EFV and NVP, E138EG/V179E could reduce the sensitivity of most NNRTI, while V106I was only resistant to DOR. The current combination of TDF, 3TC, and EFV is the first-line regimen in China. Therefore, the high-frequency mutations of K103N and E138EG/V179E may be related to EFV; thus, EFV should be carefully used. The resistance rate of DOR was relatively high in Guangxi. Studies showed an extensive cross-resistance between DOR and NNRTIs [8, 9]. Therefore, pretreatment resistance and cross-resistance on DOR should be monitored.

Surveillance reports showed that HIV-infected patients with PDR had a high proportion of virologic failure after ART initiation [33, 34]. However, the effect of PDR on ART was rarely reported in China. On the contrary, a prospective study in Japan showed that 51.2% (43/84) of HIV-infected patients had PI resistance mutations before ART, but no clinical virologic failure was observed after ART [35]. Another study in Thailand also revealed that the PDR was 7.9% and M184V/I was only related to poor viral suppression, which accounted for 1.5%–3.0% of the total mutation. However, other mutations did not affect ART. Therefore, the PDR could not predict the possibility of virological failure in clinical treatments. The efficacy of ART is affected by many factors, such as pretreatment CD4+ T-cell count and age [36]. In the study, we found that not only pretreatment CD4+ T-cell count and age, but also infection route and subtype could affect the recovery of CD4+ T-cell count and suppression of viral load. MSM and infection with CRF07_BC have higher CD4+ T-cell count and suppression than others, which may be associated with the prevalence of CRF07_BC among MSM population.

CONCLUSIONS

The increasing coverage of first-line ART has led to an increase of the PDR rate among MSM, which reached the moderate level of drug resistance and must be taken seriously by the health

department. We must continue to scale up PDR surveillance, including other populations and regions. Second, the monitoring of subtypes should be strengthened, which could affect the PDR and ART.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We thank the Guangxi Center for Disease Prevention and Control for sharing the data needed for this study. We also thank all the persons who were involved in this study for their work.

Author contributions. X. P., S. L., G. L., and Y. H. conceived the study. K. T., Q. H., and N. F. collected and tested the samples. J. H. collected the follow-up information of patients. X. P., B. X., X. X., and H. W. analyzed the data. X. P. wrote the manuscript. All authors have reviewed the manuscript.

Financial support. The study was supported by the National Natural Science Foundation of China (grant number 82160636); the Guangxi Key Laboratory of AIDS Prevention Control and Translation (grant number ZZH2020010); the Guangxi Key Laboratory of Major Infectious Disease Prevention and Control and Biosafety Emergency Response (21-220-12); the Guangxi Bagui Honor Scholarship; and the Guangxi Key Research and Development Program (grant number Guike AB22035027).

Potential conflicts of interest. All authors: No reported conflicts.

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