Survey of Pretreatment HIV Drug Resistance and The Genetic Transmission Networks Among HIV-Infected Individuals in Southwestern China, 2014-2020

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Research Article

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Abstract

Background

Pretreatment drug resistance (PDR) can limit the effectiveness of HIV antiretroviral therapy (ART). The aim of this study was to assess the prevalence of PDR among HIV-infected individuals that initiated antiretroviral therapy in 2014–2020 in southwestern China.

Methods

Consecutive cross-sectional surveys were conducted in Qinzhou, Guangxi. We obtained blood samples from individuals who were newly diagnosed with HIV in 2014–2020. PDR and genetic networks analyses were performed by HIV-1 pol sequences by using the Stanford HIV-database algorithm and HIV-TRACE, respectively. Univariate and multivariate logistic regression models were used to explore the potential factors associated with PDR.

Results

In total, 3236 eligible patients were included. The overall prevalence of PDR was 6.0% (194/3236). The PDR frequency to NNRTI (3.3%) was much higher than that to NRTI (1.7%) and PI (1.2%) ($p < 0.0001$). A multivariate logistic regression analysis revealed that PDR was significantly higher among individuals aged 18–29 (adjusted Odds Ratio (aOR): 1.79, 95% CI: 1.28–2.50) or 30–49 (aOR: 2.82, 95% CI: 1.73–4.82), and infected with CRF08_BC (aOR: 3.23, 95% CI: 1.58–6.59). A total of 1429 (43.8%) sequences were linked forming transmission clusters ranging in size from 2 to 119 individuals. Twenty-two individuals in 10 clusters same drug resistant mutations (DRMs), mostly to NNRTIs (50%, 5/10).

Conclusions

The overall prevalence of PDR was medium, numerous cases of the same DRMs among genetically linked individuals in networks further illustrated the importance of surveillance studies for mitigating PDR.

1. Background

Since the establishment of China's national free HIV antiviral therapy in 2003, the case fatality rate of HIV infection has been effectively reduced and the life span of people living with HIV/AIDS has been prolonged [1, 2]. However, with the increasing use of antiretroviral drugs, drug resistance has become an urgent problem. Pretreatment drug resistance (PDR) means that drug resistance has been identified by testing the resistance prior to antiviral therapy, including transmitted drug resistance (TDR) or primary resistance, or having received prior treatment, and then restarting antiviral therapy [3]. Studies found that

the risk of virological failure within 12 months of treatment in people who developed PDR is 2–3 times higher, which will reduce the long-term effectiveness of first-line therapy [4]. Therefore, timely monitoring of DRMs and the transmission of drug-resistant strains before initiation of ART can provide a scientific basis for large-scale prevention and control program in China.

To address the challenges posed by drug-resistant viruses, WHO formulated a global strategy for the prevention of HIV drug resistance in 2012 [5]. Subsequently, it formulated the monitoring of drug resistant people who initiated antiretroviral therapy [3], which was recommended to monitor HIV resistance levels and factors associated with HIV drug resistance. National surveillance data showed that the prevalence of PDR was still at a low level in China [6–8], but the latest studies showed that PDR has reached a medium level in many parts of the country, such as Shanghai (17.4%, 55/317) [9], Tianjin (11.5%, 35/305) [10], Guangxi (7.21%, 83/1151) [11], and Beijing (6.12%, 57/932) [12]. According to the consolidated guidelines on the use of antiretroviral drugs, the proportion of NNRTIs resistance is much higher than that of NRTIs and PIs in countries with NNRTIs-based first-line treatment, and the rate of NNRTIs is > 10%, and thus it is necessary to change the first-line treatment drugs [13].

Guangxi in southwestern China, is one of the regions with the most severe HIV epidemic in China. However, little comprehensive data are available on PDR. In this study, we conducted a large sample survey of HIV drug resistance to assess the level of PDR in recent years (2014–2020). HIV-infected individuals had genotyping and DRMs monitoring prior to initiation of antiretroviral therapy. A genetic transmission network was constructed to explore PDR related transmission.

2. Methods

2.1. Study design and study population

This was a cross-sectional study to estimate the prevalence of PDR in HIV-infected individuals that initiated ART in the Prefecture of Qinzhou, one of the regions with the most severe HIV epidemic in Guangxi. The study design was done according to the 2014 WHO protocol note for PDR [3]. Eligibility criteria were as follows: HIV-1 patients newly diagnosed between January 1, 2014 and June 30, 2020, aged ≥ 18 years, signed the informed consent for PDR testing, and blood samples were successfully collected. Excluded from this study were patients who may have acquired drug resistance from previous antiretroviral drug exposure. After providing written informed consent, participants donated a single blood sample for HIV sequencing, HIV genotyping, and CD4 + T cell count assessment.

2.2. Data collection

Basic sociodemographic data (age, sex, ethnic, education, marital status, and occupation), behavioral characteristics (route of HIV infection, unprotected sexual behavior in the past three months), and baseline CD4 + cell count before ART were collected from the National HIV/AIDS Comprehensive Response Information Management System [14].

2.3. Laboratory testing

Whole blood was sampled before the initiation of ART. For each patient, CD4 cells were determined by The Alere Pima™ Analyzer (Abbott Laboratories, Germany). Frozen plasma (obtained by centrifuging whole blood) was isolated and sent on dry ice to the laboratory at NCAIDS, China CDC. RNA was extracted from 200µl of plasma, amplified, and used to sequence the HIV pol region using an in-house Sanger sequencing protocol [8, 15]. DRMs screening was identified and interpreted according to the Stanford University Genotypic Resistance Interpretation (<https://hivdb.stanford.edu/>). Drug resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) was defined as the detection of at least one antiretroviral virus (ARV) drug in any drug class according to the WHO surveillance drug resistance guideline list [3]. Drug susceptibility was classified into four categories depending on mutation scores: susceptible- (< 15), low- (15–29), intermediate- (30–59), and high-level (> 60) resistance.

2.4. Genetic network inference

The HIV genetic transmission network was inferred with HIV-TRACE [16], establishing putative transmission links between all sequences. We aligned HIV pol sequences to an HXB2 reference sequence and calculated the pairwise genetic distances under the Tamura-Nei 93 (TN93) model [17]. Genetic networks with different genetic distances (range 0.1%-1.5%) were established in order to find the most suitable genetic distance threshold that could identify the maximum number of clusters and links in the genetic network [18]. The genetic transmission network was reconstructed after removing all of the major DRMs from the sequences so that they would not impact the genetic distance comparison [19], but the resulting network was unchanged. For visualization and analysis, the network data were processed using the Cytoscape 3.5.2 software.

2.5. Statistical analysis

Statistical analyses were done in SAS V9.4 (SAS Institute Inc., Cary, NC, USA). Categorical variables are presented as number of cases and percentages, while continuous variables are expressed as the mean ± standard deviation (SD). Categorical variables which are presented as the number of cases and percentages were compared using the Pearson's χ^2 test or Fisher's exact test, while continuous variables are expressed as the mean ± standard deviation (SD) and compared using the non-parametric Mann-Whitney U-test and Kruskal-Wallis test, where appropriate. Univariate and multivariate logistic regression models were used to explore associations between PDR with demographic and clinical variables applied to each subregion. $P < 0.05$ was considered statistically significant.

3. Results

3.1. General characteristics of the study population

Table 1 summarizes the baseline characteristics of 3262 eligible HIV-infected individuals that initiated ART in Qin Zhou in the years 2014–2020. Most patients were over 50 years of age (55.1%, 1799/3262), male (73.4%, 2396/3262), Han (89.8%, 2930/3262), educated up to primary school level or below (56.2%,

1833/3262), married or cohabiting (59.8%, 1953/3262), and farmers (79.3%, 2588/3262). The self-reported risk factors for HIV-1 infection were mainly heterosexual intercourse (94.5%, 3082/3262), and 115 (3.5%) cases and 65 (2.0%) cases via intravenous drug use and homosexual intercourse, respectively. A total of 2533 patients (77.7%) had a CD4 + cell count < 350 cells/mm³ before ART and 669 patients (20.5%) had a CD4 + cell count ≥ 350 cells/mm³. The proportions of the subtypes CRF01_AE, CRF07_BC, CRF08_BC, CRF55_01B, B, and others were 56.7% (1849/3262), 10.2% (331/3262), 27.4% (895/3262), 0.9% (30/3262), 0.4% (12/3262), and 4.5% (145/3262), respectively.

Table 1
Characteristics of HIV-infected individuals in southwestern China,
2014–2020

Variable	Number	%
Total	3262	100
Age (years)		
18–29	305	9.4
30–49	1158	35.5
≥ 50	1799	55.1
Sex		
Female	866	26.6
Male	2396	73.4
Ethnic		
Han	2930	89.8
Zhuang	290	8.9
Others	42	1.3
Education		
Primary and below	1833	56.2
Junior and high	1429	43.8
Marital status		
Single	668	20.5
Married or cohabiting	1953	59.8
Divorced or widowed	641	19.7
Occupation		
Farmer	2588	79.3
Others	674	20.7
Route of HIV infection		
Heterosexual intercourse	3082	94.5
Homosexual intercourse	65	2.0
Intravenous drug use	115	3.5

Variable	Number	%
Baseline CD4 + cell count before ART (cells/mm ³)		
< 350	2533	77.7
≥ 350	669	20.5
Missing	60	1.8
HIV-1 genotype		
CRF01_AE	1849	56.7
CRF07_BC	331	10.2
CRF08_BC	895	27.4
CRF55_01B	30	0.9
B	12	0.4
Others	145	4.5

3.2. Pretreatment HIV drug resistance

The overall prevalence of PDR was 6.0% (194/3236, 95% CI = 5.1%~6.8%). The PDR frequency to NNRTI (3.3%, 106/194) was much higher than that to NRTI (1.7%, 54/194) and PI (1.2%, 40/194) ($\chi^2=37.04, p < 0.0001$). The most frequent NNRTI associated mutation was E138A/EA/G/EG/EK, which was observed in 1.9% (60/3236) of patients followed by K103N/KN (0.4, 14/3236) and V179D/E/VD (0.4%, 13/3236). K70E/T/KT/KE (0.3%, 9/3236) was the most prevalent NRTI associated mutation, followed by T215S/D/TA/TS (0.2%, 8/3236) and V75M/VM/VA (0.2%, 8/3236) (Table 2). For NNRTI, RPV showed the highest PDR frequency (2.6%, 85/3236) ($\chi^2=27.522, p=0.0001$), but the highest proportion of high-level resistance was NVP (1.6%, 51/3236), followed by EFV (1.3%, 43/3236). The PDR frequency to ETR (0.6%, 19/3236) and DOR (0.6%, 20/3236) was similar ($\chi^2=0.0258, p = 0.8724$). For NRTIs, because the mutation levels of 3TC and FTC are mainly high-level mutation, both were 0.1% (4/3236). The degree of resistance was mainly at a low level, accounting for 0.4% (14/3236), 0.6% (18/3236), 0.3% (10/3236), 0.8% (26/3236), and 0.6% (18/3236) for ABC, AZT, TDF, D4T, and DDI, respectively. The highest number of PI resistance was NFV, with 15 (15/3236), 10 (10/3236), and 1 (1/3236) in the low, middle and high-level resistance, respectively. There was no HIV-1 strain resistant to DRV/r found in our study (Fig. 1). PDR did not significantly increase from 2014 to 2020 ($p = 0.32$, Mantel-Haenszel (M-H) χ^2 linear trend test) (Table A1).

Table 2

Pretreatment HIV drug resistance mutations among HIV-infected individuals with drug resistance

Antiretroviral drug	Number	Percentage, % (95% CI)	HIV drug resistance mutations, N (%)
Total	194	6.0 (5.1–6.8)	
NNRTIs ^a	106	3.3 (2.6–3.9)	E138A/EA/G/EG/EK, 60 (1.9)
EFV ⁺⁺	43	1.3 (0.9–1.7)	K103N/KN, 14 (0.4)
NVP ⁺⁺	51	1.6 (1.1–2.0)	V179D/E/VD, 13 (0.4)
ETR ⁺	19	0.6 (0.3–0.8)	V108I/VI, 8 (0.2)
RPV ⁺	85	2.6 (2.1–3.2)	G190A/GE/GA, 7 (0.2)
DOR	20	0.6 (0.4–0.9)	Y181C/YC/I, 7 (0.2)
NRTIs ^b	54	1.7 (1.2–2.1)	V106I/VI/M/VIM, 6 (0.2)
ABC ⁺⁺	21	0.7 (0.4–0.9)	A98G/AG, 3 (0.1)
AZT ⁺⁺	19	0.6 (0.3–0.8)	Y188L/YH, 3 (0.1)
3TC ⁺⁺	6	0.2 (0.1–0.3)	K70E/T/KT/KE, 9 (0.3)
TDF ⁺⁺	11	0.3 (0.1–0.5)	T215S/D/TA/TS, 8 (0.2)
FTC ⁺⁺	6	0.2 (0.1–0.3)	V75M/VM/VA, 8 (0.2)
D4T ⁺⁺	37	1.1 (0.8–1.5)	T69TADN/DGNS/D, 7 (0.3)
DDI [*]	33	1.0 (0.7–1.4)	L74LI/LV, 6 (0.2)
PIs ^c	40	1.2 (0.9–1.6)	M184MV/MI/I, 4 (0.1)
LPV/r ⁺⁺	3	0.1 (0–0.2)	L210W/LW, 4 (0.1)
ATV/r ⁺⁺	3	0.1 (0–0.2)	M41L/ML, 4 (0.1)
			D67DN, 3 (0.1)
			M46L/MI/I/ML/MV/IL, 20 (0.6)
			Q58E/QE, 15 (0.5)
			G73S/GS/GCFV, 3 (0.1)
			L10F/LF, 2 (0.1)

^a Non-nucleoside reverse transcriptase inhibitors, ^b Nucleoside reverse transcriptase inhibitors, ^c Protease inhibitors.

* Antiretroviral drugs recommended by WHO.

⁺ Antiretroviral drugs listed in China.

Antiretroviral drug	Number	Percentage, % (95% CI)	HIV drug resistance mutations, N (%)
DRV/r ^{*†}	0	0	
FPV/r	4	0.1 (0-0.2)	
IDV/r	5	0.2 (0-0.3)	
NFV/r	26	0.8 (0.5–1.1)	
SQV/r	5	0.2 (0-0.3)	
TPV/r	16	0.5 (0.3–0.7)	
^a Non-nucleoside reverse transcriptase inhibitors, ^b Nucleoside reverse transcriptase inhibitors, ^c Protease inhibitors.			
* Antiretroviral drugs recommended by WHO.			
† Antiretroviral drugs listed in China.			

3.3. Factors associated with HIV PDR

Factors associated with HIV PDR are listed in Table 3. In a univariate logistic regression analysis, three factors were significantly associated with HIV PDR. Compared with patients aged ≥ 50 , those aged 18–29 (OR: 2.29, 95% CI: 1.46–3.60) or 30–49 (OR: 1.91, 95% CI: 1.40–2.62) had significantly higher PDR rates. Unmarried status was also associated with PDR (OR: 2.00, 95% CI: 1.24–3.22) compared with divorced or widowed. Patients infected with CRF08_BC compared with CRF07_BC were associated with an increased PDR rate (OR: 3.23, 95% CI: 1.70–6.49). Furthermore, a multivariate logistic regression model showed that aOR for patients aged 30–49 and 18–29 versus ≥ 50 were 1.79 (95% CI: 1.28–2.50) and 2.82 (95% CI: 1.73–4.82), respectively. CRF08_BC was also an important factor with aORs of 3.23 (95% CI: 1.58–6.59).

Table 3
Factors associated with pretreatment HIV drug resistance among HIV-infected individuals

Variable	Number	PDR, N(%)	OR (95% CI)	P	Adjusted OR (95% CI)	P
Total	3262	194 (6.0)				
Age (years)						
≥ 50	1799	76 (4.2)	1.00		1.00	
30–49	1158	90 (7.8)	1.91 (1.40– 2.62)	< 0.01	1.79 (1.28– 2.50)	< 0.01
18–29	305	28 (9.2)	2.29 (1.46– 3.60)	< 0.01	2.82 (1.73– 4.82)	< 0.01
Sex						
Male	2396	140 (5.8)	1.00			
Female	866	54 (6.2)	1.07 (0.78– 1.48)	0.67		
Ethnic						
Zhuang	290	11 (3.8)				
Han	2930	181 (6.2)	1.67 (0.90– 3.12)	0.11		
Others	42	2 (4.8)	1.27 (0.27– 5.93)	0.76		
Education						
Primary or below	1833	99 (5.4)	1.00			
Junior or above	1429	95 (6.7)	1.25 (0.93– 1.67)	0.14		
Marital status						

∴ Not applicable.

Variable	Number	PDR, N(%)	OR (95% CI)	P	Adjusted OR (95% CI)	P
Divorced or widowed	641	27 (4.2)	1.00			
Married or cohabiting	1953	113 (5.8)	1.40 (0.91– 2.15)	0.13		
Single	668	54 (8.1)	2.00 (1.24– 3.22)	< 0.01		
Occupation						
Farmer	2588	153 (5.9)	1.00			
Others	674	41 (6.1)	1.03 (0.72– 1.47)	0.87		
Route of infection						
Heterosexual intercourse	3082	180 (5.8)	1.00			
Homosexual intercourse	65	3 (4.6)	0.78 (0.24– 2.51)	0.68		
Intravenous drug use	115	11 (9.6)	1.71 (0.90– 3.23)	0.10		
Baseline CD4 + cell count before ART (cells/mm ³)						
≥ 350	669	34 (5.1)	1.00			
< 350	2533	157 (6.2)	1.23 (0.84– 1.81)	0.28		
Missing	60	3 (5.0)	0.98 (0.29– 3.30)	0.98		
HIV-1 genotype						
CRF07_BC	331	10 (3.0)	1.00		1.00	

∴ Not applicable.

Variable	Number	PDR, N(%)	OR (95% CI)	P	Adjusted OR (95% CI)	P
CRF01_AE	1849	92 (5.0)	1.68 (0.87–3.26)	0.13	1.56 (0.77–3.17)	0.22
CRF08_BC	895	84 (9.4)	3.32 (1.70–6.49)	< 0.01	3.23 (1.58–6.59)	< 0.01
CRF55_01B	30	3 (10.0)	3.56 (0.93–13.74)	0.06	2.51 (0.60–10.44)	0.21
Others	145	5 (3.5)	1.15 (0.39–3.42)	0.81	1.03 (0.32–3.26)	0.96
B	12	0 (0.0)	-	-	-	-
Unprotected sexual behavior in the past three months						
Yes	737	44 (6.0)	1.00			
No	2525	150 (6.0)	1.00 (0.70–1.41)	0.98		
-: Not applicable.						

3.4. Genetic transmission networks

With the most suitable threshold genetic distance of 0.5%, a total of 1429 (43.8%) sequences were linked forming molecular transmission clusters ranging in size from 2 to 119 individuals (257 dyads, 99 clusters with 3 or more individuals). Fifty-nine sequences with PDR were in 29 clusters (10 dyads, 19 clusters of three or more individuals), mostly to NNRTIs (17 of 29 clusters). Of note, even when PDR individuals showed a lower percentage of clustering than no PDR individuals (30.4% versus 44.7%, $P=0.01$) (Table A2), within clustering individuals, no difference was observed in the degrees between PDR and no PDR. (2.00 versus 2.00, $P = 0.35$) (Table A3). There was a total of 4304 links in the network, of which, with 19 (0.4%) links were PDR connected to PDR, 277 (6.4%) were PDR linked to No-PDR, and 4008 (93.1%) were No-PDR connected to No-PDR, which accounted for the largest proportion (Fig. 2). However, same DRMs yielded ten transmission networks, distributed among CRF01_AE (10.3%, 3/29), CRF07_BC (3.4%, 1/29), CRF08_BC (17.2%, 5/29), and CRF55_01B (3.4%, 1/29). In the CRF01_AE subtype cluster, 29 cases of PDR individuals were enrolled, distributed among 18 clusters, and 12, 9, and 7 were resistant to NRTIs, NNRTIs, and PIs, respectively. In addition, there was one case of NNRTIs and NRTIs resistance with mutation sites V106I, V179VD, and V75VM. For the CRF07_BC subtype cluster, 4 cases of PDR individuals were found in 2 clusters. They currently reside in same county. Among them, 3 cases in the same cluster had a non-

marital heterosexual contact history, and all carried Q58QE resistant mutation sites. In the CRF08_BC subtype cluster, 22 cases of drug resistance entered the networks, distributed in 7 clusters, mainly NNRTIs resistance (68.2%, 15/22) with the E138A mutation site. One case harbored both NRTI and NNRTI mutations, and the mutations sites were K103N and M46MI. Three PDR patients in the CRF55_01B subtype were enrolled in the network, with E138G and V179E mutations (Fig. 3).

4. Discussion

This cross-sectional study examined the prevalence of DRMs among 3236 ART-naive patients in Qinzhou and obtained an overall PDR prevalence of 6.0% (194/3236, 95% CI: 5.1%-6.8%). According to the WHO definition of low, medium, and high levels of HIV-1 drug resistance (< 5%, 5–15% and > 15%) [20], PDR prevalence was at a medium epidemic level in the Qinzhou region. It was higher than the prevalence in Qinzhou in 2012–2013 (2.6%, 1/38), as well as in other regions of Guangxi [21]. From 2014 to 2020, the overall prevalence of PDR had no downward trend in Qinzhou, Guangxi. Similarly, PDR rates are on the rise in the provinces with the most severe HIV epidemic such as Guangxi in China, similar to Dehong of Yunnan (3.48 to 9.48%) [22] and Liangshan of Sichuan (4.1 to 12.2%) [23, 24] from 2009 to 2017. In addition, the most common mutations of NNRTIs were E138A, K103N, and V179D mutations in this study, which was consistent with the study in a nationwide pilot survey of people with HIV/AIDS not receiving ART [24]. The most common mutation of NRTIs is the K70K mutation, which is the same as a previous study.[25]. The recommended first-line regimen was AZT or D4T + 3TC + NVP in China [26]. Since 2010, D4T has been gradually replaced by AZT or TDF. Currently, the first-line therapy is TDF or AZT + 3TC + EFV or NVP, which has effectively reduced acquired drug resistance. However, with the exception of D4T, the prevalence of NNRTI PDR was 3.3% (95% CI: 2.6–3.9) in this study, which is below the 10% threshold for changing the recommended first-line antiretroviral therapy [13]. Similarly, some studies in the past have shown that PDR is primarily driven by resistance to NNRTI, with higher resistance to EFV, NVP, and/or RPV in particular [27]. These findings suggest that the current available first-line ART regimens containing D4T, EFV, and/or NVP and/or RPV need to be revised. In addition, it is recommended that there be drug resistance testing and viral load measurements prior to ART initiation.

PDR may be influenced by many complex factors. This exploratory study found that age is an influential factor for PDR. Compared with people aged 50 and above, young people aged 18–29 are more likely to have pre-treatment drug resistance, in line with studies in Jiangsu Province, Shandong Province, Guangxi, and Vietnam [28, 29]. The findings suggest that younger people who have an active sexual life, advocate individuality, and poor adherence to medication are more likely to transmit resistant strains to a newly infected individual. Additionally, the frequency of mutations in the subtype CRF08_BC was significantly higher than that of CRF01_AE and CRF07_BC, which was consistent with the findings in Guangxi [11] and in Yunnan [30]. It has been suggested that the subtype CRF08_BC strain is more prone to base mismatches at certain sites during replication, leading to higher mutation rates, and patients carrying the CRF08_BC virus with mutations E138G, M184I, Y181C, Y188C, L100I, and may be highly resistant to antiretroviral drugs including NVP, EFV, or 3TC [31].

In this study, PDR did not lead to an increase in the clustering rate, as did the findings in 13 provinces or cities in China (include high and moderate prevalence regions) [24], Liangshan Prefecture in Sichuan [23] and Shijiazhuang in Hebei [32]. Studies have suggested that the transmission capacity of resistant strains is lower than that of non-resistant strains [33, 34]. On the other hand, some of the newly diagnosed HIV-infected patients included in this study were not recently infected. They had not been treated with drugs after infection, so that the non-resistant strains became the dominant strains in the patients and drug-resistant mutations may not have been detected [35, 36]. However, there were 10 clusters containing DRMs in the genetic network of this study, and the size of clusters tend to expand with the reporting time. This result suggested that PDR may be transmitted among high-risk groups in the future, and that interventions in these populations are necessary to prevent the spread of drug-resistant strains in the region.

Our study has limitations. The sample transmission categories were based on self-reported information, and we could not confirm the authenticity of the data. We plan to conduct a more detailed study design to obtain accurate epidemiological survey data. In addition, Sanger sequencing can only detect minority drug-resistant strains at a 15%-20% frequency of HIV viral populations of patients and PDR was underestimated in this study [37]. In the future, we hope that next-generation sequencing can be used to identify HIV drug resistant variants at frequencies as low as 0.4%.

In summary, large-scale drug resistance surveillance was carried out on HIV-infected individuals that initiated ART in Qinzhou, which has provided insights into the PDR prevalence, influencing factors, and potential transmission relationships of drug-resistant strains in the region. These findings indicate that there is an urgent need for surveillance programs of HIVDR and routine drug resistance testing in the clinical management of patients. For ART-naïve patients, the results of drug resistance monitoring could guide dosing regimens to improve the therapeutic effect. Also, behavioral intervention and traceability investigation can reduce or even block the continuous transmission of drug-resistant strains. For national institutions, large-scale studies can help develop national guidelines for ART.

5. Conclusions

In conclusion, large-scale drug resistance surveillance showed that the overall prevalence of PDR is moderate in Qinzhou. Pretreatment drug resistance did not lead to an increase in the clustering rate. However, numerous cases of same DRMs among genetically linked individuals in networks further illustrate the importance of surveillance research in the development of future strategies for mitigating PDR.

Abbreviations

HIV
Human immunodeficiency virus
PDR

Pretreatment drug resistance
DRM
Drug resistance mutation
WHO
World Health Organization
ART
Antiretroviral therapy
NNRTI
Non-nucleoside reverse-transcriptase inhibitor
NRTI
Nucleoside reverse-transcriptase inhibitor
PI
Protease inhibitor
TDR
transmitted drug resistance
EFV
Efavirenz
NVP
Nevirapine
RPV
Ralpivirine
FTC
Emtricitabine
3TC
Lamivudine
ABC
Abacavir
DDI
Didanosine
D4T
Stavudine
HIVDR
HIV drug resistance
WHO
World Health Organization
OR
Odds ratio
aOR
adjusted Odds Ratio
CI

Declarations

Ethics Approval and Consent to Participate: The ethical review of this study was approved by the Medical Ethics Certification Committee of the Chinese Center for Disease Control and Prevention (approval no. X190111537). Informed consent was obtained from all subjects involved in the study.

Consent for publication: Not applicable.

Competing Interest: The authors report no conflicts of interest in this work.

Availability of data and materials: The datasets are available from the corresponding author on reasonable request.

Author Contributions: X.X., C.S., H.X., L.L. (Lingjie Liao), Z.C., Y.F., Y.S. and Y.R. were responsible for study design and planning. L.L. (Lihong Luo), J.L., H.C., Q.Z., G.L., S.L. and Z.S. contributed to data collection. X.X., C.S., Y.F., H.X., Y.S. and Y.R. contributed to data analysis and interpretation. X.X., H.X., L.L. (Lingjie Liao) and Y.R. contributed to writing the manuscript. All authors read and approved the final version of the manuscript.

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Figures

Figure 1

PDR (%) and levels of HIV-1 PDR to different antiretroviral drugs

Figure 2

Pretreatment HIV drug resistance related molecular transmission networks. (Colored nodes represent PDR, and different colors represent different categories of drugs.)

Figure 3

The composition of the links in the molecular transmission networks

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