Vital Surveillances

Changes in HIV-1 Subtypes/Sub-Subtypes, and Transmitted Drug Resistance Among ART-Naïve HIV-Infected Individuals — China, 2004–2022

Xiu Liu[1]; Dong Wang[1]; Jing Hu[1]; Chang Song[1]; Lingjie Liao[1]; Yi Feng[1]; Dan Li[1]; Hui Xing[1]; Yuhua Ruan[1,#]

ABSTRACT

Introduction: The efficacy of treatment and clinical outcomes may be jeopardized by factors such as transmitted drug resistance (TDR) and the genetic diversity of the human immunodeficiency virus type 1 (HIV-1). This comprehensive study aims to examine the alterations in HIV-1 subtypes or sub-subtypes and TDR among Chinese individuals, who have been diagnosed with HIV infection and are previously untreated with antiretroviral therapy (ART), across the span of 2004 to 2022.

Methods: Sequences of the HIV-1 *pol* gene region were obtained from ART-naïve HIV-positive individuals across 31 provincial-level administrative divisions between 2004 and 2022. To predict susceptibility to 12 antiretroviral drugs, the research utilized the Stanford HIV Drug Resistance Database. The Cochran-Armitage trend test facilitated the analysis of changes in HIV-1 subtype/sub-subtype prevalence and TDR. This analysis was conducted in alignment with the progression of the National Free Antiretroviral Treatment Program's stages between 2004 and 2022.

Results: Among the 57,902 ART-naïve individuals infected with HIV, there was a notable decline in the prevalence of CRF01_AE, B, and C from 37.3%, 24.1%, and 1.3% respectively in 2004–2007 to 29.4%, 7.3%, and 0.2% respectively in 2020–2022. Simultaneously, a significant increase was observed in the proportions of CRF07_BC, CRF08_BC, CRF55_01B, other CRFs, and URFs, from 24.1%, 11.5%, 0.1%, 0.4%, and 0.9% respectively in 2004–2007 to 40.8%, 11.5%, 3.8%, 3.7%, and 2.8% respectively in 2020–2022 (all $P<0.001$ for trend). The prevalence of TDR to overall, non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, and nevirapine also significantly increased from 2.6%, 1.8%, 1.6%, and 1.8% respectively in 2004–2007 to 7.8%, 6.7%, 6.3%, and 6.7% respectively in 2020–2022 (all $P<0.001$ for trend). However, there were no meaningful changes in the TDR prevalence of nucleoside reverse transcriptase inhibitor and protease inhibitor. Notably, in 2020–2022, the overall TDR prevalence exceeded 15% in Xinjiang.

Conclusions: The total prevalence of TDR in China has achieved a moderate level (7.8%) from 2020 to 2022, with NNRTI resistance standing prominently at 6.7%. Consequently, measures to curb TDR are urgently required, particularly among ART-naïve HIV-infected individuals in China.

In 2022, there were approximately 39 million people living with human immunodeficiency virus (HIV), 1.3 million newly infected people, and 29.8 million people who were accessing antiretroviral therapy (ART) globally (*1*). The prevalent use of ART is designed to suppress replication of human immunodeficiency virus type 1 (HIV-1), yet the development of drug resistance correlates with a higher likelihood of virological failure. This resistance potentially compromises the effectiveness of first-line ART regimens (*2*). The issue of transmitted drug resistance (TDR) is troublesome because it can escalate in prevalence, thus critically restricting treatment options available to ART-naïve individuals living with HIV. While the United States (*3*) and Europe (*4*) routinely conduct baseline testing for TDR, this is not standard practice in many countries with limited resources. Additionally, HIV drug resistance (HIVDR) testing is not a routine part of clinical management in most low- and middle-income nations, despite these countries bearing the largest global HIV-1 infection burden.

As a highly populated nation, China is making strenuous efforts in the prevention and control of HIV/AIDS, significantly contributing to the universal objective of eradicating the AIDS epidemic as a public health threat by 2030. In 2004, the Chinese National

Free Antiretroviral Treatment Program (NFATP) was fully implemented. By 2008, the NFATP had been further expanded and standardized, mandating ART initiation for those individuals having a CD4 count less than 200 cells/mm^3. Post 2012, this threshold was raised to less than 350 cells/mm^3. In 2016, all individuals living with HIV were made eligible for ART, regardless of their CD4 counts (*5*). The emergence of TDR owing to the expansion of ART is a serious public health concern, as TDR can negatively impact prognosis and potentially affect treatment efficacy. Consequently, evaluating the levels and trends of TDR in China is of vital importance in relation to the global response to HIV/AIDS. The primary aim of this broad-scale study was to examine the alterations in HIV-1 subtypes/sub-subtypes and TDR among ART-naïve HIV-infected individuals in China spanning the period 2004 to 2022.

METHODS

A total of 67,739 sequences were extracted from the HIV-1 *pol* gene region (HXB2 (*6*) positions 2,253–3,312) of ART naïve HIV-infected individuals between the period of 2004 and 2022. These sequences were procured from both the National Center for AIDS/STD Control and Prevention, China CDC and the HIV sequence databases of the Los Alamos National Laboratory (https://www.hiv.lanl.gov/, retrieved December 30, 2022).

Data verification steps were undertaken; the records from China CDC were scrutinized to ensure participants were indeed ART-naïve and HIV-infected. Furthermore, GenBank annotations and corresponding published articles were scrutinized to isolate those fulfilling the set criteria: the documentation of an ART-naïve HIV-1-infected population; the sampling year; and the recruitment site.

The reference sequence for the study was HXB2. HIV-Trace was utilized for sequence alignment, while the HIV-1 subtypes/sub-subtypes were determined via the construction of phylogenetic trees using the maximum-likelihood method of IQ-Tree v 2.0.6 (*7*).

Individuals were included in the study based on the following criteria: age of 18 years and above, availability of the sampling year and provincial-level administrative division (PLAD), protease and at least the initial 238 amino acids of the reverse transcriptase (HXB2 positions 2,280–3,263) were available, and, if multiple sequences were available for a person, the earliest one was chosen.

A total of 57,902 HIV-1 *pol* gene region sequences that covered 31 PLADs made up the final dataset (Supplementary Figure S1, available in https://weekly.chinacdc.cn/). This study received approval from the Ethics Committee of the National Center for AIDS/STD Control and Prevention, China CDC (approval number X140617334).

The Stanford HIV Drug Resistance Database (HIVdb) was leveraged to extrapolate susceptibility to 12 antiretroviral drugs, using the World Health Organization (WHO)'s 2014 HIVDR guidelines as a reference (*8*). Viruses interpreted as possessing low, intermediate, or high-level resistance were classified as resistant with a penalty score equal to or greater than 15 (*9*). The assessment of drug resistance was accomplished using Stanford University's HIVDR Database's online sequence analysis tool (https://hivdb.stanford.edu/hivdb/by-sequences/).

Statistical evaluations were conducted using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA). The collected data from 2004 to 2022 was stratified into five distinct sampling periods that aligned with the NFATP developmental stages in China. The Chi-square test was utilized to scrutinize the sociodemographic characteristics relative to these five sampling periods. For evaluating trends in subtypes, sub-subtypes, and TDR prevalence within these periods, the Cochran-Armitage trend test was employed. A two-tailed *P*-value less than 0.05 established statistical significance.

RESULTS

The study population consisted of 57,902 ART-naïve HIV-infected individuals, which were categorized according to the development stages of the NFATP. The distribution of the subjects over the years was as follows: 1,251 (2.2%) were enrolled between 2004 and 2007, 8,794 (15.2%) between 2008 and 2011, 21,467 (37.1%) between 2012 and 2015, 21,391 (36.9%) between 2016 and 2019, and 4,999 (8.6%) between 2020 and 2022 (Table 1). A Pearson's Chi-squared test revealed significant variations in sociodemographic variables across these five periods (P<0.001).

The data indicated significant decreases in the proportions of ART-naïve HIV-infected individuals over time for circulating recombinant form (CRF)01_AE, B, and C. Specifically, they fell from 37.3%, 24.1%, and 1.3% in 2004–2007 to 29.4%, 7.3%, and 0.2% in 2020–2022, respectively (all P<0.001 for trend) (Table 2). For ART-naïve HIV-

TABLE 1. Characteristics of Chinese individuals with ART-naïve HIV infection, categorized by stages of NFATP development, 2004–2022.

Characteristic	2004–2007		2008–2011		2012–2015		2016–2019		2020–2022		*P**	Total	
	N†	%§	*N*	%	*N*	%	*N*	%	*N*	%		*N*	%
Total	1,251	100.0	8,794	100.0	21,467	100.0	21,391	100.0	4,999	100.0		57,902	100.0
Age (years)											<0.001		
18–29	82	6.6	1,663	18.9	3,158	14.7	3,236	15.1	896	17.9		9,035	15.6
30–49	96	7.7	448	5.1	1,717	8.0	4,706	22.0	1,331	26.6		8,298	14.3
≥50	19	1.5	80	0.9	907	4.2	3,373	15.8	1,424	28.5		5,803	10.0
Unknown	1,054	84.3	6,603	75.1	15,685	73.1	10,076	47.1	1,348	27.0		34,766	60.0
Sex											<0.001		
Male	375	30.0	3,171	36.1	6,218	29.0	9,115	42.6	2,989	59.8		21,868	37.8
Female	98	7.8	694	7.9	1,290	6.0	2,763	12.9	663	13.3		5,508	9.5
Unknown	778	62.2	4,929	56.0	13,959	65.0	9,513	44.5	1,347	26.9		30,526	52.7
Ethnicity											<0.001		
Han	0	0.0	1,348	15.3	4,319	20.1	8,303	38.8	3,134	62.7		17,104	29.5
Others	1,105	88.3	6,330	72.0	10,702	49.9	4,727	22.1	393	7.9		23,257	40.2
Unknown	146	11.7	1,116	12.7	6,446	30.0	8,361	39.1	1,472	29.4		17,541	30.3
Education											<0.001		
Primary school or below	0	0.0	314	3.6	1,176	5.5	4,855	22.7	1,098	22.0		7,443	12.9
Junior high school	0	0.0	586	6.7	1,420	6.6	3,075	14.4	1,082	21.6		6,163	10.6
Senior high school and above	0	0.0	554	6.3	1,913	8.9	3,044	14.2	1,450	29.0		6,961	12.0
Unknown	1,251	100.0	7,340	83.5	16,958	79.0	10,417	48.7	1,369	27.4		37,335	64.5
Marital status											<0.001		
Single, or never married	0	0.0	1,048	11.9	2,266	10.6	3,624	16.9	1,382	27.6		8,320	14.4
Married	0	0.0	688	7.8	1,743	8.1	5,575	26.1	1,540	30.8		9,546	16.5
Divorced/widowed	0	0.0	166	1.9	498	2.3	1,825	8.5	712	14.2		3,201	5.5
Unknown	1,251	100.0	6,892	78.4	16,960	79.0	10,367	48.5	1,365	27.3		36,835	63.6
Risk groups											<0.001		
MSM	121	9.7	2,266	25.8	3,801	17.7	3,432	16.0	1,475	29.5		11,095	19.2
HET	164	13.1	1,153	13.1	3,126	14.6	7,197	33.6	1,982	39.6		13,622	23.5
IDU	188	15.0	651	7.4	351	1.6	1,008	4.7	31	0.6		2,229	3.8
Unknown	778	62.2	4,724	53.7	14,189	66.1	9,754	45.6	1,511	30.2		30,956	53.5
ART-naïve CD4 count (cells/mm^3)											<0.001		
<200	63	5.0	247	2.8	701	3.3	2,583	12.1	1,166	23.3		4,760	8.2
200–499	138	11.0	948	10.8	2,607	12.1	4,479	20.9	1,681	33.6		9,853	17.0
≥500	49	3.9	477	5.4	1,124	5.2	1,565	7.3	383	7.7		3,598	6.2
Unknown	1,001	80.0	7,122	81.0	17,035	79.4	12,764	59.7	1,769	35.4		39,691	68.5

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program; MSM=men who have sex with men; HET=heterosexual; IDU=injection drug use.

* *P* values were calculated using Pearson's Chi-squared test. *P* values <0.05 is statistically significant.

† Number of ART-naïve individuals infected with HIV surveyed.

§ Prevalences of ART-naïve individuals infected with HIV.

infected individuals, the proportions of CRF01_AE within cluster 1, cluster 2, cluster 3, cluster 6, cluster 7, and CRF01_AE-other also significantly decreased from 13.3%, 2.5%, 1.0%, 0.5%, 0.5%, and 6.4% in 2004–2007 to 4.2%, 2.2%, 0.7%, 0.1%, 0.0%, and 2.0% in 2020–2022, respectively (all $P<0.001$ for trend). In contrast, the proportions of ART-naïve HIV-infected individuals for CRF01_AE-cluster 4,

TABLE 2. Changes in HIV-1 subtypes/sub-subtypes among Chinese individuals naïve to ART across various stages of the NFATP from 2004 to 2022.

HIV-1 subtype/sub-subtype	2004–2007		2008–2011		2012–2015		2016–2019		2020–2022		*P**	Total	
	N[†]	%[§]	*N*	%	*N*	%	*N*	%	*N*	%		*N*	%
Total	1,251	100.0	8,794	100.0	21,467	100.0	21,391	100.0	4,999	100.0		57,902	100.0
CRF01_AE	467	37.3	3,911	44.5	9,049	42.2	7,906	37.0	1,472	29.4	<0.001	22,805	39.4
CRF01_AE-cluster 1	166	13.3	763	8.7	1,155	5.4	1,276	6.0	210	4.2	<0.001	3,570	6.2
CRF01_AE-cluster 2	31	2.5	389	4.4	388	1.8	1,424	6.7	108	2.2	<0.001	2,340	4.0
CRF01_AE-cluster 3	13	1.0	40	0.5	97	0.5	193	0.9	34	0.7	<0.001	377	0.7
CRF01_AE-cluster 4	101	8.1	1,740	19.8	5,397	25.1	2,960	13.8	681	13.6	<0.001	10,879	18.8
CRF01_AE-cluster 5	64	5.1	589	6.7	1,469	6.8	1,485	6.9	335	6.7	0.205	3,942	6.8
CRF01_AE-cluster 6	6	0.5	14	0.2	23	0.1	9	0.0	3	0.1	<0.001	55	0.1
CRF01_AE-cluster 7	6	0.5	31	0.4	40	0.2	17	0.1	1	0.0	<0.001	95	0.2
CRF01_AE-other	80	6.4	345	3.9	480	2.2	542	2.5	100	2.0	<0.001	1,547	2.7
CRF07_BC	301	24.1	2,540	28.9	7,397	34.5	8,194	38.3	2,038	40.8	<0.001	20,470	35.4
CRF07_BC-MSM	68	5.4	1,261	14.3	5,353	24.9	4,412	20.6	1,217	24.3	<0.001	12,311	21.3
CRF07_BC-other	233	18.6	1,279	14.5	2,044	9.5	3,782	17.7	821	16.4	<0.001	8,159	14.1
CRF08_BC	144	11.5	390	4.4	1,191	5.5	2,097	9.8	577	11.5	<0.001	4,399	7.6
CRF55_01B	1	0.1	221	2.5	1,170	5.5	1,125	5.3	189	3.8	<0.001	2,706	4.7
B	301	24.1	1,223	13.9	1,652	7.7	967	4.5	364	7.3	<0.001	4,507	7.8
C	16	1.3	128	1.5	113	0.5	105	0.5	12	0.2	<0.001	374	0.6
Other subtypes	5	0.4	52	0.6	80	0.4	78	0.4	24	0.5	0.179	239	0.4
Other CRFs	5	0.4	197	2.2	398	1.9	489	2.3	183	3.7	<0.001	1,272	2.2
URFs	11	0.9	132	1.5	417	1.9	430	2.0	140	2.8	<0.001	1,130	2.0

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program; CRF=circulating recombinant form; URFs=unique recombinant forms.

* *P* values were calculated using Cochran-Armitage trend test. *P* values <0.05 is statistically significant.

[†] Number of ART-naïve individuals infected with HIV surveyed.

[§] Proportions of ART-naïve individuals infected with HIV.

CRF07_BC, CRF07_BC-MSM, CRF07_BC-other, CRF08_BC, CRF55_01B, other CRFs, and unique recombinant forms (URFs) showed a significant increase from 8.1%, 24.1%, 5.4%, 18.6%, 11.5%, 0.1%, 0.4%, and 0.9% in 2004–2007 to 13.6%, 40.8%, 24.3%, 16.4%, 11.5%, 3.8%, 3.7%, and 2.8% in 2020–2022, respectively (all $P<0.001$ for trend). However, there were no significant changes observed over time in the proportions of CRF01_AE-cluster 5 and other subtypes.

The reported prevalence of TDR progressively increased from 2004–2007 to 2020–2022 (Table 3). A significant prevalence of 23.4% was recorded in Xinjiang within the 2020–2022 timeframe. The prevalence of TDR, both overall and in connection with the non-nucleoside reverse transcriptase inhibitor (NNRTI), increased gradually from 2004–2007 to 2020–2022. Over the same series of intervals, the TDR prevalence for efavirenz (EFV) and nevirapine (NVP) escalated from 2004–2007 to 2020–2022 (Supplementary Figure S2, available in https://weekly.chinacdc.cn/).

We observed an almost threefold increase in the prevalence of TDR during 2020–2022 (7.8% and 6.7%) in comparison to the period from 2004–2007 (2.6% and 1.8%), for both overall and NNRTI rates ($P<0.001$ for trend). Notably, the prevalence of transmitted NNRTI resistance specific to EFV and NVP marked a significant increase from 1.6% and 1.8% in 2004–2007 to 6.3% and 6.7% in 2020–2022, respectively ($P<0.001$ for trend). Yet, the prevalence of TDR associated with nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) demonstrated no significant variation over time. The overall TDR prevalence findings remained consistent with the trends of missing and non-missing values for each sociodemographic factor (Supplementary Table S1, available in https://weekly.chinacdc.cn/). The

TABLE 3. Changes in transmitted drug resistance among Chinese individuals with HIV, naïve to ART, according to the stages of the NFATP development, from 2004 to 2022.

Antiretroviral drug	2004–2007 (*n*=1,251)		2008–2011 (*n*=8,794)		2012–2015 (*n*=21,467)		2016–2019 (*n*=21,391)		2020–2022 (*n*=4,999)		*P**	Total (*n*=57,902)	
	N[†]	%[§]	*N*	%	*N*	%	*N*	%	*N*	%		*N*	%
Total	32	2.6	283	3.2	740	3.4	953	4.5	392	7.8	<0.001	2,400	4.1
NNRTI	23	1.8	177	2.0	479	2.2	708	3.3	336	6.7	<0.001	1,723	3.0
EFV	20	1.6	144	1.6	407	1.9	640	3.0	315	6.3	<0.001	1,526	2.6
NVP	23	1.8	177	2.0	479	2.2	708	3.3	336	6.7	<0.001	1,723	3.0
NRTI	13	1.0	117	1.3	276	1.3	293	1.4	76	1.5	0.190	775	1.3
ABC	9	0.7	57	0.6	126	0.6	148	0.7	45	0.9	0.100	385	0.7
AZT	5	0.4	47	0.5	112	0.5	102	0.5	25	0.5	0.700	291	0.5
D4T	10	0.8	90	1.0	193	0.9	221	1.0	42	0.8	0.923	556	1.0
DDI	12	1.0	57	0.6	99	0.5	136	0.6	27	0.5	0.723	331	0.6
FTC	7	0.6	45	0.5	99	0.5	112	0.5	38	0.8	0.120	301	0.5
3TC	7	0.6	45	0.5	99	0.5	112	0.5	38	0.8	0.120	301	0.5
TDF	7	0.6	34	0.4	55	0.3	87	0.4	16	0.3	0.880	199	0.3
PI	2	0.2	25	0.3	56	0.3	39	0.2	9	0.2	0.094	131	0.2
ATV/r	2	0.2	20	0.2	45	0.2	28	0.1	7	0.1	0.059	102	0.2
DRV/r	0	0.0	5	0.1	25	0.1	18	0.1	1	0.0	0.754	49	0.1
LPV/r	1	0.1	25	0.3	48	0.2	34	0.2	8	0.2	0.079	116	0.2

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program; NNRTI=non-nucleoside reverse transcriptase inhibitor; EFV=efavirenz; NVP=nevirapine; NRTI=nucleoside reverse transcriptase inhibitor; ABC=abacavir; AZT=azidothymidine; D4T=stavudine; DDI=didanosine; FTC=emtricitabine; 3TC=lamivudine; TDF=tenofovir; PI=protease inhibitor; ATV/r=atazanavir/ritonavir; DRV/r=darunavir/ritonavir; LPV/r=lopinavir/ritonavir.

* *P* values were calculated using Cochran-Armitage trend test. *P* values <0.05 is statistically significant.

[†] Number of drug resistance amongst ART-naïve individuals infected with HIV.

[§] The prevalence of ART-naïve individuals with HIV who exhibit drug resistance.

Cochran-Armitage trend test results revealed an increasing trend over time in NNRTI resistance mutations for A98, E138, G190, K101, K103, K238, P225, V106 and V179, as well as in NRTI resistance mutations for L74 and M184 (all $P<0.05$ for trend). Conversely, there were no significant developments discernible over time in the PI resistance mutations (Supplementary Table S2, available in https://weekly.chinacdc.cn/).

CONCLUSIONS

To the best of our knowledge, this study represents the largest survey conducted thus far regarding the national distribution and trends of HIV-1 subtypes/sub-subtypes and TDR. With a sample size of 57,902, it spans from 2004 to 2022, encompassing the entire period during which dependable estimates were available for ART-naïve HIV-infected individuals in China.

Between 2004 and 2015, an increasing trend was noted in CRF01_AE, while subtypes B and C displayed a decreasing trend. These findings align with the results of a systematic review of Chinese HIV-1 subtypes from 1990 to 2015 (*10*). The review indicated that CRF01_AE raised from 27.2% to 47.2% between 2005–2009 and 2010–2015, whereas subtypes B and C decreased from 38.7% and 1.7% to 17.8% and 1.6% in the same periods, respectively.

The 2006 Chinese National Molecular Epidemiologic Survey reported that the primary HIV-1 subtypes were largely recombinant, including CRF01_AE, CRF07_BC and CRF08_BC which made up to 80% of the cases, whereas subtype B and remaining subtypes constituted nearly 20%. A retrospective review of HIV/AIDS prevention and control over 30 years in China revealed the prevalence of injection drug use-linked HIV epidemic until 2008, increasing incidence in heterosexuals, and the complexity of HIV-1 subtypes as the proportion of CRFs surpassed other subtypes (*11*).

Our study corroborates the findings of the 2006 Chinese National Molecular Epidemiologic Survey that CRF01_AE, CRF07_BC and CRF08_BC

increasingly predominated in China from 2004 to 2008 (*12*). The data reveal increases in CRF01_AE-cluster 4, CRF07_BC-MSM, CRF07_BC-Other, CRF08_BC, CRF55_01B, Other CRFs, and URFs. In contrast, CRF01_AE-cluster 5 and other subtypes remained consistent, whereas instances of CRF01_AE, cluster 1, cluster 2, cluster 3, cluster 6, and cluster 7, and subtypes B and C showed a deduction.

These shifting patterns have contributed significantly to the complexity and diversity of HIV-1 subtypes and CRFs. A noteworthy observation was the varied distributions of HIV-1 subtypes and recombinant forms and alterations among ART-naïve HIV-infected individuals in different years. The genetic diversity of HIV-1 subtypes/sub-subtypes is driven by a multitude of causes, including potential biological differences between subtypes/sub-subtypes that may impact transmission and disease progression. However, other contributing NVP factors could include aspects like transportation connectivity, migration, urbanization, and population growth.

Incomplete treatment or unequal prevention coverage, and disparities in effectiveness across different geographical regions or risk groups can potentially skew control of the HIV epidemic. Such disparities might contribute to varying regional distributions of HIV-1 subtypes and recombinant forms, with particular regions or risk groups more affected by certain HIV variants.

The 2017 WHO HIV Drug Resistance Guidelines defined the prevalence of transmitted HIVDR as low (<5%), moderate (5%–15%), and high (>15%) (*13*). This study witnessed a significant increase in overall TDR prevalence, even climbing to moderate levels between the years 2020 and 2022. However, in the Xinjiang region, it exceeded 15%, indicating a high level. A comprehensive analysis of HIV-1 TDR in China from 2001 to 2017 indicated an upward trend in overall TDR prevalence, consistent with this study's findings (*14*). A review of HIV-1 TDR studies spanning 2009 to 2019 (*15*) showed that the overall TDR prevalence in Sub-Saharan Africa and North America significantly expanded from 3.6% and 12.1% respectively, in 2009–2013, to 6.0% and 14.2%, respectively, in 2014–2019, as per the WHO 2009 surveillance drug resistance definitions (*16*). There were, however, no observable changes in the overall TDR prevalence in South/Southeast Asia, Latin America/Caribbean, Europe, and Upper-Income Asian Countries in the same periods (*15*). A comprehensive U.S. study from 2004 to 2016 displayed considerable increase in overall TDR prevalence from 9.8% to 17.9% (*17*). Conversely, another large U.S. study from 2014 to 2018 found no statistically significant changes in overall TDR prevalence, which stood at 18.9% (*18*). In our study, overall TDR prevalence was 3.2%, 4.4%, and 4.5% for 2008–2011, 2012–2015, and 2016–2019, respectively. These findings are similar to those from a South/Southeast Asia study (*16*), where the majority of data originated from China. Given the size of this dataset, the study is representative and likely to credibly mirror TDR rates among ART-naïve, HIV-infected individuals in China from 2004 to 2022. Of significant concern is the sharp increase in overall TDR prevalence to 7.8% in the years 2020–2022 — a moderate level — with Xinjiang seeing overall TDR prevalence reach 23.4%, a high level. As TDR becomes a critical issue in China, the country must prioritize resistance monitoring, and reevaluate first-line antiviral treatment regimens at a regional level.

In this investigation, a marked upward trend in the prevalence of TDR specifically regarding NNRTI was identified, reaching moderate levels from 2020–2022. Yet, no significant changes were detected in the TDR prevalence for NRTI and PI. This is aligned with a comprehensive review of HIV-1 TDR in China from 2001 to 2017, underlining NNRTI resistance as the primary driver (*14*). A large-scale study in the United States from 2014 to 2018 found the prevalence of TDR for NNRTI, NRTI, and PI to be 12.0% (5,662/47,215), 6.9% (3,258/47,215), and 4.2% (1,983/47,215), respectively (*18*). These findings, particularly the elevated prevalence of transmitted NNRTI resistance (12.0%), correspond with those of the present study.

EFV and NVP-based ART regimens were most commonly initiated in countries that reported data to the WHO between 2014 and 2020 (*8*). In China, Xinjiang exhibited an overall TDR prevalence exceeding 10%, primarily due to NNRTI resistance. This suggests countries displaying a prevalence of transmitted HIVDR to NNRTI equal to or above 10% should urgently consider non-NNRTI first-line ART regimens (*13*).

From 2020–2022, moderate TDR levels were observed in the application of EFV and NVP regimens, which are the primary drug regimens recommended by China's NFATP. The detection of EFV and NVP-specific HIVDR is of paramount importance due to these drugs' widespread use. Notably, resistance mutations for NNRTI, specifically K103, E138, and V179, have seen an increase from 0.4%, 0.1%, and

0.3% in 2004–2007 to 3.4%, 0.8%, and 1.7% in 2020–2022, respectively; while resistance mutations for NRTI, particularly M184, have risen from 0.2% in 2004–2007 to 0.7% in 2020–2022.

CRFs represent the foremost subtype of HIV-1 in China, meriting further exploration of their specific mutations or polymorphisms in relation to drug resistance, using phenotypic drug resistance methods (*19*). Such surveillance is crucial for future TDR planning in the context of HIV infection. Finally, it is noteworthy to mention that in late 2019, public health services shifted their focus toward the coronavirus disease 2019 (COVID-19) pandemic (*20*), necessitating further investigation of any potential links between COVID-19 and HIV drug resistance.

This study presents several limitations. The sociodemographic indicators utilized in the research revealed certain data gaps. The comparison created between non-absent and absent values for each sociodemographic variable showed no significant shift in the overall TDR prevalence as demonstrated in Supplementary Table S1. Second, we failed to gather pertinent clinical information such as the stage of HIV, the time of HIV diagnosis, and the number of sexual partners. In future studies, incorporating this data could augment the accuracy of the results and further enable analysis of variant effects. Finally, potential sampling bias entailed by regional variation necessitates attention; future endeavors will incorporate a thorough evaluation of shifts in the spatio-temporal distribution of drug resistance amongst ART-naïve HIV-positive patients.

Our research findings suggest that the overall prevalence of TDR among ART-naïve individuals infected with HIV in China during 2020–2022 reached a moderate level, with Xinjiang exhibiting a high level. Individuals with HIV who present with drug resistance carry these resistant strains for life, consequently lowering the efficacy of antiretroviral drugs, thereby increasing new HIV infections and associated morbidity and mortality rates. As a result, these individuals should be given precedence for prevention strategies and optimal treatment. It is imperative to carry out field investigations to determine the reasons for TDR among ART-naïve individuals infected with HIV; this would enable the development of targeted interventions to reduce the occurrence and transmission of HIV drug-resistant strains. Regular monitoring and surveillance of drug resistance at national and provincial levels among ART-naïve individuals infected with HIV, along with escalating efforts to prevent TDR development, are vital to achieving the global objective of eradicating AIDS as a public health threat by 2030.

Conflicts of interest: No conflicts of interest.

Acknowledgements: Provincial CDC staff.

Funding: Supported by the Ministry of Science and Technology of China (grant numbers 2022YFC2305205, 2022YFC2305201); the National Natural Science Foundation of China (grant number 82260670); Guangxi Bagui Honor Scholarship; and Chinese State Key Laboratory of Infectious Disease Prevention and Control.

doi: 10.46234/ccdcw2023.129

[#] Corresponding author: Yuhua Ruan, ruanyuhua92@163.com.

[1] State Key Laboratory of Infectious Disease Prevention and Control (SKLID), National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention (China CDC), Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Beijing, China.

Submitted: April 18, 2023; Accepted: June 15, 2023

REFERENCES

1. UNAIDS. Global HIV & AIDS statistics — fact sheet. https://www.unaids.org/en/resources/fact-sheet. [2023-04-20].
2. Wittkop L, Günthard HF, de Wolf F, Dunn D, Cozzi-Lepri A, De Luca A, et al. Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. Lancet Infect Dis 2011;11(5):363 – 71. http://dx.doi.org/10.1016/S1473-3099(11)70032-9.
3. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. [2022-4-10].
4. European AIDS Clinical Society. Guidelines version 10.0. 2019. https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf. [2020-3-13].
5. Ma Y, Dou ZH, Guo W, Mao YR, Zhang FJ, McGoogan JM, et al. The human immunodeficiency virus care continuum in China: 1985–2015. Clin Infect Dis 2018;66(6):833 – 9. http://dx.doi.org/10.1093/cid/cix911.
6. Rose R, Cross S, Lamers SL, Astemborski J, Kirk GD, Mehta SH, et al. Persistence of HIV transmission clusters among people who inject drugs. AIDS 2020;34(14):2037 – 44. http://dx.doi.org/10.1097/QAD.0000000000002662.
7. Minh BQ, Schmidt HA, Chernomor O, Schrempf D, Woodhams MD, von Haeseler A, et al. IQ-TREE 2: new models and efficient methods for phylogenetic inference in the genomic era. Mol Biol Evol 2020;37(5):1530 – 4. http://dx.doi.org/10.1093/molbev/msaa015.
8. World Health Organization. Surveillance of HIV drug resistance in populations initiating antiretroviral therapy (pre-treatment HIV drug resistance): concept note. Geneva: World Health Organization. 2014. https://apps.who.int/iris/handle/10665/112802.
9. World Health Organization. HIV drug resistance report 2021. Geneva: World Health Organization. 2021. https://www.who.int/publications/i/item/9789240038608.
10. Hemelaar J, Elangovan R, Yun J, Dickson-Tetteh L, Fleminger I, Kirtley S, et al. Global and regional molecular epidemiology of HIV-1, 1990–2015: a systematic review, global survey, and trend analysis. Lancet Infect Dis 2019;19(2):143 – 55. http://dx.doi.org/10.1016/

S1473-3099(18)30647-9.
11. Xu JJ, Han MJ, Jiang YJ, Ding HB, Li X, Han XX, et al. Prevention and control of HIV/AIDS in China: lessons from the past three decades. Chin Med J 2021;134(23):2799 – 809. http://dx.doi.org/10.1097/CM9.0000000000001842.
12. He X, Xing H, Ruan YH, Hong KX, Cheng CL, Hu YY, et al. A comprehensive mapping of HIV-1 genotypes in various risk groups and regions across China based on a nationwide molecular epidemiologic survey. PLoS One 2012;7(10):e47289. http://dx.doi.org/10.1371/journal.pone.0047289.
13. Bennett DE, Myatt M, Bertagnolio S, Sutherland D, Gilks CF. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling up antiretroviral treatment. Antivir Ther 2008;13 Suppl 2:25 – 36. http://dx.doi.org/10.1177/135965350801302s04.
14. Zuo LL, Liu K, Liu HL, Hu YH, Zhang ZJ, Qin JR, et al. Trend of HIV-1 drug resistance in China: A systematic review and meta-analysis of data accumulated over 17 years (2001–2017). eClinicalMedicine 2020;18:100238. http://dx.doi.org/10.1016/j.eclinm.2019.100238.
15. Rhee SY, Kassaye SG, Barrow G, Sundaramurthi JC, Jordan MR, Shafer RW. HIV-1 transmitted drug resistance surveillance: shifting trends in study design and prevalence estimates. J Int AIDS Soc 2020;23(9):e25611. http://dx.doi.org/10.1002/jia2.25611.
16. Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, Kiuchi M, et al. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. PLoS One 2009;4(3):e4724. http://dx.doi.org/10.1371/journal.pone.0004724.
17. Rhee SY, Clutter D, Fessel WJ, Klein D, Slome S, Pinsky BA, et al. Trends in the molecular epidemiology and genetic mechanisms of transmitted human immunodeficiency virus type 1 drug resistance in a large US clinic population. Clin Infect Dis 2019;68(2):213 – 21. http://dx.doi.org/10.1093/cid/ciy453.
18. McClung RP, Oster AM, Ocfemia MCB, Saduvala N, Heneine W, Johnson JA, et al. Transmitted drug resistance among Human Immunodeficiency Virus (HIV)-1 diagnoses in the United States, 2014–2018. Clin Infect Dis 2022;74(6):1055 – 62. http://dx.doi.org/10.1093/cid/ciab583.
19. Walter H, Schmidt B, Korn K, Vandamme AM, Harrer T, Überla K. Rapid, phenotypic HIV-1 drug sensitivity assay for protease and reverse transcriptase inhibitors. J Clin Virol 1999;13(1 – 2):71 – 80. http://dx.doi.org/10.1016/s1386-6532(99)00010-4.
20. De Cock KM, Jaffe HW, Curran JW. Reflections on 40 years of AIDS. Emerg Infect Dis 2021;27(6):1553 – 60. http://dx.doi.org/10.3201/eid2706.210284.

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Changes in the prevalence of overall transmitted drug resistance between missing and non-missing values across each sociodemographic variable by stages of NFATP development, from 2004 to 2022.

Variable		2004–2007 (*n*=1,251)			2008–2011 (*n*=8,794)			2012–2015 (*n*=21,467)			2016–2019 (*n*=21,391)			2020–2022 (*n*=4,999)			*P**	Total (*n*=57,902)		
		N†	*n*§	%**	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%		*N*	*n*	%
Total	Missing or not	1,251	32	2.6	8,794	283	3.2	21,467	740	3.4	21,391	953	4.5	4,999	392	7.8	<0.001	57,902	2,400	4.1
Age	Yes	1,054	22	2.1	6,603	208	3.2	15,685	506	3.2	10,076	383	3.8	1,348	106	7.9	<0.001	34,766	1,225	3.5
	No	197	10	5.1	2,191	75	3.4	5,782	234	4.0	11,315	570	5.0	3,651	286	7.8	<0.001	23,136	1,175	5.1
Sex	Yes	778	16	2.1	4,929	164	3.3	13,959	469	3.4	9,513	362	3.8	1,347	106	7.9	<0.001	30,526	1,117	3.7
	No	473	16	3.4	3,865	119	3.1	7,508	271	3.6	11,878	591	5.0	3,652	286	7.8	<0.001	27,376	1,283	4.7
Ethnicity	Yes	146	32	4.1	1,116	242	6.1	6,446	576	4.2	8,361	404	3.9	1,472	106	7.7	<0.001	17,541	1,360	4.5
	No	1,105	0	2.4	7,678	41	2.8	15,021	164	3.1	13,030	549	4.8	3,527	286	7.9	<0.001	40,361	1,040	4.0
Education	Yes	1,251	32	2.6	7,340	242	3.3	16,958	576	3.4	10,417	404	3.9	1,369	106	7.7	<0.001	37,335	1,360	3.6
	No	0	0		1,454	41	2.8	4,509	164	3.6	10,974	549	5.0	3,630	286	7.9	<0.001	20,567	1,040	5.1
Marital status	Yes	1,251	32	2.6	6,892	229	3.3	16,960	560	3.3	10,367	401	3.9	1,365	106	7.8	<0.001	36,835	1,328	3.6
	No	0	0		1,902	54	2.8	4,507	180	4.0	11,024	552	5.0	3,634	286	7.9	<0.001	21,067	1,072	5.1
Risk groups	Yes	754	16	2.1	4,525	147	3.2	14,014	455	3.2	9,733	377	3.9	1,507	134	8.9	<0.001	30,533	1,129	3.7
	No	497	16	3.2	4,269	136	3.2	7,453	285	3.8	11,658	576	4.9	3,492	258	7.4	<0.001	27,369	1,271	4.6
CD4 count	Yes	1,001	19	1.9	7,122	221	3.1	17,035	553	3.2	12,764	517	4.1	1,769	123	7.0	<0.001	39,691	1,433	3.6
	No	250	13	5.2	1,672	62	3.7	4,432	187	4.2	8,627	436	5.1	3,230	269	8.3	<0.001	18,211	967	5.3

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program.
* *P* values were calculated using Cochran-Armitage trend test. *P* values <0.05 is statistically significant.
† Total number of individuals infected with HIV who have not yet received ART surveyed.
§ The number of drug resistance amongst ART-naïve individuals infected with HIV.
¶ Proportion of ART-naïve individuals infected with human immunodeficiency virus who showcase drug resistance.

SUPPLEMENTARY TABLE S2. Evolution of drug resistance mutations in Chinese individuals with HIV who are naïve to antiretroviral therapy, categorized by stages of NFATP development, from 2004 to 2022.

Drug resistance mutation	2004–2007 (*n*=1,251)		2008–2011 (*n*=8,794)		2012–2015 (*n*=21,467)		2016–2019 (*n*=21,391)		2020–2022 (*n*=4,999)		*P**	Total (*n*=57,902)	
	N†	%§	*N*	%	*N*	%	*N*	%	*N*	%		*N*	%
Total	32	2.6	283	3.2	740	3.4	953	4.5	392	7.8	**<0.001**	2,400	4.1
NNRTI (EFV, NVP)	23	1.8	177	2	479	2.2	708	3.3	336	6.7	**<0.001**	1,723	3.0
A98G	2	0.2	17	0.2	16	0.1	30	0.1	22	0.4	**0.007**	87	0.2
L100I	1	0.1	2	0	5	0	7	0	4	0.1	0.268	19	0
K101E/P/H	1	0.1	17	0.2	41	0.2	45	0.2	22	0.4	**0.010**	126	0.2
K103S/T/N	5	0.4	41	0.5	119	0.6	216	1	172	3.4	**<0.001**	553	1.0
V106I/M/A	4	0.3	24	0.3	66	0.3	97	0.5	32	0.6	**<0.001**	223	0.4
V108I	5	0.4	26	0.3	52	0.2	37	0.2	14	0.3	0.097	134	0.2
E138A/G/K/Q	1	0.1	11	0.1	96	0.4	141	0.7	39	0.8	**<0.001**	288	0.5
V179D/E/L/T	4	0.3	35	0.4	165	0.8	243	1.1	84	1.7	**<0.001**	531	0.9
Y181C/I	7	0.6	27	0.3	56	0.3	60	0.3	21	0.4	0.889	171	0.3
Y188C/F/L	0	0	14	0.2	13	0.1	22	0.1	9	0.2	0.398	58	0.1
G190A/C/E/S	3	0.2	22	0.3	52	0.2	69	0.3	25	0.5	**0.008**	171	0.3
H221Y	1	0.1	10	0.1	23	0.1	39	0.2	7	0.1	0.105	80	0.1
P225H	1	0.1	2	0	7	0	13	0.1	16	0.3	**<0.001**	39	0.1
F227C/I/L	2	0.2	4	0	14	0.1	15	0.1	1	0	0.523	36	0.1
M230I/L	2	0.2	4	0	7	0	22	0.1	2	0	0.352	37	0.1

Continued

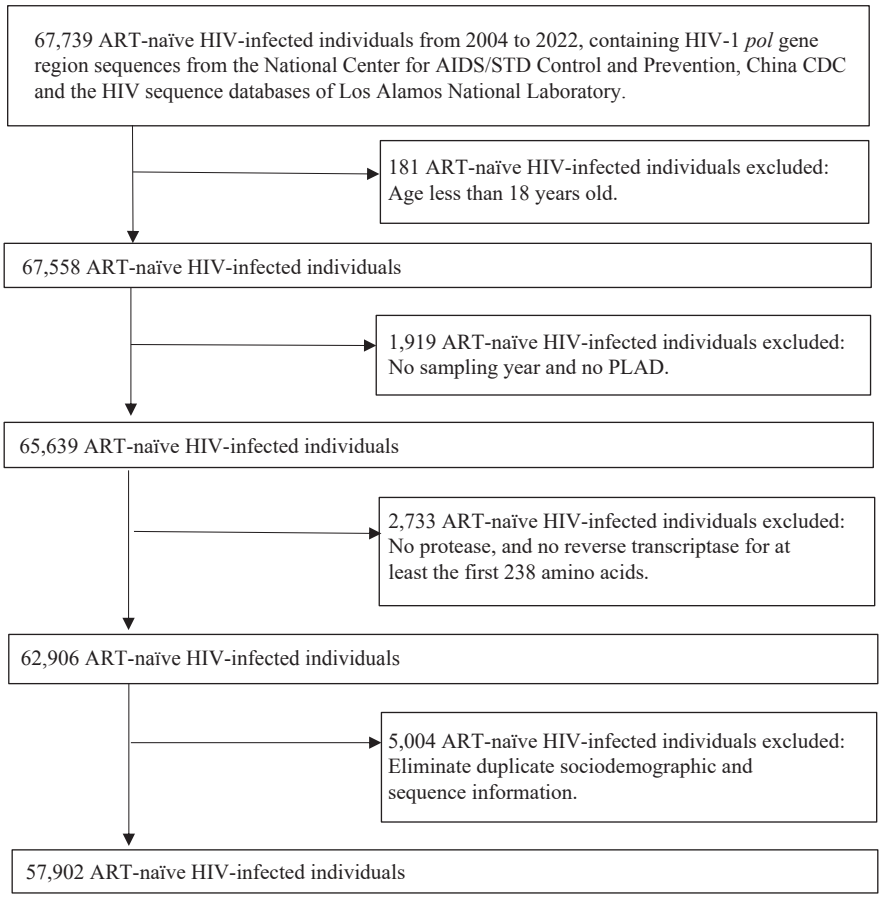
Drug resistance mutation	2004–2007 (*n*=1,251)		2008–2011 (*n*=8,794)		2012–2015 (*n*=21,467)		2016–2019 (*n*=21,391)		2020–2022 (*n*=4,999)		*P**	Total (*n*=57,902)	
	N†	%§	*N*	%	*N*	%	*N*	%	*N*	%		*N*	%
L234I	0	0	0	0	1	0	1	0	0	0	0.813	2	0
K238N/T	0	0	2	0	7	0	13	0.1	7	0.1	**0.002**	29	0.1
NRTI (any)	13	1	117	1.3	276	1.3	293	1.4	76	1.5	0.190	775	1.3
M41L	2	0.2	13	0.1	32	0.1	22	0.1	5	0.1	0.173	74	0.1
E44A/D	0	0	3	0	1	0	0	0	0	0	**0.016**	4	0
A62V	2	0.2	4	0	9	0	4	0	2	0	0.081	21	0
K65R	2	0.2	14	0.2	19	0.1	44	0.2	8	0.2	0.165	87	0.2
D67N	2	0.2	15	0.2	34	0.2	41	0.2	11	0.2	0.372	103	0.2
S68G	1	0.1	10	0.1	23	0.1	29	0.1	1	0	0.660	64	0.1
T69D/N	4	0.3	7	0.1	16	0.1	12	0.1	6	0.1	0.280	45	0.1
K70E/T/R/	2	0.2	14	0.2	35	0.2	48	0.2	7	0.1	0.442	106	0.2
L74F/I	0	0	2	0	14	0.1	19	0.1	5	0.1	**0.023**	40	0.1
V75A/M/I	1	0.1	14	0.2	13	0.1	19	0.1	2	0	0.117	49	0.1
F77L	1	0.1	1	0	0	0	1	0	1	0	0.447	4	0
Y115F	0	0	1	0	3	0	8	0	1	0	0.172	13	0
F116Y	1	0.1	2	0	0	0	0	0	0	0	**0.001**	3	0
Q151M/L	1	0.1	5	0.1	1	0	1	0	0	0	**0.001**	8	0
M184I/V	3	0.2	29	0.3	85	0.4	82	0.4	33	0.7	**0.019**	232	0.4
L210W	1	0.1	15	0.2	41	0.2	23	0.1	4	0.1	0.070	84	0.1
T215F/Y	2	0.2	36	0.4	67	0.3	61	0.3	15	0.3	0.335	181	0.3
K219E/N	3	0.2	11	0.1	6	0	15	0.1	3	0.1	0.102	38	0.1
PI (ATV/r, DRV/r, LPV/r)	2	0.2	25	0.3	56	0.3	39	0.2	9	0.2	0.094	131	0.2
L10F	0	0	1	0	1	0	1	0	1	0	0.737	4	0
K20T	0	0	0	0	1	0	2	0	0	0	0.544	3	0
L24I	0	0	0	0	0	0	0	0	1	0	0.070	1	0
V32I	0	0	1	0	6	0	1	0	0	0	0.282	8	0
L33F	0	0	0	0	1	0	3	0	1	0	0.110	5	0
K43T	0	0	1	0	0	0	0	0	1	0	0.813	2	0
M46I/L	0	0	3	0	10	0	4	0	0	0	0.193	17	0
I47V	0	0	3	0	10	0	5	0	0	0	0.273	18	0
G48R	0	0	0	0	4	0	1	0	0	0	0.719	5	0
I50V/L	1	0.1	3	0	4	0	4	0	1	0	0.286	13	0
F53L	0	0	0	0	4	0	1	0	0	0	0.719	5	0
I54M/V	0	0	3	0	9	0	5	0	2	0	0.881	19	0
Q58E	0	0	0	0	1	0	3	0	0	0	0.377	4	0
G73R/V	0	0	0	0	2	0	3	0	0	0	0.535	5	0
L76V	0	0	0	0	3	0	5	0	0	0	0.389	8	0
V82A/F	1	0.1	5	0.1	14	0.1	8	0	2	0	0.279	30	0.1
I84L/V	0	0	2	0	4	0	4	0	0	0	0.610	10	0
N88S/T	0	0	0	0	5	0	4	0	1	0	0.381	10	0
L89T	0	0	1	0	0	0	0	0	0	0	0.140	1	0
L90M	0	0	10	0.1	9	0	5	0	4	0.1	0.164	28	0

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program; NNRTI=non-nucleoside reverse transcriptase inhibitor; EFV=efavirenz; NVP=nevirapine; NRTI=nucleoside reverse transcriptase inhibitor; (any: ABC=abacavir; AZT=azidothymidine; d4T=stavudine; DDI=didanosine; FTC=emtricitabine; 3TC=lamivudine; TDF=tenofovir); PI=protease inhibitor; ATV/r=atazanavir/ritonavir; DRV/r=darunavir/ritonavir; LPV/r=lopinavir/ritonavir.

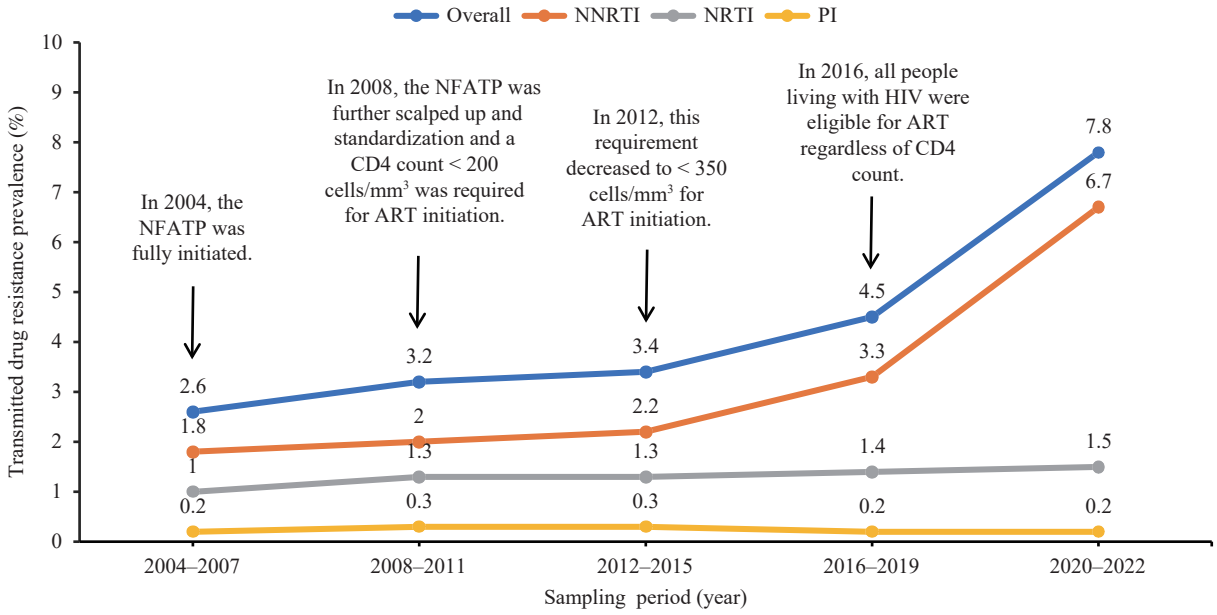
* *P* values were calculated using Cochran-Armitage trend test. *P* values <0.05 is statistically significant.

† Number of drug resistance amongst ART-naïve individuals infected with HIV surveyed.

§ Prevalence of ART-naïve individuals infected with HIV that exhibit drug resistance.



SUPPLEMENTARY FIGURE S1. Flow chart showing the derivation of study sets meeting the inclusion criteria.
Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; PLAD=provincial-level administrative division.



SUPPLEMENTARY FIGURE S2. Changes in transmitted drug resistance among Chinese ART-naïve HIV-infected individuals by the NFATP development stages, 2004−2022.
Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.