Vital Surveillances

Pretreatment HIV Drug Resistance to Integrase Strand Transfer Inhibitors Among Newly Diagnosed HIV Individuals — China, 2018–2023

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ABSTRACT

Introduction: The widespread adoption of integrase strand transfer inhibitors (INSTIs) has led to the emergence of INSTI-associated drug-resistance mutations. This cross-sectional study conducted a comprehensive national survey to investigate the prevalence of pretreatment drug resistance (PDR) to INSTIs among newly diagnosed human immunodeficiency virus (HIV) individuals in China.

Methods: The study enrolled 10,654 individuals from 31 provincial-level administrative divisions between 2018 and 2023. All participants underwent integrase region genotypic resistance testing. PDR to INSTIs was analyzed using the Stanford HIV drug resistance database, and molecular transmission networks were constructed using HIV-TRACE.

Results: The overall PDR prevalence of INSTIs was 0.95%. The predominant major and accessory mutations identified were E138K/A (*n*=19) and G163R/K (*n*=29), respectively. Multivariable logistic regression analysis revealed that age ≥50 years [adjusted odds ratio (a*OR*)=1.87, 95% confidence interval (*CI*): 1.03, 3.42] and HIV subtype B (a*OR*=3.87, 95% *CI*: 1.97, 7.58) were significant risk factors for PDR. Molecular network analysis showed that 1,257 (26.0%) CRF07_BC sequences formed 432 transmission clusters, while 811 (27.6%) CRF01_AE sequences were associated with 335 clusters. The identified drug-resistance mutations included E138K/A, R263K, Y143H, G163R/K, E157Q, and T97A.

Conclusions: The current prevalence of PDR to INSTIs in China remains low. However, given the increasingly widespread use of INSTIs, continuous surveillance of drug resistance emergence and transmission patterns is essential.

In 2022, approximately 39 million people were living with human immunodeficiency virus (HIV) globally (*1*), with 29.8 million receiving antiretroviral therapy (ART) to suppress HIV-1 replication. While China's National Free Antiretroviral Treatment Program (NFATP) was fully implemented in 2004, a significant increase in transmitted drug resistance has been observed. The prevalence of resistance to overall treatments, non-nucleoside reverse transcriptase inhibitors, efavirenz, and nevirapine rose from 2.6%, 1.8%, 1.6%, and 1.8%, respectively, during 2004–2007 to 7.8%, 6.7%, 6.3%, and 6.7% during 2020–2022 (*2*). Integrase strand transfer inhibitors (INSTIs) represent a new class of antiretroviral drugs with high genetic barriers to resistance. The World Health Organization now recommends dolutegravir (DTG) as a component of first-line ART and advocates for genotyping both reverse-transcriptase and integrase regions of HIV-1 (*3*). In China, INSTI-containing regimens were recommended as first-line treatment in 2018 (*4*), and DTG was incorporated into the NFATP for conditional use in 2023 (*5*). Regional surveys of pretreatment drug resistance (PDR) in various provincial-level administrative divisions (PLADs) have reported prevalence rates of 0.53% in Beijing (*6*), 1.7% in Jiangsu (*7*), and 0.71% in Chongqing (*8*). However, these studies were geographically limited with small sample sizes, and no large-scale national investigation of INSTI PDR has been conducted in China. To prevent drug resistance emergence a comprehensive understanding of INSTI PDR prevalence is crucial for developing second-line therapeutic strategies and maintaining vigilance against potential increases in resistance.

Molecular transmission network analysis enables the identification of active transmission clusters through

genetic analysis. While HIV-1 *pol* gene sequences are commonly used for transmission network characterization, some researchers have successfully employed integrase (*int*) gene sequences (*9*). However, no large-scale national studies have utilized *int* sequences to investigate INSTI PDR in China.

This study aimed to conduct a comprehensive national survey to determine the prevalence of INSTI PDR and characterize viral mutations among newly diagnosed HIV individuals in China, while also examining transmission networks associated with INSTI drug resistance.

METHODS

A cross-sectional study was conducted following the World Health Organization protocol for HIV pretreatment drug resistance surveillance across China's regions. Based on HIV incidence, PLADs were stratified into high-, moderate-, and low-prevalence regions. Clinics were randomly selected within each study area, and patients were sequentially enrolled at these sites during the study period. Sample sizes for each PLAD are detailed in Supplementary Table S1 (available at https://weekly.chinacdc.cn/). To assess the prevalence of PDR to INSTIs before their widespread implementation in China, we analyzed all available *int* sequences from 2018, 2022, and 2023. Inclusion criteria comprised: age ≥18 years; confirmed HIV-1 diagnosis in 2018, 2022, or 2023; *int* sequence length ≥500 bp (HXB2 positions 4230-5096); and provided informed consent. Exclusion criteria were age <18 years or prior ART exposure. This study received approval from the Ethics Committee of the National Centre for AIDS/STD Control and Prevention, China CDC (approval number X140617334).

Viral RNA extraction was performed using the QIAsymphony platform, followed by integrase fragment amplification and sequencing using an in-house PCR protocol. Sequences were aligned and filtered using BioEdit, excluding those shorter than 500 nucleotides. HIV-1 subtypes were determined through phylogenetic analysis using IQ-Tree. Drug susceptibility predictions for five INSTIs [first-generation: raltegravir (RAL), elvitegravir (EVG); second-generation: dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB)] were generated using the Stanford HIV Database genotypic resistance interpretation system.

Molecular transmission networks were constructed using the Tamura-Nei 93 model in HIV-TRACE. Each node in the network represented an HIV-infected individual with corresponding epidemiological data. Given the slower evolutionary rate of the *int* gene compared to the *pol* gene, nodes were connected using a genetic distance threshold of 0.5% substitutions per site. Network visualization was performed using web-based tools (https://veg.github.io/hivtrace-viz/) following established technical guidelines for HIV transmission network monitoring and intervention.

Statistical analyses were conducted using SAS (version 9.4, SAS Institute Inc, Cary, NC, USA). Factors associated with drug resistance were analyzed using logistic regression, with statistical significance set at $P<0.05$.

RESULTS

Among the 10,654 HIV-1-infected individuals recruited over the three-year study period, 41.9% were aged ≥50 years. The study population was predominantly comprised of men (79.0%) and individuals of Han ethnicity (83.3%). Most participants (60.1%) had educational attainment at or below junior high school level, and 35.2% were single. Heterosexual transmission was the primary route of infection (61.8%). The vast majority (98.3%) had no prior antiretroviral exposure, and 68.9% presented with CD_4 cell counts between 200–499 cells/mm^3 before initiating treatment. The HIV-1 subtype distribution showed CRF07_BC (45.4%), CRF01_AE (27.6%), CRF08_BC (8.9%), CRF55_01B (1.1%), and subtype B (3.0%) as the predominant strains (Table 1).

Among the 10,654 HIV-1 individuals in our study, the overall prevalence of PDR to INSTIs was 0.95% (*n*=101). The PDR of RAL, EVG, DTG, BIC, and CAB were 0.91% (*n*=97) for RAL, 0.87% (*n*=93) for EVG, 0.21% (*n*=22) for DTG, 0.15% (*n*=16) for BIC, and 0.34% (*n*=37) for CAB. We identified nine major and six accessory INSTI-related drug resistance mutations (DRM). The E138K/A mutation, conferring low-level resistance to RAL and EVG, was the most frequent major mutation (*n*=19). Eight cases harbored the R263K mutation, which causes low-level resistance to RAL and intermediate-level resistance to EVG, DTG, BIC, and CAB. The combination of S147G and Q148K mutations resulted in high-level resistance to RAL, EVG, and CAB. The G163R/K accessory mutation, detected in 29 cases, conferred low-level resistance to RAL and EVG (Table 2).

Multivariate analysis revealed that individuals with

TABLE 1. Demographic and clinical characteristics of newly diagnosed HIV individuals in China.

Variable	2018		2022		2023		Total	
	N	Prevalence (%)	*N*	Prevalence (%)	*N*	Prevalence (%)	*N*	Prevalence (%)
Total	905	100.0	2,757	100.0	6,992	100.0	10,654	100.0
Age (years)								
18−29	231	25.5	629	22.8	1,630	23.3	2,490	23.4
30−49	459	50.7	1,012	36.7	2,175	31.1	3,646	34.2
≥50	215	23.8	1,116	40.5	3,138	44.9	4,469	41.9
Unknown	0	−	0	−	49	0.7	49	0.5
Sex								
Male	743	82.1	2,212	80.2	5,458	78.1	8,413	79.0
Female	162	17.9	545	19.8	1,470	21.0	2,177	20.4
Unknown	0	−	0	−	64	0.9	64	0.6
Ethnicity								
Han	744	82.2	2,252	81.7	5,876	84.0	8,872	83.3
Others	161	17.8	502	18.2	1,063	15.2	1,726	16.2
Unknown	0	−	3	0.1	53	0.8	56	0.5
Education								
Junior high school or blew	386	42.7	1,679	60.9	4,334	62.0	6,399	60.1
Senior high school	249	27.5	405	14.7	972	13.9	1,626	15.3
College and above	174	19.2	653	23.7	1,612	23.1	2,439	22.9
Unknown	96	10.6	20	0.7	74	1.1	190	1.8
Marital status								
Single	369	40.8	987	35.8	2,389	34.2	3,745	35.2
Married or cohabiting	410	45.3	1,227	44.5	2,975	42.5	4,612	43.3
Divorced or widowed	112	12.4	520	18.9	1,554	22.2	2,186	20.5
Unknown	14	1.5	23	0.8	74	1.1	111	1.0
Risk								
Heterosexual	460	50.8	1,699	61.6	4,424	63.3	6,583	61.8
Homosexual	402	44.4	925	33.6%	2,327	33.3	3,654	34.3
Intravenous drug use	21	2.3	28	1.0	32	0.5	81	0.8
Others	2	0.2	4	0.1	1	0.0	7	0.1
Unknown	20	2.2	101	3.7	208	3.0	329	3.1
Prior ARV exposure								
No	905	100.0	2,616	94.9	6,947	99.4	10,468	98.3
Yes	0	−	76	2.8	38	0.5	72	0.7
Unknown	0	−	65	2.4	7	0.1	114	1.1
CD4 cell count before ART (cell/mm^3)								
<200	292	32.3	1,010	36.6	206	2.9	1,508	14.2
200–499	433	47.8	1,404	50.9	5,504	78.7	7,341	68.9
≥500	148	16.4	302	11.0	1,282	18.3	1,732	16.3
Unknown	32	3.5	41	1.5	0	−	73	0.7
Subtype								
CRF07_BC	319	35.2	1,305	47.3	3,208	45.9	4,832	45.4

Continued

Variable	2018		2022		2023		Total	
	N	Prevalence (%)	*N*	Prevalence (%)	*N*	Prevalence (%)	*N*	Prevalence (%)
CRF01_AE	290	32.0	712	25.8	1,940	27.7	2,942	27.6
CRF08_BC	135	14.9	245	8.9	566	8.1	946	8.9
CRF55_01B	8	0.9	49	1.8	65	0.9	122	1.1
B	34	3.8	70	2.5	217	3.1	321	3.0
URFs	38	4.2	161	5.8	395	5.6	594	5.6
Others	81	9.0	215	7.8	601	8.6	897	8.4

Abbreviation: ART=antiretroviral therapy; ARV=antiretroviral drugs; HIV=human immunodeficiency virus; CRF=circulating recombinant form; URFs=unique recombinant forms.

TABLE 2. Prevalence and patterns of HIV integrase strand transfer inhibitor resistance mutations among newly diagnosed individuals in China.

Antiretroviral drug	Prevalence, *N*	% (95% *CI*)	HIV drug resistance mutations and combination of mutations, *n* (%)
INSTIs	101	0.95 (0.76, 1.11)	Major mutations
Raltegravir	97	0.91 (0.73, 1.09)	E138K/A : 19
Elvitegravir	93	0.87 (0.69, 1.05)	E138K+L74I : 1
Dolutegravir	22	0.21 (0.12, 0.29)	E138K+E92Q+R263K : 1
Bictegravir	16	0.15 (0.08, 0.22)	R263K : 8
Cabotegravir	37	0.34 (0.24, 0.46)	R263K+A128T :1
			Y143S/C/H : 8
			T66A/I : 4
			T66I+E157Q : 1
			N155S/T : 3
			N155H+Q95K+E157Q : 1
			Q146P/R/L : 3
			Q146R+S153A : 1
			Q148R : 2
			Q148K+S147G : 1
			S147G : 1
			G140R : 1
			Accessory mutations
			G163R /K: 29
			G163R+E157Q : 3
			S230R : 6
			S230R+S153F : 1
			H51Y : 4
			V151A : 2
			S153F : 2
			E157Q+T97A : 1

Abbreviation: HIV=human immunodeficiency virus; *CI*=confidence interval.

HIV-1 subtype B had significantly higher odds of drug resistance compared to those with CRF07_BC [adjusted odds ratio (a*OR*)=3.87, 95% confidence interval (*CI*): 1.97, 7.58]. Additionally, individuals aged ≥50 years showed increased odds of drug resistance compared to those aged 18–29 years (a*OR*=1.87, 95% *CI*: 1.03, 3.42) (Table 3).

Molecular transmission network analysis, using a

TABLE 3. Risk factors associated with integrase strand transfer inhibitor resistance among newly diagnosed HIV individuals in China.

Variable	*N*	PDR, *n* (%)	*OR* (95% *CI*)	*P*	a*OR* (95% *CI*)	*P*
Total	10,654	101 (0.95)				
Age (years)						
18–29	2,490	14 (0.56)	1.00			
30–49	3,646	37 (1.01)	1.81 (0.98, 3.36)	0.059	1.80 (0.97, 3.35)	0.062
≥50	4,469	49 (1.10)	1.96 (1.08, 3.56)	0.027	1.87 (1.03, 3.42)	0.041
Unknown	49	1 (2.04)	3.69 (0.48, 28.59)	0.211	3.71 (0.45, 29.08)	0.212
Sex						
Male	8,413	79 (0.94)	1.00			
Female	2,177	22 (1.01)	1.08 (0.67, 1.73)	0.760		
Unknown	64	0 (0.00)	–	–		
Ethnicity						
Han	8,872	85 (0.96)	1.00			
Others	1,726	13 (0.75)	0.79 (0.44, 1.41)	0.417		
Unknown	56	3 (5.36)	5.85 (1.79, 19.09)	0.003		
Education						
Junior high school or blew	6,399	64 (1.00)	1.00			
Senior high school	1,626	17 (1.05)	1.05 (0.61, 1.79)	0.870		
College	2,439	18 (0.74)	0.74 (0.44, 1.24)	0.253		
Unknown	190	2 (1.05)	1.05 (0.26, 4.33)	0.943		
Marital status						
Single	3,745	34 (0.91)	1.00			
Married or cohabiting	4,612	50 (1.08)	1.20 (0.77, 1.85)	0.422		
Divorced or widowed	2,186	15 (0.69)	0.75 (0.41, 1.39)	0.364		
Unknown	111	2 (1.80)	2.00 (0.48, 8.44)	0.344		
Risk						
Heterosexual	6,583	64 (0.97)	1.00			
Homosexual	3,654	32 (0.88)	0.90 (0.59, 1.38)	0.628		
IDU	81	0 (0.00)	–	–		
Others	7	0 (0.00)	–	–		
Unknown	329	5 (1.52)	1.57 (0.63, 3.93)	0.334		
Prior ARV exposure						
No	10,468	101 (0.96)	1.00			
Yes	72	0 (0.00)	–	–		
Unknown	114	0 (0.00)	–	–		
CD4 cell count before ART (cell/mm^3)						
<200	1,508	12 (0.80)	1.00			
200–499	7,341	73 (0.99)	1.25 (0.68, 2.31)	0.472		
≥500	1,732	15 (0.87)	1.09 (0.51, 2.33)	0.826		
Unknown	73	1 (1.37)	1.73 (0.22, 13.50)	0.600		
HIV subtype						
CRF07_BC	4,832	44 (0.91)	1.00			
CRF01_AE	2,942	22 (0.75)	0.82 (0.49, 1.37)	0.449	0.84 (0.50, 1.41)	0.510

Continued

Variable	*N*	PDR, *n* (%)	*OR* (95% *CI*)	*P*	a*OR* (95% *CI*)	*P*
CRF08_BC	946	10 (1.06)	1.16 (0.58, 2.32)	0.669	1.10 (0.55, 2.20)	0.799
CRF55_01B	122	0 (0.00)	–	–	–	–
B	321	11 (3.43)	3.86 (1.98, 7.55)	<0.001	3.87 (1.97, 7.58)	<0.001
URF	594	7 (1.18)	1.30 (0.58, 2.89)	0.524	1.33 (0.60, 2.98)	0.481
Others	897	7 (0.78)	0.86 (0.38, 1.91)	0.703	0.87 (0.39, 1.93)	0.723
Diagnosed year						
2018	905	7 (0.77)	1.00			
2022	2,757	26 (0.94)	1.22 (0.53, 2.82)	0.640		
2023	6,992	68 (0.97)	1.26 (0.58, 2.75)	0.562		

Note: *P* values <0.05 were considered statistically significant.
"–" means not available.
Abbreviation: ART=antiretroviral therapy; ARV=antiretroviral drugs; IDU=intravenous drug use; CRF=circulating recombinant form; URFs=unique recombinant forms; HIV=human immunodeficiency virus; *CI*=confidence interval; a*OR*=adjusted odds ratio.
* *P* values were calculated using Pearson's Chi-squared test.

genetic distance threshold of 0.5% substitutions per site, identified 1,257 (26.0%) CRF07_BC sequences forming 432 clusters (size range 2–217) among 4,832 analyzed sequences. Within these clusters, 11 drug-resistant sequences were distributed across 8 clusters, harboring mutations including E138K, Y143H, E157Q, G163R/K/S, and R263K. Notably, Cluster 1 contained two nodes sharing E157Q and G163R mutations, while Cluster 2 comprised three individuals with G163R (Figure 1A). Analysis of 2,942 CRF01_AE sequences revealed 811 (27.6%) sequences forming 335 clusters (size range 2–15), with two drug-resistant strains carrying E138K/A mutations distributed across two clusters (Figure 1B).

DISCUSSION

In China, the PDR to INSTIs was 0.95%, which aligns with previous reports (*10*). This prevalence is marginally higher than surveys from six Chinese PLADs (0.80%) (*11*), Beijing (0.53%) (*6*), and Chongqing (0.71%) (*8*), yet slightly lower than reports from Jiangsu (1.7%) (*7*), Shenzhen (1.77%) (*12*), and Taiwan (2.6%) (*13*). The observed rates are notably lower than those reported in European and American regions, including Italy (1.5%) (*14*), Mediterranean Europe (2.33%) (*15*), Spain (2.5%) (*16*), and Chile (8.0%) (*17*). The higher PDR prevalence in Western countries likely reflects their earlier and more extensive INSTI implementation, exemplified by Chile, where approximately 60% of HIV patients receive INSTI-based therapy (*17*). According to WHO's qualitative classification, China's PDR prevalence of INSTIs remains at a low level.

The predominant DRM sites identified were E138, R263, Y143, T66, N155, G140, Q146, S147, and Q148. E138K/A emerged as the most frequent mutation, representing a non-polymorphic alteration that typically confers high-level resistance to RAL and EVG while inducing intermediate-level resistance to DTG. We also identified eight cases harboring the R263K mutation, a non-polymorphic variant selected in vitro by EVG, DTG, BIC, and CAB, which reduces susceptibility to all INSTIs (*18*). The prevalence of E138 and R263 as the two primary major mutations corresponds with findings from Italian studies (*14*). Among accessory DRMs, we detected G163, S230, H51, S153, E157, and T97. The G163R/K mutation, a non-polymorphic variant primarily selected by RAL, contributes to low-level resistance against first-generation INSTIs. This G163 mutation has also been frequently documented in other regions, including Italy, Ghana, and Chile (*14–19*). Continued surveillance and monitoring remain crucial for tracking the dissemination of resistant strains.

Multivariable analysis revealed that patients with subtype B had 3.87 times greater odds of PDR compared to those with subtype CRF07_BC, consistent with previous findings in China (*14*). This association likely stems from the initial deployment of INSTIs in Europe and the United States, where subtype B predominates. Additionally, individuals aged ≥50 years demonstrated 1.87 times greater odds of PDR compared to those aged 18–29 years. Research has indicated that older populations play a significant role in drug resistance transmission (*21*).

Our construction of subtype-specific molecular transmission networks using *int* sequences of

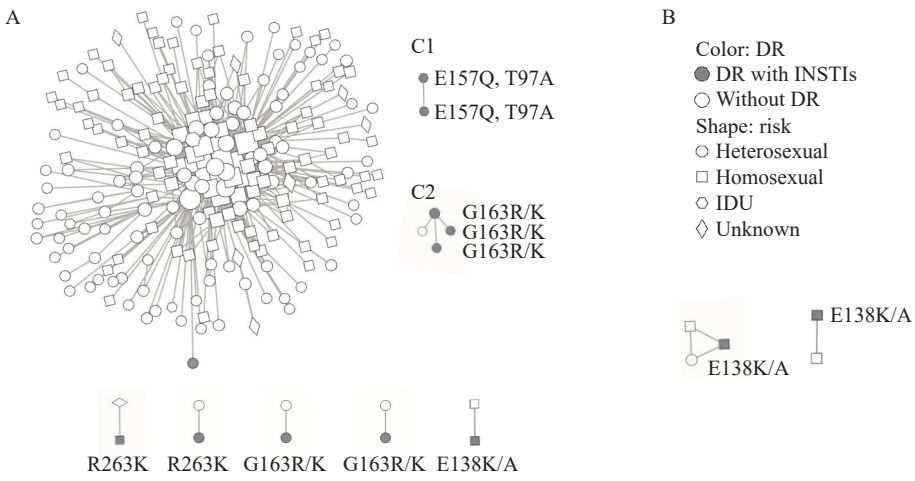

FIGURE 1. Molecular transmission clusters containing pretreatment drug resistance to INSTIs. (A) Resistance mutations identified in HIV-1 subtype CRF07_BC; (B) Resistance mutations identified in HIV-1 subtype CRF01_AE.

CRF07_BC and CRF01_AE revealed notable patterns. Within the CRF07_BC network, we identified two resistance strains in Cluster 1 and three in Cluster 2. Both nodes in Cluster 1 exhibited E157Q and G163R mutations, while all three nodes in Cluster 2 displayed G163R mutations. The presence of identical DRMs within single molecular clusters suggests strong transmission relationships among these HIV-positive individuals, though additional epidemiological investigations are necessary to confirm direct transmission links.

This study has several limitations. First, incomplete information from drug-resistant individuals may have affected the analytical accuracy. Second, the use of Sanger sequencing limited detection to drug-resistant variants present at frequencies above 20%. Additionally, the slower evolutionary rate of the HIV *int* gene compared to the *pol* gene necessitates further methodological evaluation for molecular transmission network construction using integrase sequences.

In conclusion, the prevalence of PDR to INSTIs in China remains low. While INSTIs represent a relatively new and effective class of antiretroviral drugs, patients harboring resistant strains will maintain these mutations indefinitely and potentially transmit them to others, thereby compromising therapeutic efficacy. Given the increasingly widespread use of INSTIs, continuous surveillance of these individuals is essential to provide optimal preventive interventions and therapeutic strategies. Furthermore, achieving the global objective of eliminating AIDS as a public health threat by 2030 requires coordinated national and provincial efforts in regular PDR surveillance.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTARY MATERIALS

SUPPLEMENTARY TABLE S1. Distribution of HIV-positive individuals across 31 PLADs in China, 2018, 2022, and 2023.

PLAD	2023		2022		2018		Total	
	N	Prevalence (%)	*N*	Prevalence (%)	*N*	Prevalence (%)	*N*	Prevalence (%)
Total	6,992	68 (0.97)	2,757	26 (0.94)	905	7 (0.77)	10,654	101 (0.95)
Beijing	195	0 (0)					195	0 (0)
Tianjin	78	0 (0)					78	0 (0)
Hebei	136	2 (1.47)	86	1 (1.16)			222	3 (1.35)
Shanxi	132	3 (2.27)					132	3 (2.27)
Inner Mongolia	124	1 (0.81)					124	1 (0.81)
Liaoning	150	1 (0.67)					150	1 (0.67)
Jilin	123	1 (0.81)	196	5 (2.55)			319	6 (1.88)
Heilongjiang	141	0 (0)			150	1 (0.67)	291	1 (0.34)
Shanghai	143	0 (0)					143	0 (0)
Jiangsu	362	2 (0.55)	341	2 (0.59)			703	4 (0.57)
Zhejiang	231	4 (1.73)	383	3 (0.78)	134	1 (0.75)	748	8 (1.07)
Anhui	230	2 (0.87)					230	2 (0.87)
Fujian	259	1 (0.39)					259	1 (0.39)
Jiangxi	274	5 (1.82)					274	5 (1.82)
Shandong	136	1 (0.74)					136	1 (0.74)
Henan	209	4 (1.91)					209	4 (1.91)
Hubei	126	2 (1.59)	373	3 (0.80)			499	5 (1.00)
Hunan	487	0 (0)			142	0 (0.00)	629	0 (0)
Guangdong	185	1 (0.54)			50	0 (0.00)	235	1 (0.43)
Guangxi	319	2 (0.63)			153	1 (0.65)	472	3 (0.64)
Hainan	67	0 (0)					67	0 (0)
Chongqing	307	6 (1.95)	390	4 (1.03)			697	10 (1.43)
Sichuan	1,111	12 (1.08)	348	4 (1.15)	128	2 (1.56)	1,587	18 (1.13)
Guizhou	357	2 (0.56)					357	2 (0.56)
Yunnan	455	5 (1.10)	377	1 (0.27)	148	2 (1.35)	980	8 (0.82)
Xizang	39	0 (0)					39	0 (0)
Shaanxi	189	4 (2.12)					189	4 (2.12)
Gansu	118	1 (0.85)					118	1 (0.85)
Qinghai	51	1 (1.96)					51	1 (1.96)
Ningxia	64	1 (1.56)					64	1 (1.56)
Xinjiang	194	4 (2.06)	263	3 (1.14)			457	7 (1.53)

Abbreviation: PLAD=provincial-level administrative division.