

## 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  $\geq 50$  years [adjusted odds ratio (aOR)=1.87, 95% confidence interval (CI): 1.03, 3.42] and HIV subtype B (aOR=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  $\geq 18$  years; confirmed HIV-1 diagnosis in 2018, 2022, or 2023; *int* sequence length  $\geq 500$  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 QIAasymphony 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  $\geq 50$  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<sub>4</sub> cell counts between 200–499 cells/mm<sup>3</sup> 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 below                       | 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 <sup>3</sup> ) |      |                |       |                |       |                |        |                |
| <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 (aOR)=3.87, 95% confidence interval (CI): 1.97, 7.58]. Additionally, individuals

aged  $\geq 50$  years showed increased odds of drug resistance compared to those aged 18–29 years (aOR=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     | aOR (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 <sup>3</sup> ) |        |            |                    |       |                    |       |
| <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      | aOR (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; aOR=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



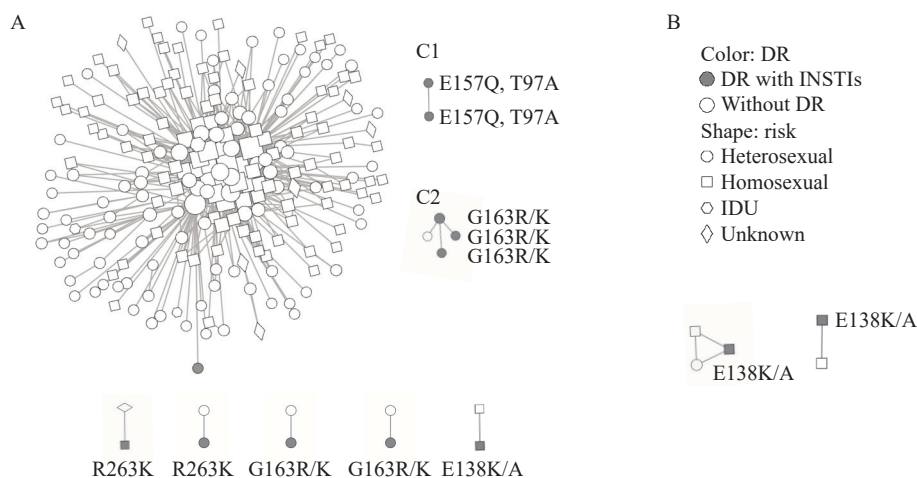


FIGURE 1. Molecular transmission clusters containing pretreatment drug resistance to INSTIs. (A) Resistance mutations identified in HIV-1 subtype CRF07\_BC; (B) Resistance mutations identified in HIV-1 subtype CRF01\_AE.

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.

**Acknowledgments:** The staff members at the provincial Centers for Disease Control and Prevention for their contributions to data collection and laboratory testing.

**Funding:** Supported by the National Key R&D Program of China (2022YFC2305201).

doi: 10.46234/ccdcw2025.007

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Submitted: July 17, 2024

Accepted: January 02, 2025

Issued: January 10, 2025

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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.