Pretreatment integrase strand transfer inhibitor resistance in Tianjin, China

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Human immunodeficiency virus (HIV) infection is a significant and pressing concern for public health worldwide.[1] Midway through the 1990s, the widespread use of antiretroviral therapy (ART) has resulted in a significant paradigm shift in the management of HIV infection, thereby altering its prognosis from a life-threatening disease to a chronic and managed health condition. According to previous studies, people who are living with HIV (PLWH) that are on current ART have shown a decrease in both the morbidity and mortality associated with HIV infection, along with a decreased risk of transmitting the virus to others.[2–5] Integrase strand transfer inhibitors (INSTIs) are the most recent category of ART medications, exhibiting strong potency, high barrier to resistance, minimal drug interactions, and excellent tolerability.[6,7] In 2009, the Chinese Food and Drug Administration (CFDA) authorized raltegravir (RAL) for the first INSTI for the treatment of HIV/acquired immune deficiency syndrome (AIDS), followed by the approval of dolutegravir (DTG), elvitegravir (EVG), bictegravir (BIC), and cabotegravir (CAB) in 2015, 2018, 2019, and 2023, respectively. Since 2018, INSTI-based regimens have been suggested as the preferred first-line ART following the Chinese National Guidelines for HIV/AIDS Diagnosis and Treatment.[8] However, the use of INSTIs is restricted in most regions of the Chinese mainland owing to their high cost. Therefore, >80% of PLWH in China receive free tenofovir/zidovudine + lamivudine + efavirenz under the National Free Antiretroviral Treatment Program (NFATP).[8,9] Since the year 2020, the cost of INSTIs such as EVG, DTG, and BIC has progressively decreased and is currently covered by Chinese medical insurance. Local health insurance in major cities could cover 50–90% of the cost, providing a substantial reimbursement policy; consequently, an increasing proportion of PLWH selected INSTI-based regimens. By the end of 2022, nearly half of the PLWH in Tianjin were on INSTI-containment regimens. There has been a notable rise in the use of INSTIs, leading to the steady emergence of INSTI-related resistance mutations. Limited investigations in China indicated a relatively low level of INSTI resistance among antiretroviral-naïve PLWH in large cities, such as Beijing and Shenzhen.[10,11] However, the prevalence of INSTI resistance among treatment-naïve individuals in Tianjin remains unknown. This study evaluated the prevalence of INSTI-associated drug resistance among ART-naïve individuals infected with HIV-1 in Tianjin, China.

The current study recruited 629 ART-naïve individuals from Tianjin Second People's Hospital between January 1, 2020, and April 1, 2023. The criteria for inclusion in the study were as follows: (1) outpatients at Tianjin Second People's Hospital; (2) HIV-1 seropositive; (3) aged ≥18 years; (4) no prior antiviral treatment; and (5) participants who provided consent and could undergo drug resistance tests. Exclusion criteria were as listed: pregnancy, breastfeeding women, incomplete data, and refusal to give informed consent. Before initiating ART, 5 mL of blood was collected from the participants. Baseline clinical and demographic data were obtained from the NFATP database, including sex, age, transmission route, CD4 count, and viral load. The study was carried out in accordance with the *Declaration of Helsinki* and with the approval of the Tianjin Second People's Hospital's Ethical Committee (No. 2015-13). All subjects participating in the study provided written informed consent.

After RNA extraction, an in-house genotyping method and standard Sanger sequencing were used to amplify and sequence HIV-1 integrase genes, as described previously.[10] HIV-1 subtypes were determined using the REGA HIV-1 Subtyping Tool (version 3.0, https://www.

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genomedetective. com/app/typingtool/hiv). We used the Stanford University HIV Drug Resistance Database (HIVDB Algorithm version 9.4.1) to examine mutations. Sequences with resistance levels classified as low, intermediate, and high were all regarded as resistant.

Statistical analysis was carried out using SPSS (version 26, IBM, Armonk, NY, USA). Mean and standard deviation were used for expressing quantitative data with a normal distribution; median and interquartile range (IQR) were used to express quantitative data with an abnormal distribution. The Fisher's exact test was used to compare categorical variables. All statistical analyses were two-tailed, with $P < 0.05$ defining statistical significance.

Of 629 newly reported cases, the HIV-1 integrase genes of 601 cases were sequenced successfully. The majority of study participants were male (93.0%, 559/601), the median age was 37 (IQR: 31–49) years, and sexual contact was the main transmission route (66.2% [398/601] homosexual and 23.1% [139/601] heterosexual contacts). The baseline median viral load and CD4 count were 55,300 (IQR: 19, 470–163, 692) copies/mL and 417 (IQR: 249–618) cells/μL, respectively. The most predominant HIV-1 subtype was circulating recombinant form (CRF)01_AE (54.1%, 325/601), followed by CRF07_BC (32.1%, 193/601), B (5.0%, 30/601), CRF55_01B (3.7%, 22/601), CRF01_AE/CRF07_BC (1.3%, 8/601), and others (3.8%, 23/601) [Supplementary Table 1, http://links.lww.com/CM9/B781].

Among the 601 cases, 14 (2.33%) cases harbored INSTI resistance mutations, with 2 (0.33%) harboring major mutations and 13 (2.16%) cases having accessory mutations. One sample had both major and accessory mutations [Table 1]. Three major mutations were detected, namely, G140A, Y143H, and Q148R. G140A mutations were non-polymorphic and generally occurred with Q148 mutations. G140A mutations alone had negligible effects on the susceptibility of INSTIs. Nevertheless, the co-occurrence of G140A mutations with Q148 mutations was shown to be linked with high resistance against EVG and RAL, and also intermediately reduced susceptibility to BIC and DTG.[12] Y143H mutations were associated with a high level of RAL resistance and potential low levels of CAB and EVG resistance, but they had no effect on DTG or BIC resistance.[13]

L74M/LIM was the most prevalent accessory mutation (8/14, 57.14%), but it had little effect on INSTI susceptibility.[12] The other accessory mutations included E157Q (2/14, 14.29%), S153A (2/14, 14.29%), and D232N (1/14, 7.14%). S153A and D232N may not reduce INSTI susceptibility,[14] whereas E157Q may induce low-level EVG and RAL resistance.[15]

Two cases developed resistance to INSTIs, with both cases showing RAL resistance at a frequency of 0.33% and one case showing BIC (0.17%), CAB (0.17%), DTG (0.17%), and EVG (0.17%) resistance.

The following HIV-1 subtypes have been identified in the 14 INSTI-resistant variants: CRF01_AE (8/14, 57.1%), CRF07_BC (4/14, 28.6%), CRF68_01B (1/14, 7.1%), and CRF124_cpx (1/14, 7.1%). There were no statistical differences in INSTI resistance among HIV-1 subtypes.

This study revealed three major INSTI-resistant mutations, G140A, Y143H, and Q148R, and four accessory mutations, L74M/LIM, S153A, E157Q, and D232N, in 14 ART-naïve individuals. These mutations were associated with different levels of resistance to the INSTIs. The frequency of INSTI resistance among ART-naïve individuals in Tianjin was 2.33%, which was slightly higher than that in Shenzhen (1.77%), Guangdong (1.49%), and Beijing (0.53%).[10,11,16]

G140A along with Q148 mutation decreases RAL and EVG sensitivity by >100-fold, reduces CAB susceptibility by approximately 10-fold, and reduces DTG and

Table 1: Characteristics of samples detected with resistance mutations.

Sample ID	Year	Gender	Age (years)	Transmission route	CD4 count (cells/μL)	Viral load (copies/mL)	Subtype	IN-related mutations		Level of drug resistance				
								Major	Accessory	BIC	CAB	DTG	EVG	RAL
1	2020	Male	50	Homosexual	463	7962	CRF01_AE	–	L74M	S	S	S	S	S
2	2020	Male	28	Homosexual	916	47,174	CRF01_AE	Y143H		S	P	S	P	H
3	2020	Male	33	Homosexual	360	79,000	CRF01_AE	–	L74M	S	S	S	S	S
4	2020	Male	27	Homosexual	510	30,000	CRF07_BC	–	L74M	S	S	S	S	S
5	2020	Male	33	Homosexual	869	2970	CRF01_AE	–	L74M	S	S	S	S	S
6	2020	Male	31	Homosexual	548	45,000	CRF07_BC	–	E157Q	S	S	S	P	P
7	2021	Male	32	Homosexual	717	1,720,000	CRF68_01B	–	L74M	S	S	S	S	S
8	2021	Male	25	Homosexual	545	32,600	CRF01_AE	–	S153A	S	S	S	S	S
9	2022	Male	67	Unknown	237	105,000	CRF124_cpx	–	L74M	S	S	S	S	S
10	2022	Male	59	Homosexual	318	153,000	CRF07_BC	–	E157Q	S	S	S	P	P
11	2022	Male	56	Heterosexual	123	17,300	CRF07_BC	–	L74M	S	S	S	S	S
12	2022	Male	44	Heterosexual	838	13,800	CRF01_AE	–	S153A	S	S	S	S	S
13	2023	Male	59	Homosexual	463	184,000	CRF01_AE	–	L74LIM	S	S	S	S	S
14	2023	Male	59	Homosexual	7	153,000	CRF01_AE	G140A, Q148R	D232N	I	H	I	H	H

BIC: Bictegravir; CAB: Cabotegravir; CRF: Circulating recombinant form; DTG: Dolutegravir; EVG: Elvitegravir; H: High-level resistance; I: Intermediate-level resistance; IN: Integrase; L: Low-level resistance; P: Potential low-level resistance; RAL: Raltegravir; S: Susceptible; –: Not available.

BIC susceptibility by approximately 2-fold to 5-fold.[17] The rare mutation Y143H may be a transitional mutation between the 2-bp mutation R and wild-type Y, which decreases RAL susceptibility by ~3-fold to 20-fold.[12] The accessory mutations identified in our study, namely, L74M/LIM, S153A, and D232N, do not lower INSTI susceptibility on their own. E157Q was associated with potential low-level of EVG and RAL resistance, but it had no influence on INSTI therapeutic response.[15]

Since 2020, EVG, BIC, and DTG have been the most commonly used INSTIs for ART in Tianjin, whereas RAL is used by an extremely small proportion of ART-treated patients. According to our findings, even though there are signs of resistance to INSTIs, the frequency of resistance to INSTIs remains lower than that to other antiretroviral drug classes,[18] indicating that INSTIs are the preferred treatment option in Tianjin. In our study, one sample exhibited high-level CAB resistance. CAB, which was recently approved by the CFDA as the first long-acting drug, is possibly used more frequently for pre-exposure prophylaxis and treatment. Hence, when CAB becomes available in China in the future, it is critical to be alert against the emergence of resistance.

In conclusion, Tianjin has a low prevalence of INSTI resistance, indicating that INSTIs are well-applicable. The selection of treatment regimens should be based on the specific pattern of regional drug resistance. Despite the low prevalence of major INSTI mutations, owing to the widespread use of first- and second-generation INSTIs, it is critical to maintain cautious monitoring of INSTI drug resistance mutations.

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Conflicts of interest

None.

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