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Trend and prevalence of transmitted drug resistance (TDR) to integrase-strand transfer inhibitors (INSTIs) and drug resistance mutations (DRMs) among HIV-1 patients in China: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 March 2025 and was last updated on 26 March 2025.

INTRODUCTION

Review question / Objective To systematically review literature and synthesize evidence on INSTI TDR among INSTI-naive HIV-1 patients in China. The specific aims are to estimate the pooled prevalence along with 95% confidence intervals (Cis), quantify temporal trends and geographical variations, and characterize the frequency and distribution of specific DRMs within this population.

Rationale Drug resistance remains a critical challenge to the effectiveness of ART, with increasing reports of resistance to INSTI worldwide following their widespread use. Although INSTIs have become a cornerstone of HIV treatment programs in China, current understanding of resistance patterns remains limited by fragmented data from studies using different methodologies, populations, and time periods. Key knowledge gaps remain, including the prevalence of resistance among treatment-naive patients (with both temporal and geographical variation), the distribution of major and minor drug resistance mutations (DRMs), and the characteristics and transmission patterns of TDR. Conducting a systematic review and meta-analysis could address these limitations by synthesizing existing evidence, yielding more precise estimates of resistance prevalence, mapping the distribution of DRMs, and elucidating TDR transmission dynamics. Such insights would provide a robust foundation for refining treatment guidelines and strengthening resistance monitoring strategies within China's HIV programs.

Condition being studied This systematic review examines transmitted drug resistance (TDR) to HIV Integrase Strand Transfer Inhibitors (INSTIs) in China. HIV infection is a chronic viral disease affecting approximately 39.9 million people globally and over 1 million individuals in China. INSTIs have become cornerstone antiretroviral medications since their introduction to China: raltegravir (2009), dolutegravir (2016), elvitegravir (2018), and bictegravir (2020).
Transmitted drug resistance specifically refers to resistance-associated mutations present in treatment-naïve HIV patients who have acquired

resistant viral strains through transmission, rather than developing resistance during treatment. This distinction is crucial as TDR can compromise first-line therapy efficacy before treatment initiation.

Initial surveillance studies from different Chinese provinces have identified INSTI transmitted drug resistance rates ranging from 0.62% to 3.82% among treatment-naïve patients. Key resistance-associated mutations include G140S, Q148H/R/K, and N155H. However, the national prevalence, regional distribution patterns, temporal trends, and specific mutation profiles of INSTI TDR across China remain incompletely characterized.

This study systematically documents the prevalence and patterns of transmitted INSTI resistance in treatment-naïve individuals in China to inform national treatment guidelines and resistance monitoring strategies.

METHODS

Search strategy

PubMed

#1 (((((((("integrase strand transfer inhibitors"[Title/Abstract]) OR ("integrase inhibitor"[Title/Abstract])) OR ("raltegravir"[Title/Abstract])) OR ("elvitegravir"[Title/Abstract])) OR ("dolutegravir"[Title/Abstract]))) OR (bictegravir[Title/Abstract])) OR (cabotegravir[Title/Abstract])) OR (integrase inhibitors[MeSH Terms]) 6749

#2 (resistance[Title/Abstract]) OR (safety[Title/Abstract]) OR (efficacy[Title/Abstract]) 2575297

#3 #1 AND #2

#4 (China[Title/Abstract]) OR (china[MeSH Terms])

#5 #3 AND #4.

Participant or population INSTI-naïve patients with HIV-1 in China.

Intervention Not applicable.

Comparator Not applicatble; historically comparison may be used to assess trends in INSTI TDR.

Study designs to be included Randomized controlled trial (RCT), cohort study, and cross sectional study.

Eligibility criteria Studies will be excluded if they: (1) involve INSTI-experienced patients, regardless of viral suppression or failure status; (2) were conducted outside of China; (3) are not available in English or Chinese; or (4) are targeted literature reviews, study protocols, letters to the editor, personal opinions or commentaries, clinical practice guidelines, ethnographic studies, surveys, conference abstracts and proceedings, case reports, or case series.

Information sources The systematic review will be conducted in accordance with the PRISMA 2020 statement for reporting systematic reviews. A comprehensive search will be performed across three English-language electronic databases (Medline, Excerpta Medica database (EMBASE), Cochrane Library), as well as two Chinese-language database (China National Knowledge Infrastructure (CNKI) and Wanfang). This search will include both Chinese and English literature published from the inception of the databases until 2025.

Main outcome(s)

Primary outcome:

Overall prevalence of INSTI TDR in INSTI-naïve HIV-1 patients

Secondary outcomes:

Stratified prevalence of INSTI TDR by geographic regions, sampling time periods, HIV-1 subtypes, or levels of resistance (potential/low/intermediate/high)

Characteristics and distribution of DRMs including prevalence of individual DRMs, distribution of resistance levels associated with each DRM, or patterns and frequencies of DRM combinations.

Quality assessment / Risk of bias analysis The methodological quality of the included studies will be assessed using appropriate, design-specific tools. For cohort studies, the Newcastle-Ottawa Scale (NOS) will be applied, which classifies studies as high quality (score ≥7), moderate quality (score 4-6), or low quality (score <4). For cross-sectional studies, the JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies will be employed, which consists of eight items to evaluate methodology, analysis, and potential bias. For RCTs, the Cochrane Risk-of-Bias tool 2.0 (RoB 2) will be adopted, in which reviewers examine five distinct domains of bias in response to one or more signaling questions, leading to a judgments of "low risk of bias," "some concerns," or "high risk of bias."

Strategy of data synthesis For the meta-analysis of INSTI TDR prevalence, prevalence estimates and corresponding 95% confidence intervals will be calculated using the number of resistant cases and total cases reported in each study. To stabilize the variance, the Freeman-Tukey double arcsine transformation will be applied. Considering potential clinical and methodological heterogeneity across studies, a random-effects model will be employed using the DerSimonian-Laird method.

Heterogeneity will be assessed using Cochran's Q test and the I^2statistic.

To evaluate the temporal trend of INSTI TDR prevalence, a GAM will be implemented with a Gaussian distribution and identity link function. Smooth spline functions will be incorporated to capture non-linear temporal variations in resistance rates, with parameters estimated using the Restricted Maximum Likelihood (REML) method. Study sample sizes will be included as weights to reflect the relative contribution of each studies. The significance of temporal trends will be evaluated using F-tests for smooth terms, while model goodness-of-fit will be assessed through adjusted R^2 values and the percentage of deviance explained.

All analyses will be performed using R software version 4.2.0, with meta-analyses conducted using the 'meta' package and temporal trend analyses implemented through the 'mgcv' package. All statistical tests are two-sided, with a significant level of $P < 0.05$.

Subgroup analysis Subgroup analyses will be conducted to explore potential sources of heterogeneity. These analyses will focus on pre-specified study-level characteristics, including sampling time (before 2020 vs. 2020 and after), geographical region (North China, South China, East China, and Central China), sample size (≤500 vs. >500), and study quality scores (low/moderate vs. high risk of bias). The geographical regions are initially based on China's official Administrative Division Regulations (https://www.gov.cn/zhengce/content/2018-11/01/content_5336379.htm), which defines seven traditional regions: East China (Shanghai, Jiangsu, Zhejiang, Anhui, Jiangxi, Shandong, Fujian); North China (Beijing, Tianjin, Shanxi, Hebei, central Inner Mongolia); Central China (Henan, Hubei, Hunan); South China (Guangdong, Guangxi, Hainan); Southwest China (Chongqing, Sichuan, Guizhou, Yunnan, Tibet); Northwest China (Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang, western Inner Mongolia); and Northeast China (Heilongjiang, Jilin, Liaoning, eastern Inner Mongolia). Based on these official divisions, we further grouped these seven regions into four larger geographical areas according to their geographical proximity: South China (including South and Southwest regions), North China (including North, Northwest, and Northeast regions), East China (including East region), and Central China (including Central region). The year 2020 was selected as the temporal division point for subgroup analysis based on our preliminary literature search, which indicated that most included studies were conducted between 2018 and 2022. This time point represents the median of our study period, effectively dividing the timeframe into two comparable segments with balanced sample distribution.

When substantial heterogeneity is detected ($I^2 > 50\%$), meta-regression analyses will be performed. These analyses will assess the relative reduction in τ^2 $[(\tau^2\text{initial} - \tau^2\text{model})/\tau^2\text{initial} \times 100\%]$ and the adjusted R^2 statistic to determine the extent to which study characteristics—such as sampling time, geographical region, sample size, study quality scores, and mean patient age—contribute to the observed heterogeneity, thereby identifying sources of variation in TDR prevalence. As this is a prevalence meta-analysis without control groups, baseline risk adjustment is not applicable to the meta-regression analyses. To maximize data utilization while maintaining independence, studies containing multiple subgroups (e.g., different regions or time periods) will be treated as separate studies in both subgroup and meta-regression analyses.

Sensitivity analysis To assess the robustness of our meta-analysis results, sensitivity analyses will be conducted. We will perform leave-one-out analyses by iteratively excluding one study at a time and recalculating the pooled prevalence to identify influential studies and evaluate result stability. We will also conduct analyses excluding studies with specific characteristics that might affect the reliability of the results: (1) studies with sample size less than 200; and (2) studies with high risk of bias. For all sensitivity analyses, we will examine changes in the point estimates, confidence intervals, and heterogeneity statistics ($I^2$and τ^2) to evaluate the robustness of our primary findings. Substantial changes in these parameters will be documented and discussed in terms of their implications for the reliability of our conclusions.

Language restriction English and Chinese.

Country(ies) involved China.

Keywords HIV; INSTI; transmitted drug resistance; prevalence; China; resistance mutations; treatment-naïve; systematic review; meta-analysis.

Contributions of each author

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