Original Article

The Prevalence of HIV Drug Resistance among Treatment-failure Individuals and Treatment-naïve Individuals in China: A Meta-analysis*

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Abstract

Objective To understand drug resistance prevalence among treatment-failure and treatment-naïve HIV-positive individuals in China.

Methods We searched five electronic databases (Wanfang, CNKI, CQVIP, SinoMed, and Pubmed) for studies of HIV drug resistance. Random-effects models were carried out to estimate the prevalence of drug resistance among treatment-failure and treatment-naïve individuals, respectively.

Results The estimated nationwide rates of HIV drug resistance to any-class drugs among treatment-failure and treatment-naïve individuals were 57% (95% CI: 49%-65%) and 3.23% (95% CI: 2.47%-4.07%), respectively. Among the drug classes, the prevalence of resistance to PIs was low (1.45%; 95% CI: 0.73%-2.33%) in treatment-failure individuals, although high rates of resistance to NNRTIs (54%; 95% CI: 45%-63%) and NRTIs (40%; 95% CI: 32%-49%) were found. Resistance to any-class drugs, NNRTIs and NRTIs manifested regional differences, but resistance to PIs did not. Positive correlations were observed between resistance to NNRTIs and NRTIs among treatment-failure and treatment-naïve individuals, respectively.

Conclusion The prevalence of HIV drug resistance to NNRTIs and NRTIs among treatment-failure individuals was high. In contrast, the prevalence of drug resistance among treatment-naïve individuals was low. The epidemics of drug resistance matched current treatment strategies and interventions in China. Surveillance for HIV drug resistance is necessary to assess the sustainability and durability of current treatment regimens.

Key words: HIV; Drug resistance; Meta-analysis; China

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INTRODUCTION

China's free antiretroviral therapy (ART) program, based on both the 2002 pilot program in Henan province and the 2003 'Four Frees and One Care' policy, has been scaled up to provide nationwide coverage[1]. Up to September 2011, 108,697 HIV-positive people were on treatment in China, including 12,794 people on second-line regimens[2]. The scale-up of antiretroviral drugs increased CD4 cell counts[3-5], decreased viral load[3-5], mortality[6-8], and HIV transmission[9-11]. However, the therapeutic and preventive effects of ART have decreased over the

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duration of treatment in China[7,11]. HIV drug resistance was found to be one reason for treatment failure and led to higher mortality[12-13] because it reduced the viruses' susceptibility to ART. The resulting problems from drug resistance have reduced available options in ART for HIV-positive people[14]. Because available HIV treatment choices in China are limited, though still free, continuous monitoring of HIV drug resistance is beneficial to policy development and treatment implementation.

Currently the standardized first- and second-line regimens in China are tenofovir/zidovudine+lamivudine+efavirenz/nevirapine (TDF/AZT+3TC+EFV/NVP), and TDF/AZT+3TC+Kaletra (LPV/r, including lopinavir, and ritonavir), respectively. Three classes of ART are commonly used in China, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). A previous meta-analysis showed that the resistance rate to NNRTIs at treatment failure (defined as viral load ≥1000 copies/mL), when measured at intervals of three months or less, was lower than the rate measured at longer intervals or under no surveillance. Also, there was no difference in resistance rates between the latter two[15]. Currently the HIV drug resistance monitoring interval for people on treatment is six months, and there is no resistance testing while initiating ART in China. Moreover, the same first-line regimen in China is presently being used to treat the majority of HIV-positive individuals[2]. Thus it is important to understand drug resistance to the three main classes of ART, in order to direct ART choices further in clinical settings and guide new ART developments or imports. Here we conducted a pooled analysis to examine the genotype drug resistance among treatment-naïve people and people in a subset of treatment failure, respectively.

METHODS

Search Strategy

We performed and reported the meta-analysis following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) items in PLoS Medicine[16] (Checklist S1). In October 2013, we searched the following online electronic databases: Wanfang data, Chinese National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Fulltext Database (CQVIP), Chinese Biomedical Literature Service System (SinoMed), and Pubmed. Text terms and medical subject headings (MeSH) terms used in the database search in both English and Chinese included: ('HIV' or 'AIDS' or 'human immunodeficiency virus' or 'acquired immune deficiency syndrome') and ('drug resistance' or 'resistance' or 'resistant' or 'mutation' or 'treatment failure' or 'virological failure' or 'immunological failure') and ('China').

Outcomes of Interest

We sought HIV drug resistance rates among treatment-failure patients and treatment-naïve patients. Only the resistances to NRTIs, NNRTIs, and PIs were analyzed because these three classes of antiretroviral drugs are currently provided freely and used widely in China. In this meta-analysis, drug resistance referred to viral mutation results that conferred high-, intermediate-, or low-level resistance. Treatment failure was defined as viral load at or more than 1000 copies/mL.

Study Selection

Studies were chosen for further analysis if they met the following criteria: conducted in mainland China; genotype drug resistance testing conducted by an in-house polymerase chain reaction protocol; reported the number of successful sequences which were equal to or greater than 20 and the number of drug-resistant patients; and reported the study sites and study periods. We excluded review papers and papers whose subjects were all HIV-positive children. However, studies with small proportions of mother-to-child transmission were included in this analysis. If the same study data were published in multiple publications, the most comprehensive articles or the articles providing more drug resistance data were included. We adopted the baseline data and/or the endpoint data of cohort studies in this study. We contacted authors to confirm the definition of drug resistance, the definition of treatment failure, drug resistance data, the study period, etc.

Data Extraction

We abstracted the following information for each article: first author, year of publication, study title, publication, study site, study period, language, transmission route, study design, mean/median/ range of age, the number of people with successful sequences, and drug resistance to any-class drugs, to

single-class drugs (NNRTIs, NRTIs, or PIs). Further information was included if the eligible articles provided the HIV drug resistance rate among treatment-failure individuals, e.g. The number of people at treatment failure, mean/median/range of treatment duration, mean/median CD4 cell counts, and $\log_{10}$ viral load, drug resistance to dual-class drugs (any two of the above classes), and to triple-class drugs (three of the above classes). Two reviewers independently assessed the title, abstract, full-text, and the extracted information, and a third reviewer settled any disagreement.

Validity Assessment

The studies were considered as higher quality if they met the following criteria: (1) clear definition of the targeted population; (2) probability sampling method; (3) the characteristics of the respondents matching the target population; (4) the rate of successful sequences ≥80%; (5) standardized data collection methods; (6) reliable survey instruments and drug resistance testing; (7) valid survey instruments and drug resistance testing; (8) appropriate statistical methods.

Statistical Analyses

All statistical analyses were conducted using META Package and STATS Package of R version 3.0.1 (R foundation for statistical computing, Vienna, Austria), metaprop, metabias, and cor functions were chosen for analyses. A Freeman-Tukey double arcsine transformation was chosen to calculate the pooled prevalence of HIV drug resistance and to minimize the variances of drug resistance rates across the eligible studies. The pooled drug resistance prevalence and 95% confidence intervals (CI) were calculated by random-effects models. Heterogeneity was tested by *Q*-test (P<0.10 represented statistical significance) and I^2 statistics (25%, 50%, 75% represented low, medium and high heterogeneity, respectively). Publication bias to assess funnel plot asymmetry was measured by the linear regression method (P<0.05 represents statistical significance). Stratified analyses were performed to find the variance source if the pooled rates of drug resistance prevalence had statistically significant heterogeneity and the number of studies was equal to or greater than 10. Spearman correlations were conducted to assess the relationships between rates of drug resistance to different classes of drugs in China. We reported the prevalence of total drug resistance to any-class drugs, and the prevalence of drug resistance to NRTIs, NNRTIs, and PIs among both treatment-failure and treatment-naïve HIV-positive individuals. In addition, the prevalence of drug resistance to NRTIs & NNRTIs, NRTIs & PIs, NNRTIs & PIs, NRTIs & NNRTIs & PIs was reported among treatment-failure HIV-infected individuals.

RESULTS

Flow and Characteristics of the Eligible Studies

We identified 1494 records from 5 electronic databases according to our search strategy. Finally, 101 studies from 93 articles were included in this meta-analysis after we deleted duplicate articles and screened abstract, title and full-text following inclusion and exclusion criteria (Figure 1). Twenty-three articles (composed of 23 studies) provided HIV drug resistance information from treatment-failure individuals, and 72 articles (composed of 78 studies) provided drug resistance information from treatment-naïve individuals. Two articles provided drug resistance information from both treatment-failure individuals and treatment-naïve individuals.

A total of 23 studies[17-39] (2 in English and 21 in Chinese) reported HIV drug resistance information of ART-failure individuals (Table S1). The median number of successful sequences was 75 with a range from 25 to 515 (IQR: 126), and the rates of successful sequences ranged from 48% to 100% (median: 93%; IQR: 24%). All specimens were collected from 2005 to 2012, and studies were issued between 2007 and 2013. The eligible studies covered 11 provinces (Anhui, Fujian, Hebei, Hunan, Jiangsu, Sichuan, Xinjiang, Yunnan, Zhejiang, Shandong, and Guangxi) out of 31 provinces in China, and about one-third of the studies (7 studies) were conducted in Henan province, where ART was initiated the earliest in China[1]. Mean/median ages of the subjects were available from 12 studies and ranged from 35 to 51. Twelve of the 23 studies provided median/mean treatment periods with a range from 12 to 30 months. The proportions of treatment failure ranged from 8% to 64% (median: 20%; IQR: 22%) in 20 studies (20/23).

A total of 78 studies[38-109] (25 in English and 53 in Chinese) reported HIV drug resistance information of treatment-naïve individuals (Table S2). The number of successful protease gene sequences ranged from 12 to 627 (median: 50; IQR: 52.5), and the number of successful reverse transcriptase gene

sequences ranged from 21 to 627 (median: 50; IQR: 52.5). Also, sixty-three studies reported the rates of successful sequences with a range from 51% to 100% (median: 83%; IQR: 19%) at protease region and from 51% to 100% (median: 84%; IQR: 18%) at reverse transcriptase region. Specimens collection periods ranged from the years 1999 to 2012, and studies were published between 2004 and 2013. Seventy-six studies (except for two nationwide studies[76,90]) were conducted in 22 out of 31 provinces in China with a range from 1 to 11 studies in each province, and there were no appropriate studies included in this article for estimating the pooled drug resistance among treatment-naïve people in the following provinces: Gansu, Hebei, Inner Mongolia, Jiangxi, Jilin, Qinghai, Shaanxi, Shanxi, and Tibet. Three-fifths of the 76 studies were carried out in Guangdong (11 studies), Yunnan (10 studies), Zhejiang (7 studies), Henan (7 studies), Guangxi (6 studies), and Beijing (5 studies). Thirty-three studies reported mean/median ages of the participants with a range from 21 to 45.

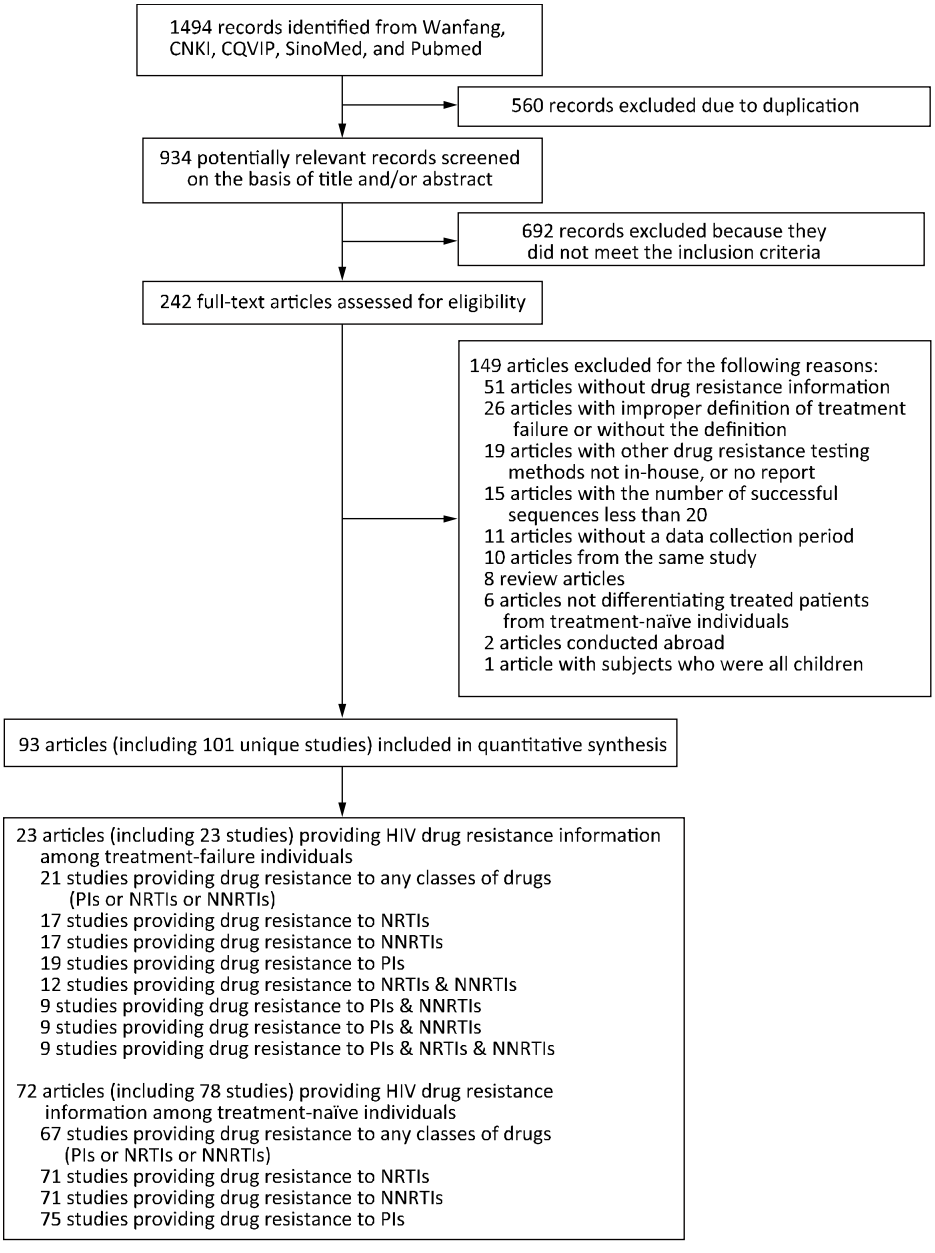

Figure 1. Flow Diagram of the Study Identification and Selection.

The Estimated Prevalence of HIV Drug Resistance in China

The total pooled prevalence of resistance to any-class drugs among ART-failure individuals in China was 57% (95% CI: 49%-65%) (Table 1), which was significantly higher than the estimated prevalence of drug resistance to NRTIs (40%; 95% CI: 32%-49%) or PIs (1.45%; 95% CI: 0.73%-2.33%) among ART-failure HIV cases. However, it didn't show any difference with the NNRTIs resistance rate (54%; 95% CI: 45%-63%). The pooled prevalence of drug resistance to NRTIs & NNRTIs (35%; 95% CI: 24%-46%) was significantly higher than the prevalence of resistance to other multiple-class drugs. However, there were no significant differences among the pooled rates of drug resistance to PIs & NNRTIs (0.69%; 95% CI: 0.14%-1.50%), PIs & NRTIs (0.65%; 95% CI: 0.16%-1.36%), or PIs & NRTIs & NNRTIs (0.64%; 95% CI: 0.12%-1.44%). Significantly high heterogeneity was found in the total prevalence of drug resistance (I^2: 94%; *Q*-test *P*=0), and in the prevalence of drug resistance to NNRTIs (I^2: 94%; *Q*-test *P*=0), NRTIs (I^2: 94%; *Q*-test *P*=0), NRTIs & NNRTIs (I^2: 95%; *Q*-test *P*=0). Low heterogeneity was shown in HIV resistance prevalence to PIs (I^2: 40%; *Q*-test *P*=0.04). No publication bias was reported in this meta-analysis (*P*>0.1) (Table 1).

The total estimated prevalence of HIV drug resistance to any-class drugs among treatment-naïve individuals in China was 3.23% (95% CI: 2.47%-4.07%) (Table 1). There were no statistically significant differences among drug resistance to NNRTIs (1.03%; 95% CI: 0.62%-1.52%), NRTIs (0.84%; 95% CI: 0.51%-1.22%), or PIs (0.64%; 95% CI: 0.33%-1.02%). Results showed low to moderate heterogeneity, with statistical significance among the pooled prevalence of HIV drug resistance to any drugs (I^2: 51%; *Q*-test *P*=0), NNRTIs (I^2: 42%; *Q*-test *P*=0), NRTIs (I^2: 22%; *Q*-test *P*=0.06), or PIs (I^2: 31%; *Q*-test *P*=0.01) among treatment-naïve individuals. Publication bias was observed in the rate of drug resistance to NRTIs among treatment-naïve people (*P*=0.02), but no bias was presented in the total rate of drug resistance (*P*=0.22), or the rates of drug resistance to NNRTIs (*P*=0.13), or PIs (*P*=0.47) (Table 1).

Regional Differences in Pooled HIV Drug Resistance Prevalence in China

Sub-group analyses results showed that regional differences appeared in whether HIV drug resistance in ART-failure or pre-ART HIV cases (Table 2). Henan showed higher prevalence than other provinces in drug resistance to any-class drugs (71% *vs*. 50%), NNRTIs (68% *vs*. 46%), and NRTIs (51% *vs*. 34%) among ART-failure patients. In North China and Central China there were significantly higher pooled

Table 1. The Pooled Prevalence of HIV Drug Resistance in China

Variables	Studies, No.	Successful Sequences, No.	DR, No.	Prevalence and 95% CI (%)	Heterogeneity		*P* Value of Publication Bias
					I^2 (%)	*P* value	
DR among ART-failure individuals							
DR to PIs or NRTIs or NNRTIs	21	2638	1571	57.29 (49.30-65.11)	93.50	0	0.51
DR to NNRTIs	17	2283	1270	53.80 (44.99-62.50)	93.90	0	0.68
DR to NRTIs	17	2283	973	40.06 (31.63-48.80)	93.80	0	0.73
DR to PIs	19	2391	51	1.45 (0.73-2.33)	39.70	0.04	0.93
DR to NRTIs & NNRTIs	12	1716	667	34.72 (24.08-46.17)	95.20	0	0.66
DR to PIs & NNRTIs	9	1339	18	0.69 (0.14-1.50)	18.70	0.28	0.51
DR to PIs & NRTIs	9	1339	17	0.65 (0.16-1.36)	7.00	0.38	0.18
DR to PIs & NRTIs & NNRTIs	9	1341	17	0.64 (0.12-1.44)	18.00	0.28	0.59
DR among treatment-naïve individuals							
DR to PIs or NRTIs or NNRTIs	67	5687	226	3.23 (2.47-4.07)	50.70	0	0.22
DR to NNRTIs	71	6148	108	1.03 (0.62-1.52)	41.50	0	0.13
DR to NRTIs	71	6148	88	0.84 (0.51-1.22)	21.50	0.06	0.02
DR to PIs	75	6285	90	0.64 (0.33-1.02)	30.70	0.01	0.47

Note. DR means drug resistance.

Table 2. The Pooled Prevalence of HIV Drug Resistance Stratified by Regions in China

Variables	Studies, No.	Successful Sequences, No.	DR, No.	Prevalence and 95% CI (%)	I^2 (%)	Q_B	*P* Value
DR among ART-failure individuals							
DR to PIs or NRTIs or NNRTIs						15.67	0
Henan	7	1202	893	71.06 (63.66-77.94)	85.4		
Other	13	1164	555	50.21 (42.99-57.42)	78.5		
DR to NNRTIs						12.01	0
Henan	6	930	669	67.66 (58.23-76.43)	87.5		
Other	10	1081	486	46.46 (39.20-53.79)	77.4		
DR to NRTIs						4.77	0.03
Henan	6	930	530	50.56 (39.65-61.45)	90.2		
Other	10	1081	347	34.45 (25.58-43.88)	87.4		
DR to PIs						2.78	0.1
Henan	6	930	13	0.88 (0.18-1.93)	26.5		
Other	12	1189	32	1.97 (0.79-3.53)	41.4		
DR among treatment-naïve individuals							
DR to PIs or NRTIs or NNRTIs						15.28	0.02
North	5	341	27	7.00 (2.79-12.67)	61.8		
East	14	692	27	3.01 (1.49-4.93)	25		
Central	8	564	41	6.61 (4.14-9.55)	32.1		
Northwest	4	147	4	1.94 (0-6.05)	17.4		
South	16	1456	46	2.81 (1.55-4.37)	52.4		
Southwest	15	1085	28	1.63 (0.54-3.11)	41		
Northeast	3	286	12	3.88 (1.76-6.64)	0		
DR to NNRTIs						23.17	0
North	7	442	16	2.54 (0.29-6.27)	66.7		
East	15	877	14	0.81 (0.13-1.88)	21.4		
Central	9	679	33	4.18 (2.27-6.54)	38.4		
Northwest	3	122	2	0.97 (0-4.27)	0		
South	15	1293	13	0.51 (0.10-1.12)	0		
Southwest	14	1060	16	0.67 (0.10-1.57)	7		
Northeast	5	421	1	0.03 (0-0.78)	0		
DR to NRTIs						16.58	0.01
North	7	442	9	1.28 (0.05-3.49)	42.8		
East	15	877	17	1.23 (0.45-2.26)	0		
Central	9	679	22	2.59 (1.05-4.63)	40.8		
Northwest	3	122	3	1.73 (0-7.31)	37.2		
South	15	1293	17	0.82 (0.29-1.53)	0		
Southwest	14	1060	4	0.03 (0-0.41)	0		
Northeast	5	421	4	0.57 (0-1.80)	0		
DR to PIs						11.86	0.07
North	7	441	11	1.74 (0.44-3.61)	14		
East	15	868	14	0.97 (0.28-1.94)	0		
Central	10	715	6	0.40 (0-1.23)	0		
Northwest	4	147	0	0 (0-1.11)	0		
South	16	1325	13	0.41 (0-1.26)	41.5		
Southwest	15	1085	8	0.14 (0-0.66)	0		
Northeast	5	424	14	2.38 (0.69-4.80)	27.6		

Note. DR means drug resistance; Regional divisions are based on the website of the Area Division Department, China Ministry of Civil Affairs (http://www.xzqh.org.cn/). North China: Beijing, Hebei, Inner Mongolia, Shanxi, Tianjin; East China: Anhui, Fujian, Jiangsu, Jiangxi, Shanghai, Shandong, Zhejiang; Central China: Henan, Hubei, Hunan; Northwest China: Gansu, Qinghai, Ningxia, Shaanxi, Xinjiang; South China: Guangdong, Guangxi, Hainan; Southwest China: Chongqing, Guizhou, Sichuan, Tibet, Yunnan; Northeast China: Heilongjiang, Jilin, Liaoning.

prevalence in drug resistance to any-class drugs (7.00% in North China; 6.61% in Central China), NNRTIs (2.54% in North China; 4.18% in Central China), NRTIs (1.28% in North China; 2.59% in Central China) among pre-ART HIV-infected individuals, compared to other Chinese regions. Beijing was the leading contributor to the pooled prevalence of drug resistance in North China among treatment-naïve people, as was Henan to the estimated prevalence in Central China. However, no significant regional difference was discovered in drug resistance to PIs among ART-failure or pre-ART HIV cases (Q_B test *P*: 0.10; 0.07).

Differences in Treatment Periods for HIV Drug Resistance Prevalence among Treatment-failure Individuals in China

Significant increasing trends were observed in HIV drug resistance to any-class drugs (Q_B test *P*=0), NNRTIs (Q_B test *P*=0), and NRTIs (Q_B test *P*=0) among treatment-failure HIV cases according to treatment duration. Prevalence was ranked from low to high in the following order: patients treated for less than two years on average, no information on treatment duration, and patients treated for two years or more on average (any drugs: 35% *vs*. 53% *vs*. 73%; NNRTIs: 33% *vs*. 50% *vs*. 71%; NRTIs: 15% *vs*. 39% *vs*. 59%). Sub-group analysis by treatment periods did not show any significant difference in the prevalence of drug resistance to PIs (Q_B test *P*=0.99) in ART-failure individuals.

Correlations between Different Rates of HIV Drug Resistance Prevalence in China

A significant positive correlation between the rates of HIV drug resistance to NRTIs and NNRTIs was observed among treatment-failure cases at the national level (*r*=0.94, *P*=0) (Figure 2). Significant correlations between drug resistance prevalence to NRTIs and NNRTIs were also found among treatment-failure HIV cases in Henan and other provinces (*r*=0.94, *P*=0.02; *r*=0.88, *P*=0, respectively). In addition, the prevalence of drug resistance to PIs was significantly positively correlated with the prevalence to NNRTIs among treatment-failure HIV patients in Henan and other provinces (*r*=0.88, *P*=0.02; *r*=0.74, *P*=0.01, respectively).

Results showed that the countrywide prevalence of drug resistance to NRTIs had a significantly positive correlation with the prevalence to NNRTIs among treatment-naïve HIV cases (*r*=0.41, *P*=0), and significant positive correlation was also observed in North China (*r*=0.81, *P*=0.05).

DISCUSSION

This is the first meta-analysis to address HIV drug resistance prevalence among both treatment-

Table 3. The Pooled Prevalence of HIV Drug Resistance Stratified by Treatment Period among Treatment-failure Individuals in China

Variables	Studies, No.	Successful Sequences, No.	DR, No.	Prevalence and 95% CI (%)	I^2 (%)	Q_B	*P* Value
DR to PIs or NRTIs or NNRTIs						50.40	0
<24 months	3	149	52	34.75 (27.16-42.72)	0		
≥24 months	7	997	755	72.57 (66.03-78.67)	26.01		
NR	11	1492	764	52.77 (44.63-60.84)	79.99		
DR to NNRTIs						42.33	0
<24 months	3	149	49	32.69 (25.24-40.57)	0		
≥24 months	5	699	520	71.40 (63.18-78.97)	79.30		
NR	9	1435	701	49.64 (41.13-58.16)	88.60		
DR to NRTIs						33.00	0
<24 months	3	149	20	14.54 (3.73-30.08)	78.20		
≥24 months	5	699	420	58.81 (53.08-64.42)	52.00		
NR	9	1435	533	38.68 (30.70-46.96)	88.10		
DR to PIs						0.01	0.99
<24 months	4	200	3	1.15 (0-3.56)	0		
≥24 months	6	756	16	1.53 (0.20-3.71)	63.90		
NR	9	1435	32	1.55 (0.58-2.84)	45.00		

Note. DR means drug resistance.

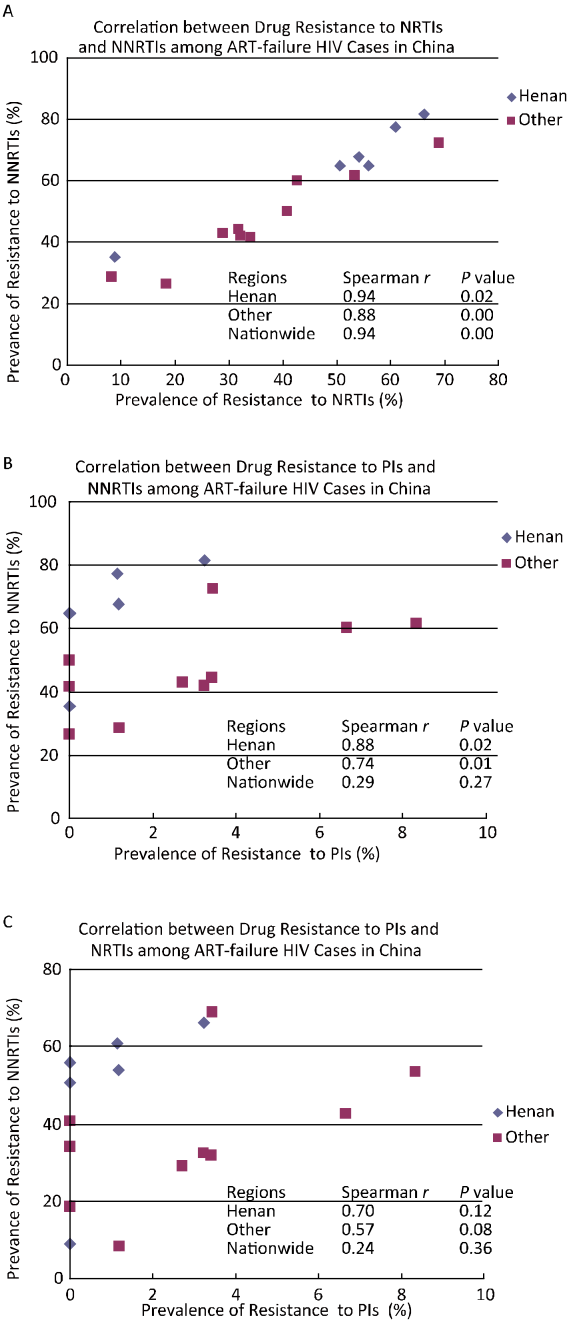

Figure 2. Correlations between drug resistance to different classes of ART among treatment-failure HIV-positive individuals in China. A. Correlation between drug resistance to NRTIs and NNRTIs; B. Correlation between drug resistance to PIs and NNRTIs; C. Correlation between drug resistance to PIs and NRTIs; All analyses were conducted by Spearman Rank Correlation.

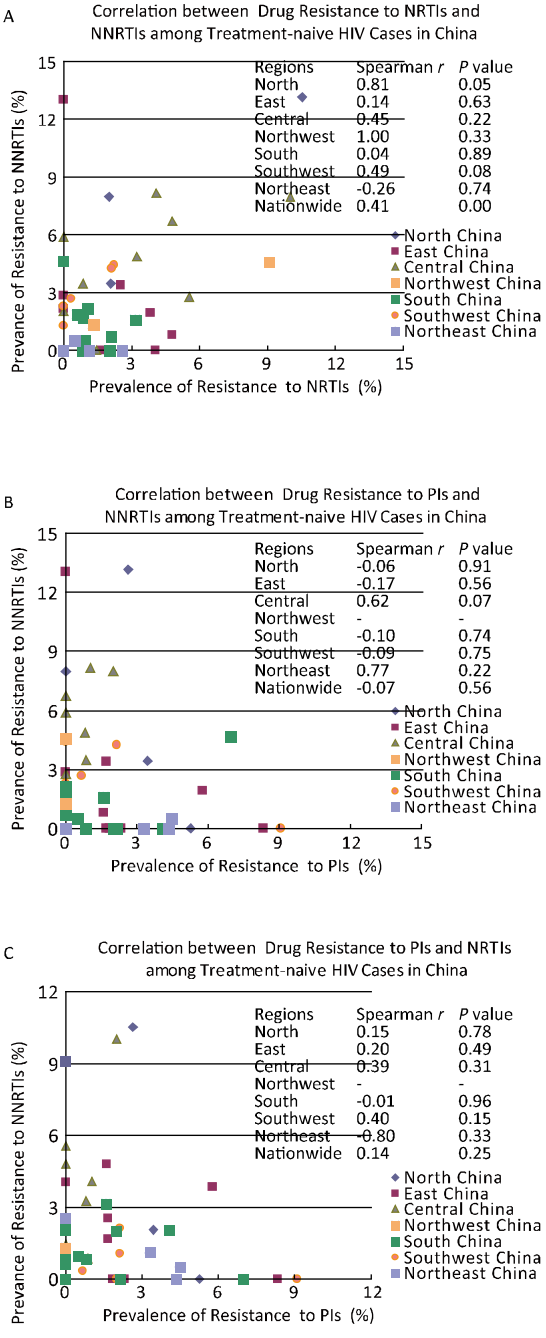

Figure 3. Correlation between drug resistance to different classes of ART among treatment-naïve HIV-positive individuals in China. A. Correlation between drug resistance to NRTIs and NNRTIs; B. Correlation between drug resistance to PIs and NNRTIs; C. Correlation between drug resistance to PIs and NRTIs; All analyses were conducted by Spearman Rank Correlation.

failure and treatment-naïve individuals in China. It is necessary to understand the differences between the two types of HIV drug resistance in order to offer guidance for continuing ART use in China. A high proportion of overall drug resistance (57%) in ART-failure HIV-positive individuals was exhibited in our study, but compared to a prior meta-analysis, the proportions of resistance to NNRTIs and NRTIs (54% and 40%, respectively) were lower than those in the subgroup at 3-to-6-month resistance monitoring or no monitoring (88% and 81%, respectively), and similar to that in the subgroup at 3-month resistance monitoring (61% and 40%, respectively)[15]. Our study evidenced that high single-resistance to NRTIs and NNRTIs, high dual-resistance to NRTIs & NNRTIs, and low resistance to PIs were consistent with the current types and levels of ART use in China. Our study data also concurred with an earlier report that found that the first-line regimen drugs accounted for the overwhelming majority of HIV drugs in China[2] (Table S1). The results of our meta-analysis indicated that optimal interventions were needed in China, e.g. sustainable ART drugs and more frequent resistance testing. At present it is practical to monitor resistance to the first-line regimens among ART-failure patients in China because a fallback exists in the available free second-line regimens. However, surveillance to resistance of second-line regimens may be perceived as less urgent at this point because of low HIV drug resistance to PIs and no further provision of free drugs.

HIV drug resistance among treatment-naïve individuals (including recently- or chronically-infected individuals) is used as a substitute for transmitted drug resistance[110]. Our study found that the total prevalence of HIV drug resistance among treatment-naïve individuals in China was 3%, similar to the results from the survey across five provinces (3%) in China[83]. The prevalence level in China was similar to those in developing countries that initiated treatment in the 2000's, and far lower than those in developed countries (up to 10%-15%)[14,111] that initiated treatment in the 1990's. The decision without baseline resistance testing was still right at population-level[112], considering the prevalence was lower than the WHO 5% threshold[113]. However, the long-term effects and durability of ART should still be evaluated through national-level resistance surveillance. Continuing surveillance data on baseline drug resistance to NNRTIs and/or NRTIs will help us analyze whether the current first-line regimens in China are appropriate. In addition, the low HIV drug resistance to PIs among both ART-failure cases and pre-ART cases in our study was consistent with the current low coverage of second-line regimens. However, baseline resistance testing may be necessary in Central China and North China due to their high prevalence of HIV drug resistance (more than 5%) among treatment-naïve individuals, especially in Henan and Beijing. Such testing can help doctors to determine the most suitable ART regimen for patients.

It is intriguing that there was no significant difference in drug resistance, whether among pre-ART individuals or among ART-failure individuals, between the study period up to and including 2007 *vs*. after 2007 (data not shown). However, realistic data and simulation results have previously demonstrated an increasing trend in HIV drug resistance over time[13,114-116]. The stable prevalence of drug resistance among treatment-failure individuals in our study can be explained by the dynamic equilibrium between new ART-failure cases and HIV deaths in China. We should further take note on whether the current values have reached a saturation level. The prevalence trend of drug resistance among pre-ART individuals over time may be too weak to be observed, as an earlier model predicted.[117]. Stable prevalence of drug resistance among pre-ART individuals may also be partially due to delayed reporting of HIV cases, which reflects prior resistance transmission. Prevalence may also be related to coverage rates; in another study, Blower et al.[117] reported that low ART coverage would lead to less than 5% transmitted drug resistance prevalence after 10 years of ART use, but only when ≥30% coverage. Her results were consistent with our meta-analysis. Low nationwide coverage of HIV-infected people corresponded to 3% drug resistance prevalence[2]; and high coverage of HIV-positive individuals coupled with quick scale-up of ART in Henan corresponded to 7% prevalence in Henan (estimated >30%, personal communication). Coverage is also expected to expand in China; with the trend toward higher CD4 count levels at treatment initiation, from 200 cells/mm^3 to 350 cells/mm^3 or higher in future[118-119], more and more HIV cases will be eligible for treatment in China. However, high treatment coverage is positively correlated with high drug resistance, even offsetting the effects of ART and leading to HIV resurgence[120-123]. Besides, drug resistance

transmission from overseas HIV cases should also be an issue of concern in larger cities, such as Beijing. Therefore, it is necessary to remain vigilant to HIV drug resistance. Although we conducted drug resistance prevalence estimation among ART-failure individuals and found a difference between different mean/median treatment periods, the pooled prevalence was crude. More accurate prevalence dynamics over time will need to be determined by cohort studies.

This analysis reported a medium positive correlation before ART use and a high positive correlation after ART use between HIV drug resistance to NNRTIs and NRTIs in China. The twin epidemics of drug resistance to NNRTIs and NRTIs reflected the current choices of two NRTIs and one NNRTI as an overwhelming majority of the first-line regimens in China. Exiting positive synergistic effects were the basis of two classes of drugs used together, but we should assess the sustainability of these effects through mechanism studies and clinical surveys. Issues for further study include hypersensitivity, cross-resistance, dominant mutations causing multiple-resistance, and the preventive and therapeutic effects of ART. We also found a positive correlation between HIV drug resistance to PIs and NNRTIs among treatment-failure individuals in Henan and other provinces, but not throughout the whole nation. The difference may be produced by a low sample size, so in the future we hope to include more studies in order to reach a definite conclusion.

There are some limitations to this pooled analysis. Potential confounding factors such as delayed reporting existed in the included studies, which provided the information on HIV drug resistance among treatment-naïve individuals for this pooled study. We could not find the epidemic trend of HIV drug resistance according to the specimen collection periods. Only three studies were performed in HIV incident cases confirmed by BED or cohort, so we did not analyze them further. There was high heterogeneity across the individual studies in this meta-analysis, as in other meta-analyses in China[124-125]. Random-effects models and sub-group analyses were adopted to address the heterogeneity.

This meta-analysis reported the high prevalence of HIV drug resistance to NNRTIs and/or NRTIs among treatment-failure individuals, and the low prevalence of HIV drug resistance among treatment-naïve individuals in China. The outcomes from this meta-analysis supported current treatment regimens in China, which are practical and feasible. But the monitoring interval should be shortened for HIV-positive patients on treatment in order to find cases with resistance earlier. In addition, we should continue to monitor the long-term effects of ART so that we can adjust the policies and interventions quickly, in case of HIV resurgence. In provinces with severe baseline resistance among treatment-naïve HIV-positive people, HIV drug resistance before treatment initiation should be provided to determine the optimal ART regimen and assure the best effects of ART.

SUPPLEMENTARY MATERIALS

All the supplementary materials (Tables S1, S2, and Checklist S1) can be found in the websit of *www.Besjournal.com*

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Checklist S1. PRISMA Checklist of this Meta-analysis

Section/Topic	#	Checklist Item	Reported on Section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction: 2nd paragraph
METHODS			
	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods: study selection
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods: search strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods: search strategy
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods: study selection
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods: data extraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	None
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods: validity assessment
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods: statistical analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods: statistical analysis

Continued

Section/topic	#	Checklist item	Reported on Section
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods: statistical analysis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods: statistical analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results: 1st section, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results: 1st section, Table S1-2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	None
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table S1-2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results: 2nd section, Table 1
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results: 2nd section, Table 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results: 3rd-5th section, Table 2-3, Figure 2-3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion: 1st – 4th paragraph
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion: 5th paragraph
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion: 6th paragraph
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	footnote

Note. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Table S1. Characteristics of Included Studies Providing HIV Drug Resistance Information of Treatment-failure Individuals

Study	Data Collection Period	Subjects	Transmission Route	Province	Drug Regimens	Age (mean/ median)	People Studied, No.	Virological Failure[#], No.	Successful Sequences, No.	Drug Resistance[*], No.
Wu JJ, 2011[1]	2009	Individuals treated between 2005 and December 31, 2009	88% infected by blood donors or transfusion	Anhui	first line regimens	NR	258	50	38	10
Qiu LJ, 2013[2]	2005-2012	Individuals treated for more than 1 year and with VL more than 1000 copies/mL	84% sexual transmission	Fujian	90% first line regimens	41[a]	NR	73	60	NR
Lu XL, 2013[3]	2011	Treated AIDS patients with VL more than 1000 copies/mL	62% people infected by blood, 32% by sexual contacts	Hebei	91% first line regimens	NR	NR	57	57	33
Liu J, 2011[4]	2005	Treated individuals with HIV	Former blood donors	Henan	first line regimens	41[a]	97	37	34	13
Zhu XP, 2008[5]	2006	Treated individuals with HIV	Most were commercial blood donors	Henan	84% first line regimens	41[a]	706	458	272	214
Yuan Y, 2012[6]	2009	Treated AIDS patients	Commercial blood donors	Henan	first line regimens	46[a], 41[b]	616	261	261	204
Zheng BF, 2011[7]	2009	Treated AIDS patients who initiated ART in 2004-2009	90% commercial blood donors	Henan	first line regimens	NR	371	87	85	55
Liu J, 2012[8]	2010	AIDS patients treated for over one year in 2010 and with VL more than 1000 copies/mL	92% commercial blood donors or infected by transfusion	Henan	first line regimens	NR	NR	276	257	176
Cui WG, 2012[9]	2010	Treated AIDS patients who initiated ART about in 2004	Most were commercial blood donors	Henan	first line regimens	51[b]	164	95	77	53
Yuan Y, 2011[10]	2008-2009	Treated AIDS patients who initiated ART in 2003-2009	92% commercial blood donors or infected by transfusion	Henan	first line regimens	NR	378	216	216	178
Tang H, 2007[11]	2006	Treated AIDS patients	NR	Hubei	first line regimens	43[a]	239	78	51	NR
Qin BY, 2012[12]	2009	AIDS patients treated for over 6 months in 2005-2009	58% IDUs, 35% sexual transmission	Hunan	first line regimens	38[a]	252	32	31	13
Xiao ZP, 2012[13]	2010	Treated AIDS patients in surveillance system until April, 2010	74% sexual transmission	Jiangsu	first line regimens	NR	591	88	75	50
Xiao ZP, 2012[14]	2011	Treated people in surveillance system in July 2011	82% sexual transmission	Jiangsu	first line regimens	NR	877	149	108	57
Lin B, 2011[15]	2010	AIDS patients treated for over one year until June, 2010 and initiating ART in 2003-2009	NR	Shandong	The majority were treated by first line regimens	NR	324	33	25	20
Sun XG, 2012[16]	2011	Treated AIDS patients	70% sexual transmission	Shandong	95% first line regimens	38[b]	758	69	53	23

Continued

Study	Data Collection Period	Subjects	Transmission route	Transmission Route	Province	Drug Regimens	Age (mean/median)	People Studied, No.	Virological Failure[#], No.	Successful Sequences, No.
Zhang J, 2012[17]	2006-2008	Individuals with HIV treated for over 6 months	NR	Shandong	91% first line regimens	NR	143	29	29	18
Yuan D, 2011[18]	2010	Individuals with HIV treated for over 1 year	NR	Sichuan	90% first line regimens in 40 people	NR	1149	88	88	40
Wang QX, 2011[19]	2010	Treated individuals with HIV who initiated ART before January 1, 2010	64% IDUs	Sichuan	first line regimens except for one patient	35[b]	317	84	84	26
Zuohela T, 2011[20]	2006-2007	Individuals with HIV treated for a year	59% IDUs	Xinjiang	first line regimens	NR	113	33	32	12
Li HP, 2013[21]	2010-2011	Treated individuals with HIV	50% sexual transmission, 39% IDUs	Yunnan	95% first line regimens	36[a]	13736	1066	515	232
Zhang JF, 2010[22]	2009	Treated individuals in 2004-2009	83% sexual transmission	Zhejiang	NR	39[a]	274	30	29	21
Xing H, 2013[23]	2009	Treated individuals in 2005-2009	55% sexual transmission, 23% IDUs	8 provinces	92% first line regimens, 6% second line regimens	39[a]	2192	272	272	123

Note. [#]means viral load ≥1000 copies/mL, [*]means HIV drug resistance mutations referred low-, intermediate-, high-level resistance. [a] means mean of age, [b] means median of age. NR means no report. VL means viral load. IDU means injected drug users. ART means antiretroviral therapy.

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Table S2. Characteristics of Included Studies Providing HIV Transmitted Drug Resistance Information of Treatment-naïve Individuals

Study	Data Collection Period	Subjects	Transmission Route	Province	Age (mean/median)	People Studied, No.	Successful Sequences, No.	Drug Resistance*, No.
Wu JJ, 2011[1]	2008	Newly diagnosed people with HIV	52% sexual transmission, 12% MTCT	Anhui	NR	49	29	0
Lei YH, 2012[2]	2011-2012	Newly diagnosed people with HIV without developing into AIDS	Homosexual transmission	Anhui	31[a]	35	35	1
Hei FX, 2011[3]	2008	Newly diagnosed people with HIV	86% sexual transmission	Beijing	23[a]	61	50	NR
Zhang XY, 2007[4]	2005-2006	Treatment-naïve people with HIV	Homosexual transmission	Beijing	NR	54	38	7
Chin BS, 2010[5]	2005-2008	Treatment-naïve people with HIV	44% people infected by blood product	Beijing	NR	NR	32	0
Ye JR, 2012[6]	2006-2007	Newly diagnosed HIV patients	67% heterosexual transmission, 15% IDUs	Beijing	NR	200	145	11
Li L, 2013[7]	2007-2010	Treatment-naïve people with HIV	Homosexual transmission	Beijing	32[a]	95	76	4
Feng LG, 2008[8]	2006	HIV incident cases confirmed by BED-CEIA	Homosexual transmission	Chongqing	NR	25	22	2
Liu J, 2007[9]	2003	Treatment-naïve people with HIV subtype AE	NR	Fujian	NR	52	52	0
Liu JF, 2007[10]	2003-2005	Treatment-naïve people with HIV	70% sexual transmission	Fujian	NR	90	74	3
Qiu LJ, 2013[11]	2003-2005,2007-2010	Treatment-naïve people with HIV	94% sexual transmission	Fujian	31[a]	NR	125	NR
Yu GL, 2009[12]	2007	Newly diagnosed people with HIV	DUs	Guangdong	NR	63	49	1
Zhao J, 2011[13]	2008	Newly diagnosed people with HIV	NR	Guangdong	NR	88	45	0
Zhao J, 2011[13]	2009	Newly diagnosed people with HIV	NR	Guangdong	NR	56	49	3
Chen S, 2012[14]	2009	Treatment-naïve people with HIV	NR	Guangdong	NR	69	63	3
Huang D, 2013[15]	2010	Newly diagnosed people with HIV	Homosexual transmission	Guangdong	28[a]	144	141	4
Zhao J, 2011[13]	2010	Newly diagnosed people with HIV	NR	Guangdong	NR	94	50	2
Wang H, 2007[16]	2002-2004	Treatment-naïve AIDS patients	42% sexual transmission, 34% people infected by blood, 23% IDUs	Guangdong	34[a]	45	41	NR
Wu YS, 2008[17]	2006-2007	Treatment-naïve AIDS patients	NR	Guangdong	NR	NR	12[c], 21[d]	NR
Zhao GL, 2009[18]	2007-2008	Treatment-naïve people with HIV	Homosexual transmission	Guangdong	NR	98	94	3
Zhao GL, 2012[19]	2008-2010	Treatment-naïve people with HIV	Homosexual transmission	Guangdong	31[a]	227	164	4
Yang CF, 2012[20]	2009-2011	Newly diagnosed HIV patients	51% heterosexual transmission, 41% IDUs	Guangdong	44[a]	157	119	2
Liang SJ, 2011[21]	2007	Newly diagnosed people with HIV	74% sexual transmission	Guangxi	22[a]	70	47	1
Su QJ, 2012[22]	2008	Treatment-naïve people with HIV	IDUs and heterosexual transmission	Guangxi	NR	144	124	2
Su QJ, 2010[23]	2008	Treatment-naïve people with HIV followed up for more than half a year	Dus about for half, others sexual transmission	Guangxi	NR	190	133	3
Li L, 2013[24]	2009	Treatment-naïve people with HIV	Heterosexual transmission	Guangxi	40[a]	253	211	4
Li HP, 2007[25]	2004-2005	Treatment-naïve people with HIV	NR	Guangxi	NR	58	43	5
Liang SJ, 2011[26]	2004-2005	Treatment-naïve people with HIV	NR	Guangxi	NR	56	51	9
Bu P, 2013[27]	2011	Newly diagnosed people with HIV	88% sexual transmission	Guizhou	NR	76	64	0
Bu P, 2012[28]	2008-2009	Newly diagnosed people with HIV	55% sexual transmission	Guizhou	23[a]	70	47	0
Deng W, 2009[29]	1991-2006	Newly diagnosed people with HIV	69% IDUs, 19% heterosexual transmission	Hainan	NR	78	73	0

Continued

Study	Data Collection Period	Subjects	Transmission Route	Province	Age (mean/median)	People Studied, No.	Successful Sequences, No.	Drug Resistance*, No.
Zhou H, 2010[30]	2005-2006	Treatment-naïve people with HIV	Most were transmitted by transfusion	Heilongjiang	NR	49	47[c], 44[d]	NR
Li WJ, 2012[31]	2009-2012	Treatment-naïve people with HIV	80% sexual transmission	Heilongjiang	40[a]	NR	39	1
Liu CH, 2011[32]	2009	Newly diagnosed people with HIV	NR	Henan	NR	141	104	8
Yang K, 2005[33]	2001-2002	Treatment-naïve AIDS patients	92% blood donors	Henan	NR	45	36	
Yin CY, 2011[34]	2004-2008	Treatment-naïve people with HIV	NR	Henan	NR	NR	36	3
Tu YQ, 2009[35]	2006-2007	HIV incident cases confirmed by BED-CEIA	NR	Henan	38[a]	39	34	2
Yuan Y, 2009[36]	2007-2008	Newly diagnosed people with HIV	44% sexual transmission, 34% MTCT	Henan	NR	69	50	1
Li LN, 2013[37]	2009-2010	Treatment-naïve people with HIV	NR	Henan	41[a]	187	98	10
Xue XJ, 2012[38]	2010-2011	Newly diagnosed people with HIV	82% sexual transmission	Henan	NR	55	50	6
Luo MQ, 2009[39]	2003-2005	Treatment-naïve people with HIV	89% people infected by blood donors or blood transfusion	Hubei	39[a]	150	123	10
Tang H, 2007[40]	2004-2005	Treatment-naïve people with HIV	94% people infected by blood	Hubei	45[a]	135	115	NR
Chen X, 2008[41]	2007	Newly diagnosed people with HIV	64% sexual transmission, 29% Dus	Hunan	22[a]	79	69	1
Yang HT, 2012[42]	2009	Newly diagnosed people with HIV	Sexual transmission	Jiangsu	NR	NR	47	0
Han XX, 2007[43]	1999-2004	Treatment-naïve people with HIV	48% sexual transmission, 43% people infected by blood	Liaoning	35[a]	NR	91	NR
Han XX, 2007[44]	1999-2007	Treatment-naïve people with HIV	Homosexual transmission	Liaoning	36[a]	NR	46	2
Zhao B, 2011[45]	2003-2009	Treatment-naïve people with HIV	Homosexual transmission	Liaoning	36[a]	217	201	9
Li HP, 2007[46]	2005	Treatment-naïve people with HIV	50% IDUs	Ningxia	33[a]	27	22	2
Zhang J, 2010[47]	2006	Newly diagnosed people with HIV	85% sexual transmission	Shandong	NR	53	47	1
Gu SM, 2006[48]	2003-2004	Treatment-naïve people with HIV	50% hemophilia patients	Shanghai	NR	NR	23	1
Liu L, 2011[49]	2008-2009	Treatment-naïve people with HIV	78% sexual transmission	Shanghai	NR	NR	118	7
Liu L, 2005[50]	2004	Treatment-naïve people with HIV	46% IDUs, 41% people infected by Blood donors or transfusion	Sichuan	NR	41	22	1
Yuan D, 2011[51]	2007-2009	Newly diagnosed people with HIV	Homosexual transmission	Sichuan	32[a]	98	77	0
Zeng PB, 2013[52]	2007-2010	Treatment-naïve people with HIV	NR	Sichuan	NR	244	159	2
Zheng MN, 2010[53]	2008	Newly diagnosed people with HIV	Homosexual transmission	Tianjin	29[a]	67	50	5
Wang X, 2012[54]	2010	Treatment-naïve people with HIV followed up for a time in Tianjin CDC	94% sexual transmission	Tianjin	33[a]	79	50[c], 51[d]	NR
Liao LG, 2007[55]	2003-2004	HIV incident cases confirmed by cohort	IDUs	Xinjiang	31[a]	23	23	0
Han J, 2009[56]	2005-2007	Treatment-naïve pregnant women with HIV	NR	Xinjiang	NR	NR	25	1
Han XX, 2012[57]	2009-2010	Treatment-naïve people with HIV	IDUs	Xinjiang	34[a]	NR	77	1

Continued

Study	Data Collection Period	Subjects	Transmission Route	Province	Age (mean/median)	People Studied, No.	Successful Sequences, No.	Drug Resistance*, No.
Bao LL, 2008[58]	2006	Treatment-naïve people with HIV	Sexual transmission	Yunnan	NR	46	45	2
Ma YL, 2011[59]	2009	Newly diagnosed people with HIV	79% sexual transmission	Yunnan	NR	56	47	4
Chen M, 2013[60]	2011	Newly diagnosed people with HIV	Sexual transmission	Yunnan	21[a]	59	41	0
Chen M, 2012[61]	2011	Newly diagnosed people with HIV	77% sexual transmission	Yunnan	NR	62	44	1
Tu YQ, 2009[62]	2005-2006	Treatment-naïve people with HIV	NR	Yunnan	27[a]	52	49	0
Han J, 2009[56]	2005-2007	Treatment-naïve pregnant women with HIV	NR	Yunnan	NR	25	25	2
Chen M, 2012[63]	2009-2010	Newly diagnosed people with HIV	76% heterosexual transmission	Yunnan	33[a]	320	299	11
Guo WZ, 2012[64]	2009-2011	Treatment-naïve people with HIV	90% sexual transmission	Yunnan	NR	50	50	1
Li HP, 2013[65]	2010-2011	Treatment-naïve people with HIV	89% heterosexual transmission	Yunnan	39[a]	101	94	2
Zhang JF, 2012[66]	2009	Newly diagnosed people with HIV	90% sexual transmission	Zhejiang	23[a]	63	52	4
Zhang S, 2010[67]	2009	Newly diagnosed people with HIV not AIDS	88% sexual transmission	Zhejiang	NR	42	36	3
Zhang JF, 2012[66]	2010	Newly diagnosed people with HIV	97% sexual transmission	Zhejiang	22[a]	62	59	2
Zhang JF, 2012[66]	2011	Newly diagnosed people with HIV	93% sexual transmission	Zhejiang	NR	57	54	1
Yao YP, 2008[68]	2004-2006	Newly diagnosed people with HIV	64% p sexual transmission	Zhejiang	NR	99	74[c], 83[d]	NR
Yao YP, 2009[69]	2004-2007	Treatment-naïve people with HIV CRF01_AE	NR	Zhejiang	NR	NR	43	1
Yin CY, 2011[34]	2004-2008	Treatment-naïve people with HIV	NR	Zhejiang	NR	NR	23	3
Wang X, 2012[70]	2011	Treatment-naïve people with HIV	70% heterosexual transmission, 25% IDUs	5 provinces	36[b]	718	627	17
Yang J, 2013[71]	2010	Treatment-naïve people with HIV	Homosexual transmission	19 provinces	NR	610	489	24
Si XF, 2004[72]	2002	Treatment-naïve people with HIV	NR	21 provinces	NR	NR	164[c], 138[d]	NR

Note. *HIV drug resistance mutations conferred low-, intermediate-, high-level resistance. [a]means mean of age and [b]means median of age. [C]means protease gene sequences, [d]means reverse transcriptase gene sequences, others mean protease and reverse transcriptase gene sequences obtained at the same time. NR means no report. IDU (DU) means (injective) drug users. MTCT means mother to children transmission.

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