Emerging Trends of HIV Drug Resistance in Chinese HIV-Infected Patients Receiving First-Line Highly Active Antiretroviral Therapy: A Systematic Review and Meta-Analysis

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Background. Highly active antiretroviral therapy (HAART) has led to a dramatic decrease in AIDS-related morbidity and mortality through sustained suppression of human immunodeficiency virus (HIV) replication and reconstitution of the immune response. Settings like China that experienced rapid HAART rollout and relatively limited drug selection face considerable challenges in controlling HIV drug resistance (DR).

Methods. We conducted a systematic review and meta-analysis to describe trends in emergent HIV DR to first-line HAART among Chinese HIV-infected patients, as reflected in the point prevalence of HIV DR at key points and fixed intervals after treatment initiation, using data from cohort studies and cross-sectional studies respectively.

Results. Pooled prevalence of HIV DR from longitudinal cohorts studies was 10.79% (95% confidence interval [CI], 5.85%–19.07%) after 12 months of HAART and 80.58% (95% CI, 76.6%–84.02%) after 72 months of HAART. The HIV DR prevalence from cross-sectional studies was measured in treatment intervals; during the 0–12-month HAART treatment interval, the pooled prevalence of HIV DR was 11.1% (95% CI, 7.49%–16.14%), which increased to 22.92% at 61–72 months (95% CI, 9.45%–45.86%). Stratified analyses showed that patients receiving a didanosine-based regimen had higher HIV DR prevalence than those not taking didanosine (15.82% vs 4.97%). Patients infected through former plasma donation and those receiving AIDS treatment at village clinics had higher HIV DR prevalence than those infected through sexual transmission or treated at a county-level hospital.

Conclusions. Our findings indicate higher prevalence of HIV DR for patients with longer cumulative HAART exposure, highlighting important subgroups for future HIV DR surveillance and control.

Keywords. highly active antiretroviral therapy; drug resistance; HIV/AIDS; meta-analysis.

Highly active antiretroviral therapy (HAART) has led to a dramatic decrease in AIDS-related morbidity and mortality [1,2] through sustained suppression of human immunodeficiency virus (HIV) replication [3] and reconstitution of the immune response [4]. However, the eventual development of HIV drug resistance (DR) over time is largely inevitable at the population level, and HIV DR is one of the strongest predictors of treatment failure [5, 6]. It can render existing therapies ineffective [7–9], increasing the risk of viral rebound and opportunistic infections. Second-line drugs provide alternative therapeutic options to suppress resistant strains, but their high cost and limited availability in some areas make them a less viable option. As HIV DR prevalence increases at the population level, the secondary transmission of transmitted DR is also a major public health concern [10]. A better understanding of long-term HIV

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DR rates and emergence of drug-resistant mutations after HAART initiation will be crucial to the effective therapeutic and preventive use of HAART.

China's National Free Antiretroviral Treatment Program (NFATP) is now a decade old [11], having begun as a pilot program with just 100 enrollees in a rural region where most patients were infected through former plasma donation in the early 1990s [11, 12]. The program today is notable in terms of both scale and impact. As of 31 December 2009, a cumulative total of 82 540 patients received HAART through the program, during which time the HIV/AIDS-related mortality rate fell from 39.3 to 14.2 deaths per 100 person-years [13].

Owing to its early rapid scale-up, as well as evolving recommendations for treatment eligibility—in 2008 China's HAART initiation threshold increased from 200 to 350 CD4 cells/μL [14]—expansion of HAART access in China outpaced program development in the early stages. Routine laboratory screening is only available at a small portion of the >3700 HAART delivery sites across the county; between 2005 and 2008, only 30% of patients had received ≥1 viral load test a year [15]. Specialized training in AIDS care for local providers is also limited, and in rural areas many AIDS care physicians lack a formal medical education [16]. These factors, along with the limited drug regimen choice in the early years of the program, have all contributed to the emergence of HIV DR in the Chinese HAART population. Observational studies have shown that the prevalence of drug-resistant strains among treated HIV/AIDS patients in China ranges from 2.38% to 54.67% [17, 18] after 1 year of HAART. However, it is difficult to draw broader conclusions owing to the heterogeneity of study populations and sampling methods. Because few studies have traced trends of HIV DR emergence during longer durations of HAART exposure, the objective of this investigation was to conduct a systematic review and meta-analysis and generate pooled estimates of the emerging trends of HIV DR after first-line HAART initiation in Chinese patients with HIV/AIDS.

METHODS

Search Strategy and Data Extraction

We conducted a literature search using the PubMed/Medline database, as well as Chinese language databases, including the China National Knowledge Infrastructure, the Chinese Biomedical Literature Database, and Wanfang, from inception to 28 February 2014, using the following search string: (*HIV* OR *human immunodeficiency virus* OR *AIDS* OR *acquired immunodeficiency syndrome*) AND (*drug resistance* OR *drug resistant*) AND *China*. Articles published in English or Chinese were considered for inclusion in this analysis.

Two independent reviewers (H. L. and Y. S.) determined study eligibility, with a third reviewer (N. W.) deciding on cases in which the opinions of the 2 main reviewers diverged. Only studies with explicitly reported HIV DR prevalence data were considered, after which the following inclusion criteria were used to determine inclusion in the final analysis: (1) adult patient population (>18 years of age); (2) treatment-naive patient at baseline; (3) treatment with first-line HAART regimen, consisting of 2 nucleoside reverse-transcriptase inhibitors and 1 nonnucleoside reverse-transcriptase inhibitor; (4) AIDS care received through the NFATP (as opposed to private care sought by patients); (5) available information on genotypic HIV DR data, determined by the Stanford HIV Drug Resistance Database Program (http://hivdb.standford.edu). If multiple articles on the same study were published, the one providing more complete information and/or larger sample size was chosen.

Two reviewers (H. L. and L. Z.) independently extracted study data, including author names, year of publication, study type, study period, sample size, demographic information, infection route, type of AIDS healthcare setting, initial HAART regimen, and prevalence of patients with genotypic HIV DR mutation(s). All HIV DR mutations that conferred low, intermediate or high-level resistance are included [19].

Statistical Analyses

When follow-up data were available, pooled HIV DR prevalence was estimated at various durations of HAART exposure by identifying common milestones or time intervals used by all studies. For cohort studies cumulative HIV DR prevalence estimates were calculated at 12, 24, 36, 48, 60, and 72 months since HAART initiation, and for cross-sectional studies estimates were calculated at the following time intervals after HAART initiation: 0–12, 13–24, 25–36, 37–48, 49–60, and 61–72 months.

Separate methods were used to calculate HIV DR prevalence for cohort studies and cross-sectional studies. For the former, the denominator included all patients enrolled at baseline, and the numerator represented the number found to be HIV drug resistant at each of the above-mentioned milestones after HAART initiation. Patients included in the numerator for a given point prevalence were carried forward in the numerator for all subsequent intervals. Patients who were lost to follow-up at any point without a recorded HIV DR event were excluded from the calculation entirely. For cross-sectional studies, patients were stratified into the aforementioned time intervals that corresponded to their duration of HAART exposure. The HIV DR prevalence was then calculated using the number of patients in each treatment interval in the denominator and the number who tested positive for HIV DR in the numerator.

Statistical heterogeneity was evaluated using the I^2 test [20] with a cutoff of $I^2 > 50\%$ to represent moderate to substantial heterogeneity, in which case random-effects models were used to pooled the summary estimates. In cases with strong evidence of heterogeneity, the HIV DR prevalence data were calculated

Table 1. Study Characteristics

Author (Year)	Study Design	Location	Treatment Regimen	Study Period[a]	Patients, No.	
					Enrolled, No.[b]	Lost to Follow-up[c]
Wang et al (2007) [22]	Cohort	Henan	AZT + ddI + NVP	24 mo	107	NR
Huang (2008) [23]	Cohort	Anhui	d4T + ddI + NVP	24 mo	90	NR
Li et al (2008) [24]	Cohort	14 Clinical Centers	AZT/d4T + ddI/3TC + NVP	12 mo	198	14
Zhang et al (2008) [25]	Cohort	Henan	AZT/d4T + ddI/3TC + NVP	36 mo	88	NR
Ruan et al (2010) [26]	Cohort	Hunan, Henan, Anhui	AZT/d4T + ddI/3TC + NVP/EFV	12 mo	341	76
Chen et al (2011) [27]	Cohort	Guangzhou	AZT/d4T + ddI/3TC + NVP/EFV	24 mo	74	6
Cao et al (2011) [28]	Cohort	Henan	AZT/d4T + 3TC + NVP/EFV	12 mo	105	3
Li et al (2011) [18]	Cohort	Henan	AZT + ddI + NVP	72 mo	75	NR
Wang et al (2011) [29]	Cohort	Yunnan, Guangxi, Xinjiang	AZT/d4T + 3TC + NVP	12 mo	435	84
Wang (2012) [30]	Cohort	12 centers	AZT/d4T + 3TC + NVP	12 mo	517	36
Liao et al (2013) [31]	Cohort	Henan and Anhui	AZT/d4T + ddI + NVP	72 mo	365	NR
Wang et al (2014) [32]	Cohort	8 cities	TDF/AZT/d4T + 3TC + NVP/EFV	12 mo	513	65
Zhang et al (2008) [33]	Cross-sectional	7 provinces	AZT/d4T + ddI/3TC + NVP/EFV	2005	113	. . .
Yao (2009) [34]	Cross-sectional	Yunnan	AZT/d4T + ddI/3TC + NVP/EFV	2008–2009	569	. . .
Yuan et al (2011) [35]	Cross-sectional	Henan	AZT/d4T + ddI/3TC + NVP/EFV	2008–2009	299	. . .
Zheng et al (2011) [36]	Cross-sectional	Zhejiang	AZT/d4T + ddI/3TC + NVP/EFV	2009	274	. . .
Zheng (2011) [37]	Cross-sectional	Henan	AZT/d4T + ddI/3TC + NVP/EFV	2008–2009	105	. . .
Cui et al (2012) [38]	Cross-sectional	Henan	AZT/d4T + ddI/3TC + NVP/EFV	2010	164	. . .
Qin et al (2012) [39]	Cross-sectional	Hunan	AZT/d4T + ddI/3TC + NVP/EFV	2009	211	. . .
Sun et al (2012) [40]	Cross-sectional	Shandong	2 NRTIs + 1 NNRTI	2011	502	. . .
Xiao et al (2012) [41]	Cross-sectional	Jiangsu	AZT/d4T + 3TC + NVP/EFV	2010	588	. . .
Yuan et al (2012) [42]	Cross-sectional	Henan	AZT/d4T + ddI/3TC + NVP/EFV	2009	450	. . .
Cui et al (2013) [43]	Cross-sectional	Henan	AZT/d4T + ddI/3TC + NVP	Unavailable	120	. . .
Zhao et al (2013) [44]	Cross-sectional	8 provinces	AZT/d4T + ddI/3TC + NVP/EFV	2010	631	. . .
Xing et al (2013) [45]	Cross-sectional	31 provinces	AZT/d4T + ddI/4TC + NVP/EFV	2004–2006	2527	. . .

Abbreviations: 3TC, lamivudine; AZT, zidovudine; d4T, stavudine; ddI, didanosine; EFV, efavirenz; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NR, not reported; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; TDF, tenofovir.

[a] Duration of follow-up for cohort studies.

[b] Number of patients enrolled at baseline of cohort studies or recruited into cross-sectional studies.

[c] Number of patients lost to follow-up without any human immunodeficiency virus drug resistance test results in cohort studies.

for key subgroups, such as treatment regimen, original HIV transmission route, and type of healthcare facility where patients receive routine HIV/AIDS care. R software [21] and SAS software (version 9.3; SAS Institute) were used for all statistical analyses.

RESULTS

Study Selection and Characteristic

The search strategy yielded a total of 5095 abstracts (439 in PubMed, 2070 in Wanfang, 1128 in the Chinese Biomedical Literature Database, and 1458 in the China National Knowledge Infrastructure). After removing duplicate articles, 2128 unique studies were screened by title and abstract. Of these, 86 were reviewed in full text to determine eligibility based on the inclusion criteria described above, yielding a final count of 25 articles included in the final analysis (Supplementary Figure 1). Most articles were excluded owing to lack of information on treatment duration, HIV DR prevalence, or details on type of treatment regimen. Longitudinal data on total of 2908 cohort study participants and cross-sectional data from 6553 patients were abstracted from the 12 cohort and 13 cross-sectional studies, respectively. Most of the study sites were located in rural provinces (Henan, Anhui, and Yunnan), and the most commonly used nucleoside reverse-transcriptase inhibitors before 2005 were zidovudine and didanosine (ddI), which was largely replaced by lamivudine, and the most commonly used nonnucleoside reverse-transcriptase inhibitors was nevirapine. Cohort studies provided data on HIV DR at follow-up as long as 72 months, but all data for HIV DR prevalence beyond 36

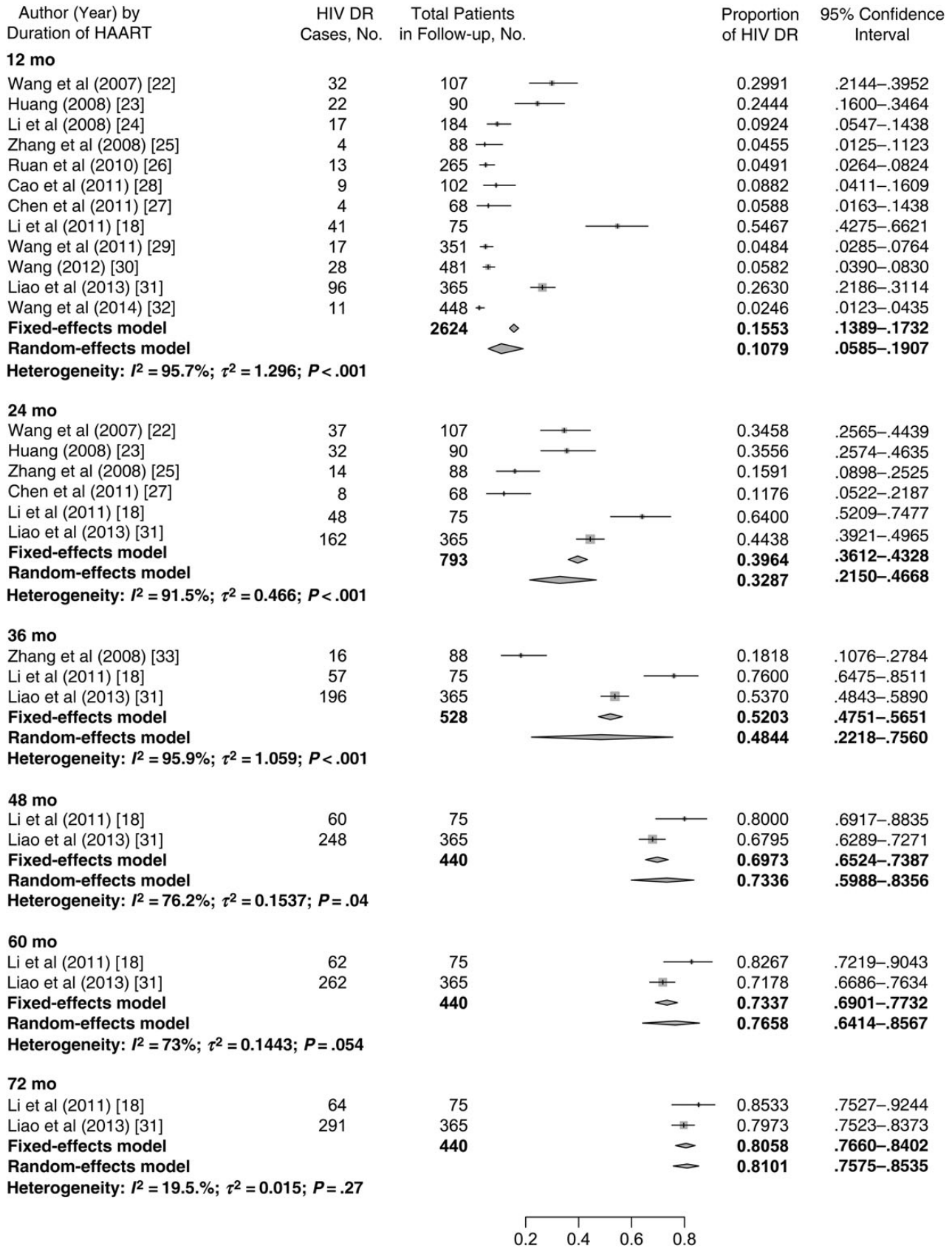

Figure 1. Pooled cumulative human immunodeficiency virus (HIV) drug resistance (DR) prevalence at each key point after highly active antiretroviral therapy (HAART) initiation (data from cohort studies).

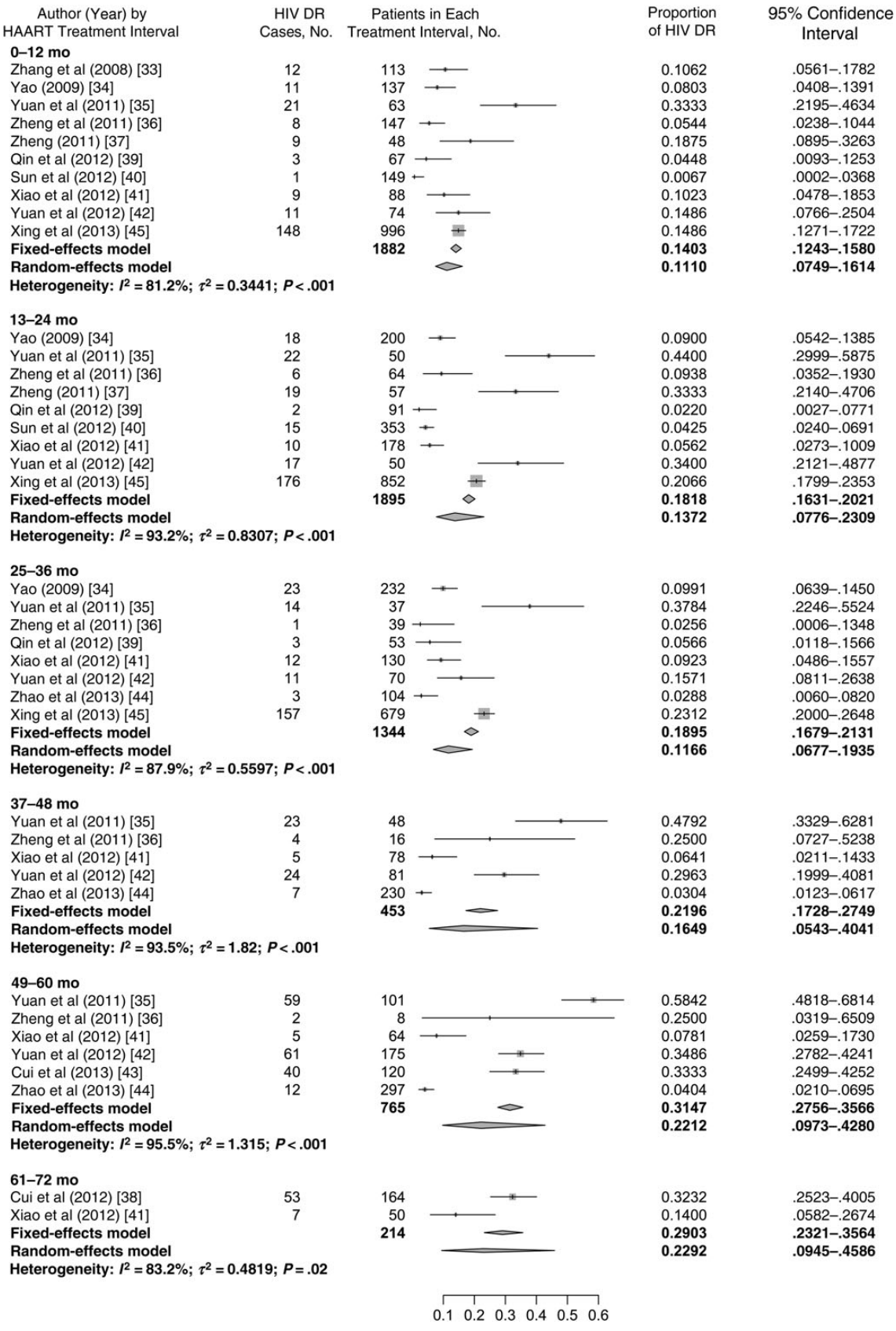

Figure 2. Pooled human immunodeficiency virus (HIV) drug resistance (DR) prevalence at each treatment interval since highly active antiretroviral therapy (HAART) initiation (data from cross-sectional studies).

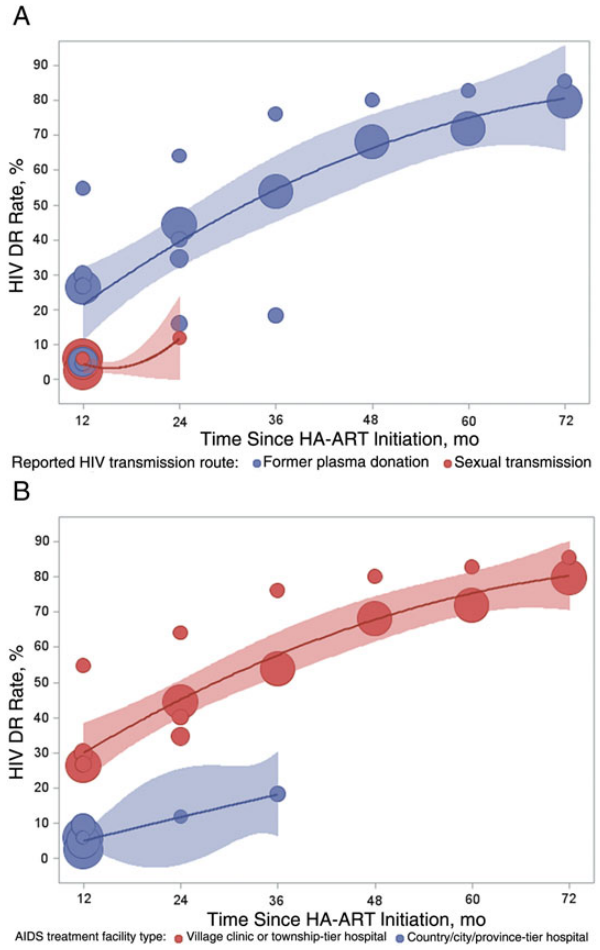

Figure 3. Emergence trends of human immunodeficiency virus (HIV) drug resistance (DR) after highly active antiretroviral therapy (HAART) initiation stratified by infection route (*A*) and treatment agency (*B*), based on data from cohort studies. Each bubble represents a study, and the size of the bubble figure corresponds to the study sample size; trend lines represent predicted prevalence with 95% confidence intervals. Abbreviation: ART, antiretroviral therapy.

months came from 2 longitudinal studies set in Henan province. Two cross-sectional studies provided HIV DR prevalence data beyond 60 months, informed by data from studies set in Henan and Jiangsu provinces (Table 1).

HIV DR Prevalence

We calculated pooled estimates of cumulative prevalence of HIV DR after HAART initiation separately for cohort studies and cross-sectional studies, respectively. Data from cohort studies (Figure 1) showed that the pooled HIV DR prevalence was 10.79% (95% confidence interval [CI], 5.85%–19.07%) at 12 months after HAART initiation, and at 72 months after initiation, this same estimate was 80.58% (95% CI, 76.6%–84.02%). The pooled HIV DR for the 0–12-month interval calculated from cross-sectional studies (11.1%, 95% CI, 7.49%–16.14%) was similar to that for cohort studies (10.79%, 95% CI, 5.85%–19.07%); however, estimates from the 2 study types began to diverge after 13 months of HAART (13.72% at 13–24 months for cross-sectional studies and 32.87% at 24 months for cohort studies) (Figure 2).

Subgroup Analysis

We conducted subgroup analyses for cohort studies according to type of HAART regimen (with or without ddI), HIV transmission route, and type of primary healthcare facility (village clinic vs public hospital) where patients received AIDS care. Because no cohort study in this analysis in which any patients received ddI-based regimens exceeded 12 months of follow-up, we were able to stratify HIV DR data only by treatment regimen at 12 months of HAART. Patients treated with a regimen containing ddI had much higher HIV DR rates than those with regimens without ddI (15.82% vs 4.97%, Supplementary Figure 2). When the HIV DR prevalence data were divided into groups by patients' infection route and treated agency, the patients who were infected through former plasma donation had higher HIV DR prevalence than those infected through sexual contact (Figure 3*A*), and the HIV DR prevalence was also higher among patients treated at village clinic or township hospitals than among those treated at county or city hospitals (Figure 3*B*).

DISCUSSION

China's NFATP was initially piloted in the former plasma donor population in the early 2000s [11, 12], when patients and healthcare providers had limited understanding of clinical management of AIDS and treatment optimization. In that time, patients were more likely to be treated at village clinic or township hospital with regimens containing ddI, an antiviral agent that has been predictive of virologic failure in past analyses [24]. By 2005, however, lamivudine had largely replaced ddI in NFATP-subsidized regimens [45], and <20% of HIV/AIDS patients were being treated at village clinics as opposed to county hospitals by 2013 (data not published).

Results of our analysis showed that the cumulative HIV DR prevalence rates increased with longer duration of HAART exposure. The 12-month pooled estimates of HIV DR—10.79% from cohort and 11.1% from cross-sectional studies—are higher than rates reported by other meta-analyses (2.35%) [10]. One possible explanation is that most Chinese patients who started HAART at the early rollout phase (2003–2005) were more likely to be exposed to a ddI-based regimen, which would lead to a higher HIV DR prevalence. Although the pooled prevalence of HIV DR after 72 months of HAART from cohort studies was as high as 80.58%, the fact that only 2 studies, both from Henan, provided the data for that subgroup analysis warns us

to interpret the rate with some caution. As a rural area, Henan patients have little adherence support and may have been more likely to have ddI-based regimens.

The pooled estimates of HIV DR prevalence at each treatment interval from cross-sectional were lower than corresponding estimates from cohort studies, probably for some of the following reasons. First, by design, cross-sectional studies are more vulnerable to selection bias because only patients with prevalent HAART exposure who remain HIV DR negative (the "survivors") are eligible for inclusion in the study. It is therefore likely that patients with a higher baseline risk of HIV DR—whether from poorer treatment adherence or for other reasons—are systematically excluded from inclusion in these studies. Second, because we were calculating cumulative prevalence of HIV DR, we carried forward all HIV DR–positive cases for subsequent intervals. Finally, the HIV DR prevalence data used to calculate pooled HIV DR prevalence after 36 months of HAART most likely reflect treatment outcomes in patients in resource-poor areas of rural China, where treatment adherence support is scarce and exposure to more toxic antivirals (eg, ddI) is more common, both of which conditions could lead to a higher HIV DR prevalence.

Subgroup analysis results showed that patients infected through former plasma donation had the highest rates of HIV DR. This is probably because the NFATP was initially piloted in this population made up of mostly poor famers with limited education and low health literacy. The stratified analysis also showed that patients receiving HAART at village- or town-level clinics had higher HIV DR rates than those treated at county hospitals, a finding corroborated by the fact that most former plasma donors seek medical care at village- or town-level clinics. Resource limitations and undertrained staff at these community-based healthcare settings present major challenges for the prevention of HIV DR in their patient populations.

Our study had several limitations. First, most subjects included in this analysis were originally infected through plasma donation, limiting the generalizability of results since China's epidemic has shifted to a sexually driven one [46], and most new patients with HIV/AIDS bear little resemblance to former plasma donors; they are younger, have more diverse risk behaviors, and have varied access to healthcare. Second, the HIV DR testing is generally reserved for patients with a detectable viral load (≥1000 copies/mL), leading to possible mismeasurement of HIV DR. The high correlation between HIV DR virus and higher viral load suggest that this issue was probably not a source of major bias.

Observational data and modeling exercises have suggested that other regions of the world with longer HIV treatment histories are experiencing a rise in the incidence of acquired HIV DR [47, 48]. The rapid scale-up of China's HAART program has hinged on leveraging existing community-based infrastructures, which provided rapid delivery of program drugs but may have contributed to an inflated rate of population-level HIV DR [16]. Although the overall pooled estimates of HIV DR in this analysis are by no means low, China's HIV DR problem does not seem more serious than in other developing country settings. As China continues to build healthcare infrastructure, routine virologic monitoring and adherence support will be critical for controlling the emergence of HIV DR.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Contributions. All authors had complete access to all data and approved the final version.

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Potential conflicts of interest. All authors: No reported conflicts.

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