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