Incidence and Associated Factors of HIV Drug Resistance in Chinese HIV-Infected Patients Receiving Antiretroviral Treatment

Hui Xing1, Xia Wang1, Lingjie Liao1, Yanling Ma2, Bin Su3, Jihua Fu4, Jianmei He5, Lin Chen6, Xiaohong Pan7, Yonghui Dong8, Wei Liu9, Jenny H. Hsi1, Liting Yang1, Yuhua Ruan1, Yiming Shao1*

1 State Key Laboratory for Infectious Disease Prevention and Control, and National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China, 2 Yunnan Center for Disease Control and Prevention, Kunming, China, 3 Anhui Center for Disease Control and Prevention, Hefei, China, 4 Shandong Center for Disease Control and Prevention, Jinan, China, 5 Hunan Center for Disease Control and Prevention, Changsha, China, 6 Shenzhen Center for Disease Control and Prevention, Shenzhen, China, 7 Zhejiang Center for Disease Control and Prevention, Hangzhou, China, 8 Xinjiang Center for Disease Control and Prevention, Urumqi, China, 9 Guangxi Center for Disease Control and Prevention, Nanning, China

Abstract

Background: A critical indicator of the future success of highly active antiretroviral therapy (HAART) is the incidence of HIV drug resistance, which has not been studied in China on the national scale.

Methods: HIV drug resistance baseline survey was conducted in the eight provinces with the largest numbers of patients on HAART in 2009, and a prospective cohort study with 12-month follow-up was completed in 2010. Patients completed an interviewer-administered questionnaire and provided blood for CD4+ T-lymphocyte count (CD4 count), HIV viral load (VL), and HIV drug resistance genotyping. Factors associated with incidence of HIVDR were identified by Cox regression analysis.

Results: The overall prevalence of HIV RNA \( \geq 1000 \) copies/ml and HIVDR at baseline was 12.4% and 5.6%, respectively. Incidence of HIVDR in the one year follow-up was 3.5 per 100 person years. Independently associated factors were started treatment with a didanosine-based regimen, received care at township hospital or village clinic, low baseline CD4 counts, and high baseline VL.

Conclusions: The incidence of HIVDR in China was higher than that of some developed countries. China urgently needs to provide comprehensive education and training to doctors at village clinics and township hospitals to improve quality community-based care and treatment.

Introduction

Since the introduction of combination drug regimens to treat human immunodeficiency virus (HIV) infection, known as highly active antiretroviral therapy (HAART), the rates of HIV-related morbidity and mortality have been markedly reduced. [1,2] However, the presence of antiretroviral drug resistance mutations in the infecting viruses may hamper the effectiveness of antiretroviral treatment (ART) because the mutations reduce the chances of full viral suppression. The increasing use of ART would lead to an increase in the incidence and prevalence of drug resistance especially in developing countries under WHO guidelines [3]. Previous studies on the prevalence of HIV drug resistance (HIVDR) in China and their associated factors [4,5] have served as assessments of the HIVDR consequences of China’s National Free Antiretroviral Treatment Program (NFATP). However, incidence of HIVDR is also a critical indicator of the future success of HAART but currently remains poorly studied in China. A few studies have investigated HIVDR incidence in limited risk populations, which showed that the crude incidence of both multidrug resistance and full-drug-class has decreased over time. [6–8] In this study, we aim to evaluate the incidence rate of HIVDR in China as well as to identify their associated factors.

Methods

Study Design and Study Participants

In 2009, the baseline survey on HIV drug resistance was conducted in the eight provinces in China with the largest numbers of patients on ART under the NFATP. The county in each province with the most patients was selected to receive the survey, and up to 250 patients were recruited for each province. If not enough eligible patients were found in the county, the county...
with the next largest number of patients was selected. All patients who received treatment from 2005 onwards were chronologically contacted for recruiting to the study; detailed subject recruitment procedure has been previously described. [4] The eligibility criteria include: receiving HIV antiretroviral therapy through NFATP from 2005 to 2009, being 10 years or older, and willingness and consent to participate. Treatments in the NFATP were first-line ART regimens consisting of 2 NRTIs [azidothymidine (AZT)+didanosine (DDI) or stavudine (D4T)+lamivudine (3TC)] and one NNRTI [nevirapine (NVP) or efavirenz (EFV)]. AZT, D4T, DDI, and NVP are generically produced in China, whereas 3TC and EFV are branded drugs which became available in 2005. All subjects provided written informed consent to participate in this study. The institutional review board (IRB) of the NCAIDS, China CDC approved this study.

Following the baseline survey, all patients were followed up one year later in 2010 to evaluate the incidence of HIV drug resistance (HIVDR). The survey sites were (outside parenthesis, provinces; inside parentheses, counties or municipalities): Yunnan (Longchuan), Anhui (Jieshou and Linquan), Shandong, Hunan (Hengyang), Guangdong (Shenzhen), Zhejiang (Hangzhou, Ningbo and Wenzhou), Xinjiang (Yining), and Guangxi (Hezhou). Shandong province has fewer patients who are dispersed throughout the province, hence patients were recruited from the whole province as opposed to in one county only.

Data Collection

In the survey, an interviewer-administered questionnaire interview was conducted to collect demographic data and data on ART treatment. Demographic variables include height, weight, ethnicity, education, residency, occupation, average monthly family income, and residency status (permanent vs. migrant). Treatment and behavior variables include initial treatment date, spouse ART status, taking traditional Chinese herbal medicines, receiving counseling and instructions on ART use (currently and before starting ART), clinical symptoms in the recent month, recent sexual behavior, recent alcohol use, recent drug, source of ART drug distribution, interval of refilling drug in the past month, treatment termination date, and reasons for terminating treatment. The variables on self-reported ART adherence include missed doses in the past month, and the proportion of medicines taken on time in the past month. Venous blood specimen samples were also collected for testing CD4+ T-lymphocyte count (CD4 count), HIV viral load, and HIVDR mutations.

Laboratory Analysis

CD4 count was measured within 24 hours by flow cytometry in the local CDCs and was quality assured by the National HIV Reference Laboratory. Plasma was separated by centrifugation and stored at −80°C, then they were transported to NCAIDS through cold chain. HIV viral load and drug resistance mutation tests were performed at the National Center for AIDS/STD Control and Prevention (NCAIDS), China CDC. Plasma HIV-1 RNA copy was quantified with real-time Nucleic Acid Sequence Based Amplification (NASBA) (NucliSense Easy Q, BioMerieux, France) or COBAS (Roche Applied Science, Germany) according to the manufacturers’ protocols. In samples with viral load ≥1,000 copies/ml, HIV drug resistance genotyping was carried out by an in-house polymerase chain reaction (PCR) protocol as previously described. [9,10] The HIV-1 pol gene (protease, amino acids 1–99; and part of reverse transcriptase, amino acids 1–252) was amplified. For analyzing HIV-1 drug resistance mutations, each sequence was compared with the subtype B consensus sequence in the Stanford HIV Drug Resistance Database (http://hivdb.stanford.edu) and was interpreted using the HIV db program. We included mutation results that conferred low-, intermediate-, and high-level resistance. [11].

Statistical Analysis

Primary outcome variables: we defined a case of drug resistance as the combined condition of having a HIV viral load ≥1,000 copies/ml and displaying genotypic HIVDR mutation(s). We used Cox proportional hazard models to evaluate hazard ratios of HIVDR incidence. Time zero was defined as the enrollment date at the surveys, and incidence of HIVDR was defined as those who developed resistant mutations during the one year interval before follow-up. Variables that were significantly (P≤0.05) associated with death in the univariate analysis were considered for inclusion in multivariate Cox regression models. All tests of significance were two-sided, with a P-value ≤0.05.

Results

Demographic Characteristics

The baseline cross-sectional survey in 2009 included 2192 patients, among whom 2005 were followed up in 2010, 46 patients died. Of the remaining 136 patients were not retained, 6 transferring out, 50 moving out of the area, and 80 losing to follow-up. The demographic and disease characteristics of the followed up patients are shown in Table 1. These include: 62.3% was male, mean age was 38.7±9.9, 68.3% was married, 38.8% had up to primary school education or less, 39.5% were farmers. The patients were primarily infected through sexual contact (55.1%), drug injection (23.0%) and blood/plasma transmission (15.6%).

Initial ART regimens (the regimen was used when the treatment was started) used were AZT/D4T+DDI+NVP (5.2%), AZT/D4T +3TC+NVP (72.2%), AZT/D4T +3TC+EFV (19.7%), and others (2.9%). However, in 2009, only 1.4% of patients still received DDI based regimens and 6.1% had been switched to second-line regimens. At the time of the baseline survey, the median duration of treatment was 17.6 months (interquartile range [IQR], 8.3–31.5). The mean CD4 count was 341.6 cells/μl, and the proportions of patients with CD4 count of 0–199, 200–349, and ≥350 cells/μl were 40.3%, 34.9% and 24.8%, respectively. The great majority of patients (1920/2192, 87.6%) had plasma HIV viral load <1,000 copies/ml. Among the patients with virologic failure, 123 (45.2%) had resistance mutations identified, including 90 (33.1%) with dual-class resistance.

Among the 2005 patients followed up in 2010, the mean CD4 count was 384.6 cells/μl, and the proportions of patients with CD4 count of 0–199, 200–349, ≥350 cells/μl were 23.2%, 31.4% and 45.4%, respectively. Approximately the same proportion of patients, 89.2% (1785/2002), had plasma HIV viral load <1,000 copies/ml. The incidence rate of death was 2.0 per 100 person years, with 46 patients having died during the follow-up period. Among patients retained at the 2010 follow-up and who had no HIVDR mutations in 2009, the incidence of resistance to any type of HIV drugs, as well as to NNRTIs, NRTIs, and PIs alone, were 3.5 per 100 person years (64/1837.3), 3.4 (63/1837.3), 2.6 (47/1837.3), 0.1 (1/1837.3), respectively, and 2.4% (46/1930) were resistant to both NRTIs and NNRTIs (Table 2). The most common NNRTI mutations were K103 and Y181 and the most common NRTI mutations were M184 and D67.

The risk factors for incidence of HIVDR were assessed through a Cox regression model (Table 3). The four factors that remained independently associated in the adjusted model were: initial ART regimen, ART drug distribution institute, baseline viral load, and
Those used AZT/D4T+DDI+NVP were 3.1 fold (95% CI 1.1–9.1) more likely to develop HIVDR compared to those used AZT/D4T+3TC+EFV, and those who received ART drugs in village clinics or township hospitals were 2.0 fold (95% CI 1.1–3.5) more likely to develop HIVDR than those who received treatment in county hospitals or CDCs. Patients with baseline viral load $\geq 1000$ copies/ml were 5.9 fold (95% CI 3.2–10.6) more likely to develop HIVDR than those whose baseline viral load was less than 1000 copies/ml. Compared to patients with baseline CD4 counts of $\geq 350$ cells/ml, patients with 0–199 cells/ml were 2.3 times (95% CI 1.2–4.5) more likely to develop HIVDR, and those with CD4 counts of 200–349 cells/ml were 1.6 times (95% CI 0.8–3.1) more likely to develop HIVDR.

**Discussion**

In this one-year prospective follow-up survey of HIVDR across eight provinces in China from January 2009 to December 2010, we found that the overall prevalence of HIVDR at baseline was 5.6%, virtually all with NNRTI mutations and three-fourths with NRTI mutations, which is comparable to proportions observed in

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**Table 1. Baseline characteristics of HIV patients in the study.**

| Variable                  | Number | Percentage (%) |
|---------------------------|--------|----------------|
| Total                     | 2192   |                |
| Sex                       |        |                |
| Male                      | 1365   | 62.3           |
| Female                    | 827    | 37.7           |
| Age in years: mean (SD), range | 38.7 (9.9), 32–44 |        |
| Married                   |        |                |
| Yes                       | 1497   | 68.3           |
| No                        | 695    | 31.7           |
| Education                 |        |                |
| Illiterate                | 273    | 12.5           |
| Primary school            | 577    | 26.3           |
| Middle school             | 839    | 38.3           |
| Junior high school or more | 503    | 23.0           |
| Occupation                |        |                |
| Farmer                    | 1109   | 50.6           |
| Other                     | 1083   | 49.4           |
| HIV transmission route    |        |                |
| Sexual contact            | 1208   | 55.1           |
| Blood/plasma transmission | 341    | 15.6           |
| Drug injection            | 505    | 23.0           |
| Other                     | 138    | 6.3            |
| Initial ART regimen       |        |                |
| AZT/D4T+DDI+NVP/EFV       | 114    | 5.2            |
| AZT/D4T+3TC+NVP/EFV       | 2015   | 91.9           |
| Other                     | 63     | 2.9            |
| Baseline ART regimen(2009) |       |                |
| AZT/D4T+DDI+NVP/EFV       | 31     | 1.4            |
| AZT/D4T+3TC+NVP/EFV       | 1986   | 90.6           |
| Second-line regimens      | 133    | 6.1            |
| Other                     | 42     | 1.9            |
| Duration of HAART treatment (months) |     |                |
| 0–12                      | 813    | 37.1           |
| 13–24                     | 556    | 25.4           |
| 25–36                     | 393    | 17.9           |
| >37                       | 430    | 19.6           |
| Baseline CD4(2009)        |        |                |
| <200                      | 405    | 18.5           |
| 200–349                   | 479    | 21.9           |
| 350–499                   | 764    | 34.9           |
| $\geq 500$                | 544    | 24.8           |
| Baseline viral load $\geq 1000$ copies/ml(2009) | 272 | 12.4           |
| HIV drug resistance(2009) |        |                |
| Resistance to any drugs   | 123    | 5.6            |
| Resistance to NNRTIs      | 115    | 5.3            |
| Resistance to NRTIs       | 96     | 4.4            |
| Resistance to NNRTIs and NRTIs | 90 | 4.1            |
| Resistance to PIs         | 6      | 0.3            |

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**Table 2. HIVDR mutations among patients with drug resistance.**

| Mutations        | Number | %  |
|------------------|--------|----|
| Total            | 64     | 100.0|
| NRTIs            | 47     | 73.4|
| V75A/M/T         | 1      | 1.6 |
| L74I/V           | 2      | 3.1 |
| L100I            | 2      | 3.1 |
| L210W            | 2      | 3.1 |
| Q151L/M          | 2      | 3.1 |
| M41L             | 3      | 4.7 |
| T215C/D/F/I/S/Y  | 6      | 9.4 |
| K70E/R           | 8      | 12.5|
| D67G/N           | 12     | 18.8|
| M184I/I          | 46     | 71.9|
| NNRTIs           | 63     | 98.4|
| M230L            | 1      | 1.6 |
| A98G             | 2      | 3.1 |
| P225H            | 3      | 4.7 |
| Y188C/L/H        | 3      | 4.7 |
| F227L            | 4      | 6.3 |
| V106A/M          | 8      | 12.5|
| K101E/H/P        | 13     | 20.3|
| G190A/S          | 20     | 31.3|
| Y181C/V          | 22     | 34.4|
| K103H/N/S/T      | 25     | 39.1|
| PI               | 1      | 1.6 |
| M46I             | 1      | 1.6 |
| I54V             | 1      | 1.6 |
| L76V             | 1      | 1.6 |
| V82F             | 1      | 1.6 |

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*Table 1.* Baseline characteristics of HIV patients in the study.

*Table 2.* HIVDR mutations among patients with drug resistance.
Table 3. Factors associated with incidence of drug resistance in 2010.

| Variable                                      | Number | HIVDR  | Person year | Incidence/100 person year | HR (95% CI) | P-value | Adjusted HR (95% CI) | P-value |
|-----------------------------------------------|--------|--------|-------------|----------------------------|-------------|---------|----------------------|---------|
| Total                                         | 1893   | 64     | 1837.3      | 3.5                        |             |         |                      |         |
| Sex                                           |        |        |             |                            |             |         |                      |         |
| Male                                          | 1166   | 47     | 1128.3      | 4.2                        |             |         |                      |         |
| Female                                        | 727    | 17     | 709.0       | 2.4                        | 0.6(0.3,1.0) | 0.07    |                      |         |
| Age                                           |        |        |             |                            |             |         |                      |         |
| ≤30                                           | 376    | 12     | 366.1       | 3.3                        |             |         |                      |         |
| 31–40                                         | 862    | 33     | 842.2       | 3.9                        | 1.3(0.6,2.4) | 0.50    |                      |         |
| 41–50                                         | 422    | 15     | 406.0       | 3.7                        | 1.2(0.5,2.5) | 0.70    |                      |         |
| >50                                           | 233    | 4      | 223.1       | 1.8                        | 0.7(0.2,2.1) | 0.49    |                      |         |
| Married                                       |        |        |             |                            |             |         |                      |         |
| Yes                                           | 1309   | 43     | 1276.0      | 3.4                        |             |         |                      |         |
| No                                            | 584    | 21     | 561.4       | 3.7                        | 1.1(0.7,1.9) | 0.65    |                      |         |
| Education                                     |        |        |             |                            |             |         |                      |         |
| Junior high school or more                    | 1172   | 36     | 1140.1      | 3.2                        |             |         |                      |         |
| Primary school or less                        | 721    | 28     | 697.3       | 4.0                        |             |         |                      |         |
| Occupation                                    |        |        |             |                            |             |         |                      |         |
| Farmer                                        | 987    | 32     | 947.8       | 3.4                        |             |         |                      |         |
| Other                                         | 906    | 32     | 889.6       | 3.6                        | 1.3(0.8,2.2) | 0.27    |                      |         |
| Monthly income per person within the family (RMB) |    |        |             |                            |             |         |                      |         |
| <400                                          | 875    | 39     | 861.5       | 4.5                        |             |         |                      |         |
| ≥400                                          | 1018   | 25     | 975.8       | 2.6                        | 0.8(0.5,1.3) | 0.29    |                      |         |
| Spouse receives ART                           |        |        |             |                            |             |         |                      |         |
| No                                            | 1452   | 53     | 1405.5      | 3.8                        |             |         |                      |         |
| Yes                                           | 441    | 11     | 431.8       | 2.5                        | 0.7(0.4,1.3) | 0.28    |                      |         |
| HIV transmission route                        |        |        |             |                            |             |         |                      |         |
| Sexual intercourse                            | 1084   | 34     | 1056.7      | 3.2                        |             |         |                      |         |
| Drug injection                                | 393    | 17     | 387.9       | 4.4                        | 1.1(0.6,2.0) | 0.73    |                      |         |
| Blood donation or transfusion                 | 301    | 10     | 281.2       | 3.6                        | 1.3(0.7,2.7) | 0.42    |                      |         |
| Other                                         | 115    | 3      | 111.5       | 2.7                        | 0.9(0.3,3.1) | 0.91    |                      |         |
| Initial ART regimen                           |        |        |             |                            |             |         |                      |         |
| AZT/D4T +3TC+EFV                              | 376    | 10     | 362.0       | 2.8                        |             |         |                      |         |
| AZT/D4T+DDI+NVP                               | 85     | 6      | 79.2        | 7.6                        | 4.1(1.5,11.3) | 0.01   | 4.5(1.6,12.6) | <0.01  |
| AZT/D4T +3TC+NVP                              | 1375   | 48     | 1343.8      | 3.6                        | 1.1(0.5,2.1) | 0.9     | 0.8(0.4,1.7) | 0.58   |
| Other                                         | 57     | 0      | 52.4        | 0.0                        |             |         |                      |         |
| Baseline ART regimen(2009)                    |        |        |             |                            |             |         |                      |         |
| AZT/D4T +3TC+EFV                              | 569    | 19     | 549.9       | 3.5                        |             |         |                      |         |
| AZT/D4T+DDI+NVP                               | 33     | 2      | 32.3        | 6.2                        |             |         |                      |         |
| AZT/D4T +3TC+NVP                              | 1187   | 39     | 1160.9      | 3.4                        |             |         |                      |         |
| Second-line regimen                           | 49     | 1      | 43.6        | 2.3                        |             |         |                      |         |
| Other                                         | 55     | 3      | 50.7        | 5.9                        |             |         |                      |         |
| Duration of ART (year)                        |        |        |             |                            |             |         |                      |         |
| 0–12                                          | 694    | 27     | 660.8       | 4.1                        |             |         |                      |         |
| 13–24                                         | 477    | 18     | 467.0       | 3.9                        | 0.7(0.4,1.3) | 0.29    |                      |         |
| 25–36                                         | 354    | 8      | 349.6       | 2.3                        | 0.4(0.2,0.8) | 0.01    |                      |         |
| >37                                           | 368    | 11     | 360.0       | 3.1                        | 0.5(0.2,1.0) | 0.04    |                      |         |
| Missed doses in the past month                |        |        |             |                            |             |         |                      |         |
| No                                            | 1838   | 59     | 1786.2      | 3.3                        |             |         |                      |         |
| Yes                                           | 92     | 5      | 85.7        | 5.8                        | 2.3(0.9,5.9) | 0.07    |                      |         |
Table 3. Cont.

| Variable                                      | Number | HIVDR Person Year | Incidence/100 person year | HR (95% CI) | P-value | Adjusted HR(95% CI) | P-value |
|-----------------------------------------------|--------|-------------------|----------------------------|-------------|---------|---------------------|---------|
| Taking drugs on time                          |        |                   |                            |             |         |                     |         |
| <90%                                          | 73      | 5                 | 70.9                       | 7.1         |         |                    |         |
| ≥90%                                          | 1820    | 59                | 1766.4                     | 3.3         | 0.5(0.2,1.2) | 0.12               |         |
| ART drug distribution institute               |        |                   |                            |             |         |                     |         |
| County hospital or CDC                        | 1525    | 44                | 1483.6                     | 3.0         |         |                    |         |
| Village clinic or township hospital           | 368     | 20                | 353.7                      | 5.7         | 1.6(0.9,2.7) | 0.10               | <0.05   |
| Interval of refilling drug in the past month  |        |                   |                            |             |         |                     |         |
| Less than one month                           | 1081    | 36                | 1026.1                     | 3.5         |         |                    |         |
| More than one month                           | 812     | 28                | 811.2                      | 3.5         | 0.8(0.5,1.3) | 0.37               |         |
| CD4 cell counts at baseline(2009)             |        |                   |                            |             |         |                     |         |
| ≥350                                          | 797     | 18                | 785.5                      | 2.3         |         |                    |         |
| <2000                                         | 647     | 23                | 626.7                      | 3.7         | 2.1(1.1,3.9) | 0.02               | 2.0(1.1,3.7) | 0.03 |
| <200                                          | 449     | 23                | 425.1                      | 5.4         | 4.1(2.1,7.8) | <0.01              | 3.5(1.6,6.9) | <0.01 |
| Viral Load at baseline(2009)                  |        |                   |                            |             |         |                     |         |
| VL<1000                                       | 1773    | 45                | 1724.2                     | 2.6         |         |                    |         |
| VL≥1000                                       | 120     | 19                | 113.1                      | 16.8        | 9.5(5.5,16.5) | <0.01              | 7.1(4.0,12.7) | <0.01 |

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other countries. [3,12] The incidence of HIVDR during the one year follow-up was 3.5 per 100 person years, and NNRTI mutations and NRTI mutations were 3.4/100 person years and 2.6 per 100 person years, respectively. Factors independently associated with incidence of HIVDR were: initial treatment with a didanosine (DDI)-based regimen; receiving care at township hospital or village clinic; low baseline CD4 cell counts; and high baseline viral load.

An important concern for widespread ART use is the potential for emerging HIVDR mutations given improperly administered regimens and lack of drug adherence support in resource-limited settings. Our results here revealed that the HIVDR incidence rates in China are higher than those of a number of countries. An ecological study among ART treated patients in British Columbia, Canada reported that the incidence of HIVDR decreased dramatically from 1.73 per 100 person-months of therapy in 1997 to 0.13 per 100 person-months of therapy in 2008. [7] A study in Denmark showed that among 1829 treatment-naïve patients who initiated ART in or after 1998, the incidence of NRTIs and NNRTIs were 0.59 and 1.06 per 100 person-years. [6] In Portugal, a study showed that the annual incidence of HIVDR decreased from 5.7% in July 2001 to 2.7% in July 2006 in Portugal for patients who initiated ART in or after 1998, the incidence of NRTIs and NNRTIs were 0.59 and 1.06 per 100 person-years. [6] It is therefore important for policymakers and care providers to address the factors driving China’s relatively high HIVDR incidence rates.

The first risk factor we identified is the use of DDI-based regimens, which resulted in higher HIVDR incidence compared with lamivudine (3TC)-based regimens. Previous studies have reported that DDI-based regimens are associated with higher rates of emergence of liver disease, [13] virologic failure, [14] prevalence of HIVDR [15–17] and mortality. [18] It is possible that because DDI is associated with more side effects compared with 3TC-based regimens, patients are less likely to stay adherent to drug intake and clinical visits. [18] The World Health Organization (WHO) suggested that DDI had serious constraints for use in first-line regimens because of toxicities and cost. [19] Although DDI is not recommended in the NFATP first-line cART regimens and few patients still use it, health care providers in China should pay close attention to the patients whose initial regimens contain DDI and has switched to other regimens.

Secondly, our findings show that patients who received care in rural village clinics or township hospitals were significantly more likely to experience incident HIVDR than those treated at county-level CDCs or hospitals staffed by trained physicians. Patients with low income are also more likely to develop drug resistance. As our previous study reported, patients in rural or lower-income regions in China have significantly lower levels education and socio-economic status, and health care providers have less advanced technical infrastructure and capacity. [20] It is likely that patients cannot properly adhere to complex treatment regimens without adequate assistance, and that improper use of these drugs by health care systems with low infrastructure will blunt their effectiveness and favor the emergence of antiretroviral resistance. [21] China urgently needs to improve health education among patients and training for doctors at village clinics and township hospitals to provide quality community-based care and treatment.

Finally, we found that lower baseline CD4 cell count and higher baseline viral load are significantly associated with incidence of drug resistance. Our results are consistent with previous studies reporting that initiating HAART at higher CD4 cell counts may decrease the risk of developing drug resistance [22,23] and that higher baseline viral load was a major predictor of drug resistance. [24] HIV viral load and CD4 cell count are the primary clinical indicators that should be used to guide the initiation of antiretroviral therapy and subsequent changes in therapy. It is also consistent with other findings that starting antiretroviral therapy earlier yields better clinical outcomes for survival. [25,26] At the start of China’s NFATP in 2002, treatment was provided for patients with CD4 count <200 cells/µL; in 2008, the eligibility criterion was changed to 350 cells/µL to improve the outcomes of treatment. Care must be taken to continuously monitor NFATP patients for emerging HIVDR in order to assess potential needs for amending these eligibility indicators.
In conclusion, Chinese policymakers and care providers need to consider the relatively high incidence of HIVDR in China and address the related factors, and provide comprehensive education and training to community health workers or nurses to improve health care quality.

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Author Contributions

Conceived and designed the study and experiment: HX YR YS. Participated in designing the survey and performed the survey within their own provinces: YM BS [J] JH LC XP YD WL. Revised the paper and gave suggestions to revise the paper: JHH. Data collection and management: LY. Performed the experiments: LL. Analyzed the data: XW. Wrote the paper: XW.