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Effect of Viral Load and Drug Resistance on Mortality among Chinese HIV-Infected Patients Receiving Antiretroviral Treatment

Xia Wang, Hui Xing, Yuhua Ruan, Lingjie Liao, Haiwei Zhou, Bin Chen, Junqi Su, Wei Zheng and Yiming Shao*

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

Abstract

Background: The Chinese National Free Antiretroviral Treatment Program (NFATP) for HIV-infected patients has saved lives. However, there is no data on the effect of HIV drug resistance on mortality among Chinese patients receiving antiretroviral treatment.

Methods: We linked patient records from two national databases: baseline HIV drug resistance and viral load data were obtained from four national drug resistance surveys in 2004, 2005, 2006 and 2009, and all-cause mortality was ascertained in a prospective way in NFATP database. Factors associated with death were identified by Cox regression model.

Results: A total of 5421 HIV-infected patients who participated in the drug resistance surveys and received combination antiretroviral therapy (cART) from NFATP were included in the analysis. Approximately one-third of patients (1462/5421) had baseline plasma HIV-1 viral load ≥1,000 copies/ml, and 48.4% (708/1462) of these patients with virologic failure had resistance to any type of HIV drug. The mortality rate was 2.8 per 100 person-years in all participating patients, 4.8 in patients with virologic failure, and 5.7 in patients with drug resistance. Multivariate Cox regression analyses showed that older age, female, transmission through plasma/blood and drug injection, lower CD4 count, virologic failure and drug resistance, and didanosine-based regimens had statistically significant associations with increased risk of mortality.

Conclusions: Virologic failure and drug resistance are common among Chinese HIV-infected patients receiving antiretroviral treatment. Virologic failure and drug resistance are associated with an increased risk of mortality. Treatment adherence should be promoted to reduce the risks of both virologic failure and drug resistance, and virologic and clinical monitoring of treatment should be enhanced to guide more appropriate use of cART drugs.

Keywords: HIV drug resistance; Combination antiretroviral therapy; Mortality; China

Introduction

The rapid expansion of HIV combination antiretroviral therapy (cART) in resource-limited countries is saving lives and improving the quality of life for patients, households, and communities [1]. In China, the National Free Antiretroviral Treatment Program (NFATP) initiated in 2002 has also significantly reduced mortality among HIV patients, from 27 deaths per 100 person-years prior to treatment to 4-5 after 6 months of cART [2,3]. Overall mortality decreased from 39.3 per 100 person-years in 2002 to 14.2 per 100 person-years in 2009, with treatment coverage concomitantly increasing from almost zero to 63.4% [4]. However, like other developing countries using first-line generic antiretroviral regimens, [5-7] China is facing an emerging problem of drug resistance [8-10] and challenged by high AIDS-related deaths in spite of the expansion of treatment coverage [11]. HIV drug resistance is associated with faster clinical progression and elevated mortality [13-15], yet there is currently no evaluation of the effect of virologic failure and drug resistance on mortality among Chinese patients. As the Chinese NFATP database has significant missing data on HIV viral load and drug resistance, we linked the NFATP database with results from four national HIV drug resistance surveys in 2004, 2005, 2006 and 2009, and investigated the relationship between HIV virologic failure, drug resistance and mortality.

Methods

Study design and study population

We combined data from two national databases on antiretroviral treatment and on drug resistance, respectively. Baseline HIV viral load and drug resistance mutations were obtained from four national drug resistance surveys in 2004, 2005, 2006 and 2009 by the Chinese National HIV Drug Resistance Surveillance and Monitoring Network. All-cause mortality was ascertained prospectively in the NFATP database. All HIV-infected patients who were enrolled in NFATP and who also participated in the national drug resistance survey were included in this analysis.

A total of 5,781 patients participated in the four cross-sectional surveys in 2004, 2005, 2006 and 2009. For patients surveyed more than once, we used data from the first survey showing drug resistance. Data from the four surveys were combined, and records were linked to patient records in the NFATP database by the individual patient's NFATP identification number. A total of 5,421 patients were included in our analysis; 234 patients were excluded because their drug resistance records could not be matched with the NFATP database, and

***Corresponding author:** Yiming Shao, 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 No. 155 Changbai Road, Changping District, Beijing 102206, PR China, Telephone: +86-10-58900981; Fax: +86-10-58900980; E-mail: yshao08@gmail.com

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another 126 patients were excluded due to missing data on viral load. The study was approved by the institutional review boards (IRB) of the National Center for AIDS/STD Control and Prevention of the China Center for Disease Control and Prevention (NCAIDS/China CDC). All participants provided written informed consent.

Data source: national drug resistance surveys

The four national HIV drug resistance surveys were cross-sectional surveys conducted in 2004, 2005, 2006 and 2009. For the surveys from 2004 to 2006, stratified cluster sampling was used to select patients who received cART in NFATP, using county or district as the smallest sampling unit. Approximately 10% of registered patients in NFATP were sampled, and the number of patients from each province was roughly in reverse proportion to the number of patients in treatment in order to oversample participants from provinces with smaller numbers of patients. When a county or district was selected, all patients in this county or district were invited for eligibility screening. In 2004 and 2005, screening and recruitment into the study was performed as per Figure 1. In 2006, in addition to this algorithm, all patients previously surveyed in 2004 or 2005 and could be located were also followed-up.

In 2009, the survey was conducted in the nine provinces with the largest numbers of patients on cART, and the prefecture in each province with the most patients was selected. Up to 250 patients were enrolled per province, according to the eligibility criteria above. If not enough eligible patients were found in the prefecture, the prefecture with the next largest number of patients was then selected. Since Henan began cART treatment before all other provinces and had by far the largest number of treated patients, a different selection process was used. Two high HIV prevalence counties where resistance surveillance had not previously been done were selected. From each county, the villages with the highest number of treated patients from 2003 and 2004 were selected, and all patients in those two villages were recruited. From the rest of the two counties, everyone treated from 2005 onwards were chronologically recruited to participate in the survey. The inclusion criteria for the four surveys were: receiving HIV antiretroviral therapy, being 18 years or older, and willingness and consent to participate. Treatments provided through the NFATP were first-line cART 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.

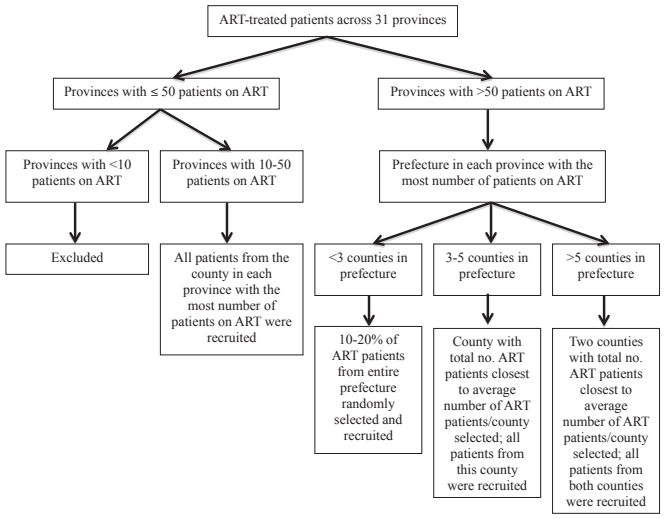


Figure 1: Patient recruitment algorithm for antiretroviral therapy experienced patients screened for the 2004, 2005, and 2006 cross-sectional surveys.

The drug resistance survey consisted of a questionnaire for the patient and blood specimen collection. The questionnaire included questions on: the patients' identification number in NFATP; demographic information such as sex, age, ethnicity, years of education, marital status, and occupation; HIV infection route; and AIDS-defining clinical symptoms in the past month. It also included questions on treatment history, including initiation date and duration of cART treatment, cART regimens, cART drug distribution institute, counseling and instruction on cART use, cART adherence, reason for non-adherence, etc.

Laboratory analysis

All participants donated a blood sample for testing CD4 count and HIV viral load. CD4 count was measured by flow cytometry in the provincial Centers of Disease Control and Prevention. HIV viral load and drug resistance mutation tests were performed in four central laboratories (NCAIDS, China CDC; Academy of Military Medical Science; China Medical University; Shanghai Municipal Center for Disease Control and Prevention). Plasma HIV-1 RNA copy was quantified with real-time Nucleic Acid Sequence Based Amplification (NASBA), NASBA (NucliSense Easy Q, BioMerieux, France) or COBAS (Roche Applied Science, Germany) according to the manufacturer's protocol. In samples with viral load ≥1,000 copies/ml, HIV drug resistance genotyping was carried out by an in-house polymerase chain reaction (PCR) procedure as previously described.[9,16] 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.

Statistical analysis

We performed prospective cohort analysis on data from NFATP and the four national HIV drug resistance surveys. The primary outcome variable was death, and was reported through the NFATP database. The primary predictor variables were HIV viral load and drug resistance; these, as well as other covariates such as CD4 count, were reported through the drug resistance surveys. According to WHO criteria, virologic failure was defined as HIV viral load ≥1,000 copies/ml [17]. We used Cox proportional hazard models to evaluate hazard ratios of death associated with baseline virologic failure, while adjusting for other baseline covariates such as age, duration on cART and HIV transmission route. Time zero was defined as the enrollment date at the surveys, and mortality was censored by May 1, 2011. Variables that were significantly ($P \leq 0.05$) 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 indicating that an association was statistically significant.

Results

Demographic characteristics

Of the 5421 participants in the four national drug resistance surveys, 57% were male; 82.7% were of Han ethnicity; 23.6% were single; 45.4% were farmers; median age was 39 years (range, 16-80 years); 20% of participants had no education, and over 50% had attended primary or

Variable	Number	Percentage
Overall	5421	
Sex		
Male	3088	57.0
Female	2333	43.0
Age (mean ± SD, year)	39 ± 9.6	
Ethnicity		
Han	4482	82.7
Other Minorities	939	17.3
Education		
Primary school or less	2646	48.8
Junior high school or more	2775	51.2
Married		
Yes	4142	76.4
No	1279	23.6
Occupation		
Farmer	2462	45.4
Others	2959	54.6
HIV transmission route		
Sexual intercourse	1782	32.9
Blood/plasma transmission	2646	48.8
Drug injection	690	12.7
Other	303	5.6
Initial HAART regimen		
DDI based regimens	1332	24.6
3TC based regimens	3336	61.5
Others	753	13.9
Duration of HAART treatment (months)		
0-12	2677	49.4
13-24	1276	23.5
25-36	736	13.6
37-60	631	11.6
>61	101	1.9
Discontinued treatment	156	2.9
CD4 cell account at survey		
≥ 500	972	17.9
350-499	1030	19.0
200-349	1783	32.9
100-199	1099	20.3
<100	537	9.9
HIV RNA ≥ 1000 copies/ml	1462	27.0

Table 1: Demographic characteristics of HIV patients in the study.

junior middle school (1-9 years of schooling) (Table 1). Forty-eight percent of participants were former plasma donors who contracted HIV through the use of contaminated blood collection equipment during commercial blood/plasma donation practices in the 1990s [18,19]. Other reported transmission routes were sexual contact (32.9%), and drug injection (12.7%). A large number of patients were from provinces where the primary risk of HIV infection was contaminated plasma collection, including Henan (n=1589, or 29.3% of total participants), Anhui (195, 9.1%),and Hubei (246, 4.5%), or from provinces where the primary risks were sexual contact and injection drug use, such as Yunnan (464, 8.6%), Xinjiang (505, 9.3%), Guangxi (453, 8.4%) and Hunan (246, 4.5%); the remaining 1723 patients (31.8%) represented mixed risk groups and were from the other 22 provinces.

cART regimens and baseline virologic and immunologic profiles

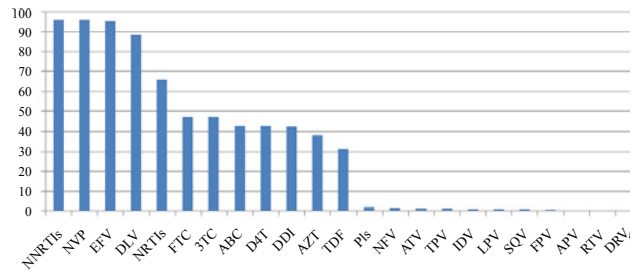
All patients received free cART treatment through the NFATP. The initial regimens used by study participants were: AZT+DDI+NVP (13.0% or 704 out of 5421 patients used this regimen), D4T+DDI+NVP (8.8%), AZT/D4T+DDI+EFV (2.8%), AZT+3TC+NVP (21.9%), D4T+3TC+NVP (29.6%), AZT+3TC+EFV (5.3%), D4T+3TC+EFV (4.5%) and others (13.9%). Median duration on cART prior to 2006 baseline survey was 13 months (interquartile range [IQR], 6-26 months). The proportion of patients with CD4 counts of 0-99, 100-199, 200-349, 350-499 and ≥500 cells/mL at the baseline survey was 9.9%, 20.3%, 32.9%, 19%, and 17.9% respectively. The majority of patients did not experience virologic failure; 73.0% (3959/5421) had plasma HIV viral load <1,000 copies/mL, while 27.0% of patients (1462/5421) had viral load ≥1,000 copies/mL. Patients with viral load ≥1,000 copies/mL had a longer median duration of cART treatment than those with viral load <1,000 copies/mL (15 versus 12 months).

HIV-1 drug resistance and mutations

According to WHO guidelines, patients with HIV viral load <1,000 copies/ml have a low risk of drug resistance, and therefore were not tested for drug resistance. Of the 1462 patients with HIV viral load ≥1,000 copies/mL, 708 (48.4%) had resistance to any type of HIV drugs (Figure 2). The prevalence of resistance to NNRTI drugs (46.6%) was higher than that to NRTI drugs (32.1%). Nearly 0.3% of patients who were never exposed to protease inhibitor (PI) drugs had resistance to PI drugs. The drug resistance prevalence rates among patients with viral load ≥1,000 copies/mL who had received cART for 0-11, 12-23, 24-35, and ≥36 months prior to the baseline survey were 36.5% (232/636), 49.2% (184/374), 52.5% (115/219) and 76.0% (177/233) respectively. Overall prevalence was highest among former plasma donors (52.4%), followed by injection drug users (45.5%), those infected via sexual contact (37.7%), and unspecified group (34.3%).

Mortality and risk factors

Among all study patients, 543 deaths occurred, with a median 13-month treatment during a median of 28.5 months follow-up period (IQR, 6-26 months). The mortality rate was 2.8 per 100 person-years among all patients, and 5.7 per 100 person-years among patients with HIV drug resistance (HIVDR). For all subsequent analysis, we further excluded patients with viral load (VL) ≥ 1000 but whose genetic sequence was not successfully determined so as to accurately evaluate the association between drug resistance and mortality. Therefore, 5152 subjects were included in the Cox regression model. Univariate analyses were performed first, and variables that were statistically significant (*P*



Note: NNRTIs, Non-nucleoside reverse transcriptase inhibitors; NVP, Nevirapine; EFV, Efavirenz; DLV, Delavirdine; NRTIs Nucleoside reverse transcriptase inhibitors; FTC, Emtricitabine; 3TC, Lamivudine; ABC, Abacavir; D4T, Stavudine; DDI, Didanosine; AZT, Azidothymidine; TDF, Tenofovir; PIs, Protease inhibitors; NFV, Nelfinavir; ATV, Atazanavir; TPV, Tipranavir; IDV, Indinavir; LPV, Lopinavir; SQV, Saquinavir; FPV, Fosamprenavir; APV, Amprenavir; RTV, Ritonavir; DRV, Darunavir.

Figure 2: HIV drug resistance for each drug among 708 patients with plasma HIV-1 RNA concentrations ≥ 1000 copies/ml and with drug resistance.

≤ 0.05) were included in a multivariate Cox regression model. Seven variables were independently associated with death: older age (per 1 year increase adjusted hazard ratio [AHR]=1.04, 95% confidence interval [CI]: 1.03-1.05), female (compared to male: AHR=0.8, 95% CI: 0.7-1.0), route of HIV transmission (compared to sexual transmission: plasma/blood transmission AHR=1.6, 95% CI: 1.2-2.1; injection drug use AHR=3.7, 95% CI: 2.6-5.2; others AHR=1.5, 95% CI: 0.9-2.4), lower CD4 count (compared to CD4 ≥ 350/ul : 200-349 AHR=1.7, 95% CI: 1.3-2.3; 100-199: AHR=2.8, 95% CI: 2.1-3.7; 0-199: AHR=5.1, 95% CI: 3.8-6.7), and HIV viral load (compared to viral load <1,000 copies/mL: VL ≥ 1000 and VL<10,000 without HIVDR AHR=1.4, 95% CI: 0.8-2.4; VL ≥ 1000 and VL <10,000 with HIVDR AHR=1.0, 95% CI: 0.6-1.5; VL ≥ 10,000 without HIVDR AHR=1.7, 95% CI: 1.3-2.3; VL ≥ 10,000 with HIVDR AHR=2.4, 95% CI: 1.9-3.0). Compared to didanosine-based regimens, lamivudine-based regimens were protective against developing drug resistance (AHR=0.7, 95% CI 0.5-0.8) (Table 2).

In order to identify whether drug resistance was independently associated with death, subgroup analysis was conducted to compare mortality between HIV patients VL ≥ 10000 with HIVDR and VL ≥ 10000 without HIVDR. After controlling for potential confounding factors, including sex, age, education, occupation, HIV transmission route, initial cART regimens, and baseline CD4 cell count, the final multivariate Cox regression model showed drug resistance was significantly associated with increased risk of death (AHR=1.4, 95% CI 1.0-1.9) (Table 3).

Variable	Death	Person year	Death/100 person year	HR(95% CI)	*P-value*	Adjusted HR (95% CI)	*P-value*
Total	463	17032.8	2.7				
Sex							
Male	290	9161.2	3.2				
Female	173	7871.6	2.2	0.7(0.6,0.8)	<0.01	0.8(0.7,1.0)	0.03
Age (per one year)				1.04(1.03,1.05)	<0.01	1.04(1.03,1.05)	<0.01
Ethnicity							
Han	393	14293.9	2.7				
Other Minorities	70	2738.9	2.6	0.9(0.7,1.2)	0.65		
Married							
Yes	342	13015.5	2.6				
No	121	4017.3	3.0	1.2(0.9,1.4)	0.17		
Education							
Primary school or less	271	8651.6	3.1				
Junior high school or more	192	8381.2	2.3	0.7(0.6,0.9)	<0.01		
HIV transmission route							
Sexual intercourse	67	4861.7	1.4				
Blood/plasma transmission	293	9380.7	3.1	2.3(1.7,2.9)	<0.01	1.6(1.2,2.1)	<0.01
Drug injection	79	1789.0	4.4	3.2(2.3,4.4)	<0.01	3.7(2.6,5.2)	<0.01
Other	67	4861.7	1.4	1.7(1.1,2.8)	0.02	1.5(0.9,2.4)	0.10
Initial Regimens							
DDI based Regimens	196	5584.0	3.5				
3TC based Regimens	201	9085.4	2.2	0.6(0.5,0.8)	<0.01	0.7(0.5,0.8)	<0.01
Others	66	2363.4	2.8	0.8(0.6,1.0)	0.10	0.8(0.6,1.1)	0.26
Duration of treatment (per one year)				1.0(0.99,1.0)	0.46		
Missed doses in the past month							
No	392	14931.7	2.6				
Yes	71	2101.1	3.4	1.3(1.0,1.7)	0.05		
Discontinued treatment							
No	440	16509.5	2.7				
Yes	23	523.3	4.4	1.6(1.1,2.5)	0.02		
ART drug distribution location							
County hospital or CDC	223	9345.2	2.4				
Township hospital or village clinic	240	7687.5	3.1	1.3(1.1,1.6)	<0.01		
CD4 cell account at survey							
≥350	80	6266.2	1.3				
200-349	130	5636.7	2.3	1.8(1.4,2.4)	<0.01	1.7(1.3,2.3)	<0.01
100-199	130	3564.5	3.6	2.9(2.2,3.8)	<0.01	2.8(2.1,3.7)	<0.01
<100	123	1565.3	7.9	6.2(4.7,8.2)	<0.01	5.1(3.8,6.7)	<0.01
HIV viral load at survey							
VL<1000	260	13068.1	2.0				
VL ≥ 1000 and VL<10000 without HIVDR	15	537.5	2.8	1.4(0.8,2.4)	0.20	1.4(0.8,2.4)	0.21
VL ≥ 1000 and VL<10000 with HIVDR	20	868.2	2.3	1.2(0.7,1.8)	0.51	1.0(0.6,1.5)	0.88
VL ≥ 10000 without HIVDR	60	1199.5	5.0	2.5 (1.9,3.3)	<0.01	1.7(1.3,2.3)	<0.01
VL ≥ 10000 with HIVDR	108	1359.5	7.9	4.0(3.0,5.0)	<0.01	2.4(1.9,3.0)	<0.01

Table 2: Factors associated with death among patients who received HAART.

HIV viral load*	Death	Person year	Death/100 person year	Adjusted HR (95% CI)	*P-value*
VL ≥ 10000 without HIVDR	60	1199.5	5.0		
VL ≥ 10000 with HIVDR	108	1359.5	7.9	1.4(1.0,1.9)	<0.05

* Adjusted for sex, age, education, occupation, HIV transmission route, initial cART regimens and CD4 cell account at time of survey.

Table 3: Subgroup analysis for HIV viral load ≥ 10000.

Discussion

Our main findings for this study are the mortality rates of cART-treated HIV patients in China: 2.8 deaths per 100 person-years in all participating patients, 4.8 in patients with virologic failure, and 5.7 in patients with HIVDR. These rates are consistent with findings from developed countries and lower than the rates in other resource-limited countries [20-22]. Patients at greatest risk of death were older; female; plasma donors and injecting drug users; those with low baseline CD4 cell counts; those initially treated with a didanosine-based cART regimen; those with higher viral load; and those infected with drug resistant HIV, independently.

We stratified viral load as five groups in order to indentify whether higher viral load and emergence of resistance were linked to increased mortality rates. Our results showed that patients with VL ≥ 10,000 copies/ml and with HIVDR was 2.4 times as likely to die as patients with VL < 1,000 copies/ml; similarly, those with VL ≥ 10,000 copies/ml and without HIVDR was 1.7 times as likely to die. Higher viral load and drug resistance therefore significantly increase the risk of death. As well, we conducted sensitivity analysis in patients with viral load levels of ≥ 10,000 copies/ml to assess the risk of death due to drug resistance alone. We found that within this high viral load cohort, patients infected with drug resistant HIV were 1.4 times more likely to die than those infected with non-resistant HIV. This effect was found in some previous studies [14,23], while others have failed to demonstrate the same [24,25]. Our finding reinforces the concept that ongoing viral replications[26] and few treatment options are associated with an increased probability of disease progression [27]. It has been reported that the use of boosted protease inhibitors (Boosted PI) is associated with multiple clinical benefits, including higher efficacy against resistant HIV strains [28], lower rates of resistance emergence at high-adherence levels [29] and a lack of PI-associated resistance mutations after virologic failure in treatment-naïve patients [30]. As well, studies have shown that Boosted PI offers a marginal independent protective effect on disease progression [23,31]. As the prevalence of HIV drug resistance accumulates in China, the need for scaling up second-line therapy is clear and must be a priority in China's efforts to control HIV/AIDS.

Among the other risk factors for death we identified, the risks due to HIV transmission routes were particular to China's epidemic. Plasma donors and IDUs experience higher mortality rates as compared to those infected through sexual routes. As a cohort, plasma donors were poor farmers who participated in commercial plasma donation in the 1990s, and were infected through use of contaminated equipment and through infusion of pooled red blood cells from multiple donors [18,19]. As China's cART program was first piloted among HIV-infected farmer plasma donors before scale-up to the entire country, the quality of cART and other healthcare services delivered were likely to be suboptimal as compared to later, more fine-tuned implementation. This may have contributed to the high rates of virologic failure,[8] drug resistance, and mortality in this cohort. On the other hand, many studies have shown that IDUs have higher rates of mortality than non-IDUs [32,33]. This may be attributed to several reasons: IDUs display lower adherence rates to cART regimens [34,35]; they are more likely to be co-infected with hepatitis C [36], which independently increases the risk of mortality among HIV patients even when on HAART [37]; and they have been found to have a lower virologic response to HAART than non-IDUs [38].

This study has several limitations. First, HIV viral load and drug resistance data are obtained at the survey baseline, and do not reflect the change in HIV viral load and emergence of new drug resistance over the follow-up period. Secondly, only patients who were still alive at the time of the HIV drug resistance surveys were included in the analysis; mortality rate may therefore be underestimated, and the statistical relationship between drug resistance and mortality may be reduced. Lastly, adherence to ART is an important factor in treatment success, but we assessed adherence using self-reported data, whose reliability for accurately reflecting true adherence levels is limited. However, these limitations should not affect our conclusion on the association of virologic failure and mortality. To our knowledge, this is the first study evaluating the effect of HIV virologic failure and drug resistance on mortality in China. Our results provide evidence to guide policy-makers in refining cART regimens, training healthcare providers in rural areas, and enhancing patient education to improve cART treatment adherence.

Sponsorship

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