

# BMJ Open Predictors of HIV virological failure and drug resistance in Chinese patients after 48 months of antiretroviral treatment, 2008–2012: a prospective cohort study

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## ABSTRACT

**Objective** To explore factors associated with HIV virological failure (VF) and HIV drug resistance (HIVDR) among HIV-positive Chinese individuals 4 years after initiating first-line lamivudine-based antiretroviral treatment (ART) in 2008 at five sentinel sites.

**Design** First-line ART initiators who were previously treatment naïve were selected using consecutive ID numbers from the 2008 National Surveillance Database into a prospective cohort study. Questionnaires and blood samples were collected in 2011 and 2012 to assess the outcomes of interest: VF (defined as viral load  $\geq 1000$  copies/mL) and HIVDR (defined as VF with genetic drug-resistant mutations). Questionnaires and data from National Surveillance Database assessed demographics and drug adherence data.

**Results** 536 individuals with HIV were analysed; the 4-year risk of VF was 63 (11.8%) and HIVDR was 27 (5.0%). Female participants initiating stavudine (D4T)-based regimens were more susceptible to both VF (adjusted OR (aOR)=2.5, 95% CI 1 to 6.1,  $p=0.04$ ) and HIVDR (aOR=3.6, 95% CI 1 to 12.6,  $p=0.05$ ) versus zidovudine-based regimens. Male participants missing doses in past month were more susceptible to both VF (aOR=2.8, 95% CI 1.1 to 7,  $p=0.03$ ) and HIVDR (aOR=9.7, 95% CI 2.1 to 44.1,  $p<0.01$ ). Participants of non-Han nationality were of increased risk for HIVDR (aOR from 4.8 to 12.2,  $p<0.05$ ) and non-Han men were at increased risk for VF (aOR=2.9, 95% CI 1.1 to 7.3,  $p=0.02$ ). All 27 participants detected with HIVDR had non-nucleoside reverse-transcriptase inhibitor mutations, 21 (77.8%) also had nucleoside reverse-transcriptase inhibitor mutations, and no protease inhibitor mutations were detected.

**Conclusions** Our findings suggest successful treatment outcomes at 4 years for roughly 90% of patients. We suggest conducting further study on whether and when to change ART regimen for women initiated with D4T-based regimen, and reinforcing adherence counselling for men. Increased VF and HIVDR risk among non-Han minorities warrants further exploration, and ethnic minorities may be an important group to tailor adherence-focused interventions.

## Strengths and limitations of this study

- We studied 48-month risk of virological failure (VF) and HIV drug resistance (HIVDR) and their associations with demographic and behavioural information among individuals across five sentinel sites.
- Study found drug adherence and adverse effects influenced VF and HIVDR differently across gender.
- The outcomes were measured in 2011 and 2012, and thus we may be missing transient VF outcomes.

## INTRODUCTION

Antiretroviral treatment (ART) has dramatically improved health outcomes and decreased HIV-associated morbidity and mortality through virological suppression and subsequent CD4 recovery.<sup>1–4</sup> In 2003, China launched a National Free Antiretroviral Treatment Program (NFATP) that includes lifelong provision of free ART for people living with HIV who met the national treatment criteria.<sup>5,6</sup> The national treatment criteria from 2008 to 2011 were: (1) CD4 cell count  $\leq 0.2 \times 10^9/L$ ; (2) WHO stage III/IV diseases; or (3) willingness to receive ART, regardless of criteria 1 and 2.<sup>7</sup>

The State Council AIDS Working Committee Office and the United Nations Theme Group on AIDS estimated that there were more than 700 000 persons living with HIV in China in 2008, and more than 52 000 individuals with HIV across 31 provinces, autonomous regions and municipalities had received ART (made freely available by the NFATP) by August 2008.<sup>8</sup>

With the rapid scale-up of treatment and challenges with adherence, virological failure (VF) and HIV drug resistance (HIVDR) are ever present and mounting concerns. Incomplete virological suppression, a major cause

of HIVDR, compromises therapeutic efficacy for the individual receiving treatment, increasing the risk of viral rebound and opportunistic infections, and increases the risk of transmitting drug-resistant strains to other individuals in the general population.<sup>9–11</sup>

Observational studies in China have documented the prevalence of VF and HIVDR strains among treated individuals living with HIV. A cross-sectional study conducted in Yunnan, Guangxi and Xinjiang provinces in 2010 stated that 1-year HIVDR prevalence was 4.1%.<sup>5</sup> VF prevalence for sexual transmitted population and intravenous drug users (IDUs) was 8.3% and 19.3%, separately. A 6-year follow-up study in 2010 suggested an incidence of 14.1 per 100 person-years for VF and 11.9 per 100 person-years for HIVDR among former plasma donors in Anhui Province.<sup>12</sup>

NFATP recommended to switch the first-line regimen from didanosine to lamivudine (3TC) in 2008, and there are few nationwide, prospective studies in China reporting frequency or predictors of VF and HIVDR for people after initiating 3TC-based regimens.

The aim of this study is to evaluate predictors of VF and HIVDR in a prospective cohort of Chinese HIV individuals with HIV 4 years after first initiating first-line 3TC-based ART in 2008 at five sentinel sites. We stratified our analyses by gender based on conflicting findings on gender differences both in virological responses and drug resistance to different ART regimen, as well as gender differences in ART adherence.<sup>13–16</sup> To our knowledge, this is the first long-term study to evaluate VF and HIVDR on 3TC-based regimens.

## ETHICS STATEMENT

The study was approved by the Institutional Review Board of the National Center for AIDS/STD Control and Prevention of the Chinese Center for Disease Control and Prevention (NCAIDS, China CDC). All participants provided written informed consent before participation. Signed informed consent was obtained from each of the participants prior to the interviews and blood collection.

## METHODS

### Study design and data collection

This study was designed under the WHO surveillance of HIVDR in adults receiving ART for 48 months.<sup>10 17 18</sup> Five provinces in China with highest rate of transmission were selected to conduct a prospective cohort study with a follow-up study at 12 months: Guangxi, Henan, Hubei, Xinjiang and Yunnan. Participants were sampled from the 2008 National HIV Surveillance Database through sequential sampling from each province. Participant eligibility criteria included being aged  $\geq 18$  years; having initiated NFATP-sponsored first-line ART in 2008; having been ART free before 2008; having been on ART for  $36 \pm 6$  months in 2011; and providing consent to participate in the study.

Questionnaires administered by trained study personnel from provincial CDC in private rooms using structured interviews collected data in 2011 and 2012. Each study participant was assigned a confidential identification number used to label questionnaire and blood specimen. Additional HIV-specific data including route of transmission, initial ART regimen, latest ART regimen, ART distribution location and CD4 cell count were collected from the 2011–2012 National HIV Surveillance Database. There were no missing demographic data, missed questionnaire data were fed back to local CDC for recollection at the time.

### Laboratory analysis

Blood specimens were collected from all participants to determine CD4 cell count, HIV-1 RNA viral load (VL) and HIV-1 drug resistance mutations in both 2011 and 2012. CD4 cell count estimation was conducted at provincial CDC laboratories using flow cytometry (FACSCalibur, BD, USA) within 24 hours after specimen collection. Plasma was isolated and stored at  $-80^{\circ}\text{C}$  at a provincial CDC laboratory and then transferred to NCAIDS for testing HIV VL and drug mutation. Plasma HIV RNA was quantified with real-time NASBA (NucliSENS EasyQ, bioMerieux, France) or COBAS (Roche Applied Biosystems, Germany) according to manufacturer's recommendations using in-house PCR, both of the assays were performed automatically.<sup>19</sup> VF was defined as  $\text{VL} \geq 1000$  copies/mL. According to WHO protocol,<sup>20</sup> HIVDR tests were performed on samples with  $\text{VL} \geq 1000$  copies/mL. HIV-1 *pol* gene (protease 1–99 amino acids and part of reverse-transcriptase 1–252 amino acids) was amplified, purified and analysed using the Stanford HIV Drug Resistance Database (<https://hivdb.stanford.edu/hivdb>). Levels of HIVDR were classified according to the algorithm of Stanford HIVdb program. The scores are the sum of each mutation penalty score for a drug. Scores less than 10 indicate susceptible; scores between 10 and 14 indicate potential low-level resistance; scores between 15 and 29 indicate low-level resistance; scores between 30 and 59 indicate intermediate resistance. Scores of 60 or greater indicate high-level resistance. Any low, intermediate or high-level resistance identified was defined as HIVDR.<sup>21–24</sup>

### Data analysis

Questionnaire data were double entered using EpiData V.3.1 (The EpiData Association, Odense, Denmark). Statistical Analysis System (SAS V.9.4, SAS Institute) was then used for data cleaning and analyses.

A 48-month risk for the outcomes of interest was calculated as the proportion of unique persons who had experienced incident VF or HIVDR by the end of follow-up in 2012.

Covariates of interest were described using counts and percentages overall and by the outcome of interest, stratified by gender. Univariate logistic regression models were constructed to explore associations between covariates of interest and VF or HIVDR. OR and 95% CIs are reported.

Variables that were significant ( $p < 0.05$ ) in the univariate models were then fit into multivariate logistic regression models assessment for removal of collinear variables that had the weakest association with the outcome. Adjusted ORs (aOR) and 95% CIs were presented.  $p < 0.05$  was defined as statistically significant, and all tests were two sided. Descriptive analysis on HIVDR mutation results was conducted among 27 HIVDR participants, stratified by sex.

## RESULTS

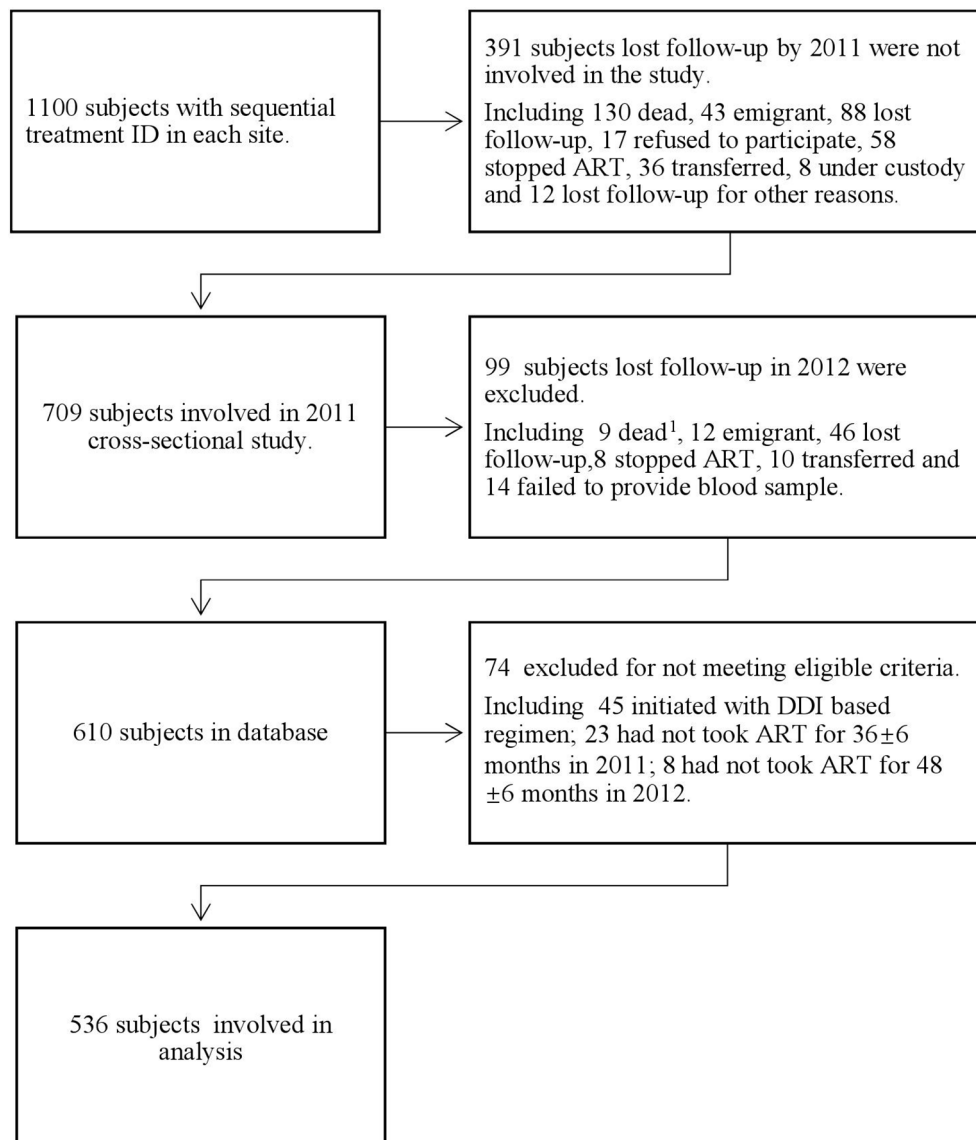
Up to 1100 subjects were selected using consecutive ID numbers from 2008 National Surveillance Database; of those, 490 were lost to follow-up by December 2012. Among those lost to follow-up, 139 died, 55 emigrated, 134 lost contact, 17 refused to participate, 65 stopped ART before 30 months, 36 transferred, 8 were under custody, 6 failed to provide a blood sample, 3 switched from ART

to Tangcao tablet (an antiviral Chinese herbal therapy), 2 became pregnant and switched to other regimens and 1 was paralysed. After excluding 74 participants for failing the eligibility criteria, 536 participants were included in the final 24-month analysis (figure 1). The 48-month risk of VF was 11.8% and risk of drug resistance was 5%.

### Demographic and ART information (tables 1 and 2)

Of the 536 eligible participants, 51.8% were male, 76.5% were of Han nationality, 45.0% had an education level of elementary school or less, 56.2% were farmers and 10.6% were unemployed with the rest having regular income.

All regimens in this cohort remained 3TC based from 2008 to 2012. Initiated nucleoside reverse-transcriptase inhibitor (NRTI) regimens included zidovudine (AZT) ( $n=349$ , 65.1%) or stavudine (D4T) ( $n=187$ , 34.9%). Sixty-six (12.3%) participants later changed to tenofovir (TDF)-based regimen. Initiated non-nucleoside reverse-transcriptase inhibitor (NNRTI) regimens



**Figure 1** Figure of exclusion on study cohort. <sup>1</sup>None HIV-related death. ART, antiretroviral treatment; DDI, didanosine.

**Table 1** Factors associated with virological failure (viral load  $\geq 1000$  copies/mL) stratified by sex

	Female			Male				
	Total	Virological failure risk, N (%)	OR (95% CI)	P-value	Total	Virological failure risk, N (%)	OR (95% CI)	P-value
<b>Total</b>	258	29 (11.2)			278	34 (12.2)		
<i>Demographic factors</i>								
<b>Ethnicity</b>								
Han nationality	191	19 (9.9)	1		219	20 (9.1)	1	
Other minorities	67	10 (14.9)	1.6 (0.7 to 3.6)	0.27	59	14 (23.7)	3.1 (1.5 to 6.6)	<0.01
<b>Education</b>								
Elementary school or less	134	15 (11.2)	1		107	12 (11.2)	1	
Junior school or more	124	14 (11.3)	1 (0.5 to 2.2)	0.98	171	22 (12.9)	1.2 (0.6 to 2.5)	0.68
<b>Marital status</b>								
Single	59	6 (10.2)	1		75	9 (12)	1	
Married or cohabited	199	23 (11.6)	1.2 (0.4 to 3.0)	0.77	203	25 (12.3)	1 (0.5 to 2.3)	0.94
<b>Residence</b>								
Rural	197	19 (9.6)	1		172	17 (9.9)	1	
City	61	10 (16.4)	1.8 (0.8 to 4.2)	0.15	106	17 (16)	1.7 (0.8 to 3.6)	0.13
<b>Occupation</b>								
Peasant	163	15 (9.2)	1		138	9 (6.5)	1	
Employee	64	11 (17.2)	2 (0.9 to 4.7)	0.09	114	17 (14.9)	2.5 (1.1 to 5.9)	0.03
Unemployed	31	3 (9.7)	1.1 (0.3 to 3.9)	0.93	26	8 (30.8)	6.4 (2.2 to 18.6)	<0.01
<b>Age (years)</b>								
<35	73	6 (8.2)	1		53	7 (13.2)	1	
35–45	108	15 (13.9)	1.8 (0.7 to 4.9)	0.25	119	15 (12.6)	0.9 (0.4 to 2.5)	0.91
>45	77	8 (10.4)	1.3 (0.4 to 3.9)	0.65	106	12 (11.3)	0.8 (0.3 to 2.3)	0.73
<b>Weight (kg)</b>								
<50	89	14 (15.7)	1		49	7 (14.3)	1	
50–70	156	13 (8.3)	0.5 (0.2 to 1.1)	0.08	193	21 (10.9)	0.7 (0.3 to 1.8)	0.51
>70	13	2 (15.4)	1 (0.2 to 4.9)	0.97	36	6 (16.7)	1.2 (0.4 to 3.9)	0.76
<i>HIV characteristics and treatment factors</i>								
<b>Route of infection</b>								
Heterosexual transmission	159	12 (7.5)	1		154	11 (7.1)	1	
Blood transmission	86	13 (15.1)	2.2 (0.9 to 5)	0.07	61	10 (16.4)	2.5 (1 to 6.4)	0.04

Continued

**Table 1** Continued

	Female			Male				
	Total	Virological failure risk, N (%)	OR (95% CI)	P-value	Total	Virological failure risk, N (%)	OR (95% CI)	P-value
Intravenous drug use	13	4 (30.8)	5.4 (1.5 to 20.3)	0.01	63	13 (20.6)	3.4 (1.4 to 8)	0.01
Initial NRTI ART regimen								
AZT-based regimen	161	11 (6.8)	1		188	26 (13.8)	1	
D4T-based regimen	97	18 (18.6)	3.1 (1.4 to 6.9)	<0.01	90	8 (8.9)	0.6 (0.3 to 1.4)	0.24
Latest NRTI ART regimen								
AZT-based regimen	181	15 (8.3)	1		195	27 (13.8)	1	
D4T-based regimen	77	14 (18.2)	2.5 (1.1 to 5.4)	0.02	83	7 (8.4)	0.6 (0.2 to 1.4)	0.21
Switch ART regimen								
No	193	21 (10.9)	1		174	21 (12.1)	1	
Yes	65	8 (12.3)	1.2 (0.5 to 2.7)	0.75	104	13 (12.5)	1 (0.5 to 2.2)	0.92
ART drug distribution location								
County hospital or CDC	96	15 (15.6)	1		63	14 (22.2)	1	
Township hospital/village clinic/medication monitor	162	14 (8.6)	0.5 (0.2 to 1.1)	0.09	215	20 (9.3)	0.4 (0.2 to 0.8)	0.01
Adverse effects								
No	195	17 (8.7)	1		206	23 (11.2)	1	
Yes	63	12 (19)	2.5 (1.1 to 5.5)	0.03	72	11 (15.3)	1.4 (0.7 to 3.1)	0.36
CD4 cell/mL at baseline (2008)								
<350	244	28 (11.5)	1		272	31 (11.4)	1	
≥350	14	1 (7.1)	0.6 (0.1 to 4.7)	0.62	6	3 (50)	7.8 (1.5 to 40.2)	0.01
CD4 cell/mL at 36 months (2011)								
0–350	91	18 (19.8)	1		138	21 (15.2)	1	
≥350	167	11 (6.6)	0.3 (0.1 to 0.6)	<0.01	140	13 (9.3)	0.6 (0.3 to 1.2)	0.13
CD4 cell/mL at 48 months (2012)								
0–350	81	14 (17.3)	1		122	20 (16.4)	1	
≥350	177	15 (8.5)	0.4 (0.2 to 1)	0.04	156	14 (9)	0.5 (0.2 to 1)	0.06
Drug compliance factors								
Missed doses in past month								
No	226	26 (11.5)	1		246	24 (9.8)	1	
Yes	32	3 (9.4)	0.8 (0.2 to 2.8)	0.72	32	10 (31.3)	4.2 (1.8 to 9.9)	<0.01

Continued



	Female				Male			
	Virological failure		P-value		Virological failure		P-value	
	Total	risk, N (%)	OR (95% CI)		Total	risk, N (%)	OR (95% CI)	
Willing to receive ART in the future								
Always	153	15 (9.8)	1		177	19 (10.7)	1	
Not always	105	14 (13.3)	1.4 (0.7 to 3.1)	0.38	101	15 (14.9)	1.5 (0.7 to 3)	0.32
Believe ART is health promoting								
Always	158	16 (10.1)	1		181	19 (10.5)	1	
Not always	100	13 (13)	1.3 (0.6 to 2.9)	0.48	97	15 (15.5)	1.6 (0.8 to 3.2)	0.24
Believe poor compliance contributes to HIVDR								
Always	139	16 (11.5)	1		169	19 (11.2)	1	
Not always	119	13 (10.9)	0.9 (0.4 to 2.1)	0.88	109	15 (13.8)	1.3 (0.6 to 2.6)	0.53
Degree of satisfaction on support of friends or relatives								
Always satisfied	153	15 (9.8)	1		166	17 (10.2)	1	
Not always satisfied	105	14 (13.3)	1.4 (0.7 to 3.1)	0.38	112	17 (15.2)	1.6 (0.8 to 3.2)	0.22
Frequency of taking drugs reminded by friends or relatives								
Often	172	19 (11)	1		168	22 (13.1)	1	
Not often	86	10 (11.6)	1.4 (0.7 to 3.1)	0.38	110	12 (10.9)	0.8 (0.4 to 1.7)	0.58
Frequency of taking drugs reminded by doctors								
Often	178	23 (12.9)	1		184	28 (15.2)	1	
Not often	80	6 (7.5)	0.5 (0.2 to 1.4)	0.19	94	6 (6.4)	0.4 (0.2 to 1)	0.03

ART, antiretroviral treatment; AZT, zidovudine; CDC, Centers for Disease Control and Prevention; D4T, stavudine; HIVDR, HIV drug resistance; NRTI, nucleoside reverse-transcriptase inhibitors.

**Table 2** Factors associated with HIVDR (viral load  $\geq 1000$  copies/mL with drug resistance) stratified by sex

	Female			Male				
	Total	HIVDR risk, N (%)	OR (95% CI)	P-value	Total	HIVDR risk, N (%)	OR (95% CI)	P-value
<b>Demographic factors</b>	258	14 (5.4)			278	13 (4.7)		
<b>Ethnicity</b>								
Han nationality	191	6 (3.1)	1		219	5 (2.3)	1	
Other minorities	67	8 (11.9)	4.2 (1.4 to 12.5)	0.01	59	8 (13.6)	6.7 (2.1 to 21.4)	<0.01
<b>Education</b>								
Elementary school or less	134	5 (3.7)	1		107	5 (4.7)	1	
Junior school or more	124	9 (7.3)	2 (0.7 to 6.2)	0.22	171	8 (4.7)	1 (0.3 to 3.1)	1
<b>Marital status</b>								
Single	59	4 (6.8)	1		75	4 (5.3)	1	
Married or cohabited	199	10 (5)	0.7 (0.2 to 2.4)	0.60	203	9 (4.4)	0.8 (0.2 to 2.8)	0.75
<b>Residence</b>								
Rural	197	7 (3.6)	1		172	5 (2.9)	1	
City	61	7 (11.5)	3.5 (1.2 to 10.5)	0.02	106	8 (7.5)	2.7 (0.9 to 8.6)	0.09
<b>Occupation</b>								
Peasant	163	5 (3.1)	1		138	0	1	
Employee	64	6 (9.4)	3.3 (1 to 11.1)	0.06	114	9 (7.9)	2 (1 to 12.6)	<0.01
Unemployed	31	3 (9.7)	3.4 (0.8 to 15)	0.11	26	4 (15.4)	3 (1 to 13.4)	<0.01
<b>Age (years)</b>								
<35	73	5 (6.8)	1		53	6 (11.3)	1	
35–45	108	6 (5.6)	0.8 (0.2 to 2.7)	0.72	119	6 (5)	0.4 (0.1 to 1.4)	0.15
>45	77	3 (3.9)	0.6 (0.1 to 2.4)	0.43	106	1 (0.9)	0.1 (0 to 0.6)	0.02
<b>Weight (kg)</b>								
<50	89	8 (9)	1		49	4 (8.2)	1	
50–70	156	4 (2.6)	0.3 (0.1 to 0.9)	0.04	193	7 (3.6)	0.4 (0.1 to 1.5)	0.19
>70	13	2 (15.4)	1.8 (0.3 to 9.8)	0.47	36	2 (5.6)	0.7 (0.1 to 3.8)	0.64
<b>HIV characteristics and treatment factors</b>								
<b>Route of infection</b>								
Heterosexual transmission	159	8 (5)	1		154	2 (0.6)	1	
Blood transmission	86	4 (4.7)	0.9 (0.3 to 3.2)	0.9	61	3 (2)	3.9 (0.6 to 24.1)	0.14

Continued

Table 2 Continued

	Female				Male			
	HIVDR risk, N (%)		OR (95% CI)		HIVDR risk, N (%)		OR (95% CI)	
	Total	P-value	Total	P-value	Total	P-value	Total	P-value
Intravenous drug use	13	2 (15.4)	3.4 (0.6 to 18.2)	0.15	63	8 (10.5)	11.1 (2.3 to 53.7)	<0.01
Initial NRTI ART regimen								
AZT-based regimen	161	5 (3.1)	1		188	10 (2.9)	1	
D4T-based regimen	97	9 (9.3)	3.2 (1 to 9.8)	0.04	90	3 (1.6)	0.6 (0.2 to 2.3)	0.47
Latest ART regimen								
AZT-based regimen	181	8 (4.4)	1		195	12 (3.2)	1	
D4T-based regimen	77	6 (7.8)	1.8 (0.6 to 5.5)	0.28	83	1 (0.6)	0.2 (0 to 1.5)	0.11
Switch ART regimen								
No	193	10 (5.2)	1		174	6 (3.4)	1	
Yes	65	4 (6.2)	1.2 (0.4 to 4)	0.76	104	7 (6.7)	2 (0.7 to 6.2)	0.22
Adverse effect								
No	195	9 (4.6)	1		206	10 (4.9)	1	
Yes	63	5 (7.9)	1.8 (0.6 to 5.5)	0.32	72	3 (4.2)	0.9 (0.2 to 3.2)	0.81
CD4 cell at baseline (2008)								
<350	244	14 (5.7)			272	12 (2.3)	1	
≥350	14	0	-	0.36	6	1 (5)	4.3 (0.5 to 40)	0.2
CD4 cell at 36 months (2011)								
0–350	91	9 (9.9)	1		138	11 (4.8)	1	
≥350	167	5 (3)	0.3 (0.1 to 0.9)	0.03	140	2 (0.7)	0.2 (0 to 0.8)	0.02
CD4 cell at 48 months (2012)								
0–350	81	7 (8.6)	1		122	11 (5.4)	1	
≥350	177	7 (4)	0.4 (0.1 to 1.3)	0.13	156	2 (0.6)	0.1 (0 to 0.6)	0.01
<b>Drug compliance factors</b>								
Missed doses in past month								
No	226	13 (5.8)	1		246	6 (2.4)	1	
Yes	32	1 (3.1)	0.5 (0.1 to 4.2)	0.55	32	7 (21.9)	11.2 (3.5 to 35.9)	<0.01

ART drug distribution location, willing to receive ART in the future, believe ART is health promoting, believe poor compliance contributes to HIVDR, degree of satisfaction on support of friends or relatives, frequency of taking drugs reminded by friends or relatives, and frequency of taking drugs reminded by doctors are not displayed as no statistical significant difference was found between categories.

ART, antiretroviral treatment; AZT, zidovudine; D4T, stavudine; HIVDR, HIV drug resistance; NRTI, nucleoside reverse-transcriptase inhibitors.



included nevirapine (n=421, 78.5%) or etravirine (n=115, 21.5%). Fifty-five (10.3%) participants later changed to LPV/r(Lopinavir/Ritonavir)-based regimen. One hundred and sixty-nine (31.5%) participants switched the initial ART regimen during 2008–2012, but no statistical significant difference was found in VF (p=0.74) and HIVDR (p=0.29) risk between participants who switched regimens and participants who did not switch regimens.

We found that 38.4% of participants were hesitant to accept ART in the future, 36.8% participants reported doubts whether ART was health promoting and 42.5% participants did not report that poor ART adherence necessarily contributed to HIVDR. Additionally, 40.5% of participants were not always satisfied with support from friends or relatives. Four hundred and seventy-two (88.1%) participants reported not missing a dose in the month prior to the date of the survey.

### Multivariate model results (table 3)

As shown in table 3, minority male participants were at higher risk for both VF (aOR=2.9, 95% CI 1.1 to 7.3, p=0.02) and HIVDR (aOR=12.2, 95% CI 1.8 to 84.8, p=0.01) compared with Han nationality male participants, while female minorities were only at a higher risk for HIVDR (aOR=4.8, 95% CI 1.2 to 19.7, p=0.03).

Female participants initiating D4T-based regimens were at a higher risk for both VF (aOR=2.5, 95% CI 1 to 6.1, p=0.04) and HIVDR (aOR=3.6, 95% CI 1 to 12.6, p=0.05) versus those initiating an AZT-based regimen; interestingly, different from their female counterparts, male participants showed no such association (OR=0.6, 95% CI 0.3 to 1.4, p=0.24). Also, female participants had a higher risk of VF given adverse side effects (aOR=2.3, 95% CI 1 to 5.6, p=0.06). Male participants with missed doses in the month prior to the survey were at a higher risk of both VF (aOR=2.8, 95% CI 1.1 to 7, p=0.03) and HIVDR (aOR=9.7, 95% CI 2.1 to 44.1, p<0.01) versus those without missed doses in the preceding month. Conversely, missed doses in prior month were not significantly associated with VF or HIVDR for women.

### HIVDR and subtype (table 4)

HIVDR identified in our study was consistent with the NFATP-recommended ART regimen. All 27 participants detected with drug resistance had NNRTI mutations, 21 (77.8%) had NRTI mutations. The dominant subtype was CRF07\_BC for both men (61.5%) and women (50%). All participants found with HIVDR had developed HIVDR towards NNRTI; 85.7% of male participants and 69.2% of female participants developed HIVDR towards NRTI; no protease inhibitor mutation was detected. There were no CRF08\_BC subtypes detected in the study population.

## DISCUSSION

The 48-month risk of VF was 11.8% and HIVDR was 5.0%, which indicated relatively good treatment outcomes given meta-analysis suggested a 37 to 48-month HIVDR

prevalence ranging from 3.04% to 47.92% in China,<sup>9</sup> similar to studies in China which estimated a 1-year HIVDR incidence of 3.5% in 2009 and 2.1% in 2012.<sup>25 26</sup> Our study substantiates the finding that VF and HIVDR largely decreased since the wide spread of 3TC-based regimens.<sup>27</sup> Studies have shown mixed findings of gender differences on ART adherence and treatment outcomes.<sup>14 16 28 29</sup> In our study, we found male participants had slightly higher risk of VF (12.2% vs 11.2%, p=0.72) but lower risk of HIVDR (4.7% vs 5.4%, p=0.69) than women. Drug adherence and adverse effects influenced our outcomes differently for men compared with women. Women's risks of VF and HIVDR were not associated with missing doses in the past month; also, few women missed doses relative to men, similar to two other studies in China suggesting women have better adherence behaviours.<sup>30 31</sup> Male participants were at higher risk of both VF and HIVDR if they reported missed doses. More detailed studies need to be conducted on the frequency and factors associated with missing treatment. However, female participants showed a higher risk of VF if they had adverse effect while men did not. This calls for further research of what types of adverse effects are occurring and how they affect ART adherence and virological outcomes across gender.

We found in this study that women, not men, who initiated D4T-based regimens were more susceptible to VF (women vs men: OR=2.3, 95% CI 1.0 to 5.7, p=0.06) and HIVDR (women vs men: OR=3.0, 95% CI 0.8 to 11.3, p=0.11), consistent with previous findings that D4T was more likely to increase the risk of mitochondrial toxicity in women.<sup>32 33</sup> Mitochondrial toxicity caused by D4T had been reported to cause many adverse effects such as lactic acidosis, lipodystrophy and peripheral neuropathy.<sup>34 35</sup> Following the WHO recommendation,<sup>36</sup> the NFATP advocated switching the first-line regimen from D4T to TDF in 2012. The percentage of people living with HIV initiating D4T-based regimen changed from 34.3% in 2010 to 10% in 2012 and 0.9% in 2014<sup>37</sup>; however, there were still 29.9% of participants in our study who were on D4T-based regimens in 2012. It was noteworthy that we did not see a statistical difference in VF (OR=1.4, 95% CI 0.4 to 4.2, p=0.60) and HIVDR (OR=1.0, 95% CI 0.2 to 4.2, p=0.98) between women who initiated and remained on D4T-based regimens and those who switched to AZT/TDF-based regimens. It is possible that women switched regimens because of VF; however, further studies need to be done to explore when to switch ART regimen for women receiving D4T-based regimens. It is important to mention that data on ART adherence and adverse effects were collected in 2012, when there were only four female participants still using D4T-based regimens who experienced VF. The sample size was not sufficient to explore whether D4T-based regimens affect drug adherence and adverse effects for women.

Though not associated with the VF and HIVDR outcomes, 38.4% of study participants reported that they would not 'always' be willing to take ART in the future, 36.8% reported not believing that ART is 'always' health

**Table 3** Multivariate models of factors associated with virological failure (viral load  $\geq 1000$  copies/mL) and HIVDR (viral load  $\geq 1000$  copies/mL with drug resistance) stratified by sex

Variables	Female (n=256)			Male (n=278)		
	Virological failure		HIVDR	Virological failure		HIVDR
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)
Ethnicity						
Han nationality	1		1	1		1
Other minorities	4.8 (1.2 to 19.7)	0.03		2.9 (1.1 to 7.3)	0.02	12.2 (1.8 to 84.8)
Residence						
Rural	1					
City	2.4 (0.6 to 9.5)	0.22				
Age (years)						
<35						1
35–45						0.3 (0.1 to 1.4)
>45						0.03 (0 to 0.6)
Weight (kg)						
<50	1		1			
50–70	0.3 (0.1 to 1.1)	0.08				
>70	4.2 (0.6 to 30)	0.15				
Route of infection						
Heterosexual transmission	1		1			1
Blood transmission	1.2 (0.5 to 3)	0.74		1.8 (0.6 to 5.8)	0.33	7 (0.8 to 64.4)
Intravenous drug use	4.1 (1 to 17.7)	0.06		2.1 (0.8 to 5.4)	0.12	2.3 (0.3 to 16.1)
Initial NRTI ART regimen						
AZT-based regimen	1		1			
D4T-based regimen	2.5 (1 to 6.1)	0.04	3.6 (1 to 12.6)	0.05		
ART drug distribution location						
County hospital or CDC			1			
Township hospital/village clinic/medication monitor				0.5 (0.2 to 1.3)	0.18	
Adverse effect						
No	1					
Yes	2.3 (1 to 5.6)	0.06				
CD4 cell at baseline (2008)						

Continued

**Table 3** Continued

Variables	Female (n=258)				Male (n=278)			
	Virological failure		HIVDR		Virological failure		HIVDR	
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
<350					1			
≥350					7.1 (1.1 to 45.8)	0.04		
CD4 cell at 36 months (2011)								
<350	1		1				1	
≥350	0.4 (0.2 to 1.1)	0.07	0.3 (0.1 to 0.9)	0.04			0.3 (0 to 1.9)	0.2
CD4 cell at 48 months (2012)								
<350	1						1	
≥350	0.6 (0.3 to 1.6)	0.36					0.1 (0 to 1)	0.05
Missed doses in past month								
No					1		1	
Yes					2.8 (1.1 to 7)	0.03	9.7 (2.1 to 44.1)	<0.01
Frequency of taking drugs reminded by doctors								
Often					1			
Not often					0.4 (0.2 to 1.2)	0.12		

ART, antiretroviral treatment; AZT, zidovudine; CDC, Centers for Disease Control and Prevention; D4T, stavudine; HIVDR, HIV drug resistance; NRTI, nucleoside reverse-transcriptase inhibitors.

**Table 4** HIVDR and subtype among 27 patients with HIVDR mutation detected at 2011 and/or 2012 stratified by sex

	Female (%)	Male (%)	Mutations	N (%)
Overall	14	13		
Subtype				
B	5 (35.7)	3 (23.1)		
C		1 (7.7)		
CRF01_AE	2 (14.3)	1 (7.7)		
CRF07_BC	7 (50)	8 (61.5)		
Antiretroviral drug				
NNRTI (any)	14 (100)	13 (100)	NNRTI mutations (total)	27
Efavirenz (EFV)	14 (100)	13 (100)	V90I	1 (3.7)
Nevirapine (NVP)	14 (100)	13 (100)	A98G	2 (7.4)
Etravirine (ETR)	6 (42.9)	8 (61.5)	K101E	6 (22.2)
			K103N	11 (40.7)
			V106A	4 (14.8)
			V108I	6 (22.2)
			E138A	1 (3.7)
			V179D/F	3 (11.1)
			Y181C	5 (18.5)
			G190A	5 (18.5)
			H221Y	1 (3.7)
			P225H	3 (11.1)
			F227L	1 (3.7)
			M230L	1 (3.7)
NRTI (any)	12 (85.7)	9 (69.2)	NRTI mutations (total)	21
Lamivudine (3TC)	12 (85.7)	9 (69.2)	A62V	1 (4.8)
Azidothymidine (AZT)	2 (14.3)	2 (15.4)	D67G	1 (4.8)
Tenofovir (TDF)	1 (7.1)	3 (23.1)	T69N	2 (9.5)
Stavudine (D4T)	3 (21.4)	3 (23.1)	K70R/Q	4 (19)
Didanosine (DDI)	5 (35.7)	3 (23.1)	V75I/M	2 (9.5)
Abacavir (ABC)	12 (85.7)	9 (69.2)	M184V	17 (81.0)
Emtricitabine (FTC)	12 (85.7)	9 (69.2)	T215N	1 (4.8)
			K219E/Q	2 (9.5)
PI (any)	0	0	PI mutations (total)	0

HIVDR, HIV drug resistance; NNRTI, non-nucleoside reverse-transcriptase inhibitors; NRTI, nucleoside reverse-transcriptase inhibitors; PI, protease inhibitor.

promoting, and 42.5% reported not believing that poor compliance 'always' contributed to HIVDR. As willingness and these knowledge factors may impact more long-term VF and HIVDR outcomes, the motivations behind willingness and knowledge about VF and HIVDR warrant exploration.

Caution is needed when interpreting the study results from multivariate model that older age (>45) was protective for HIVDR in men. There were only four male IDU participants with older age (>45) in this study, the number is not sufficient to test for interaction. There is no association between HIVDR and age (OR=6.5, 95% CI 1.1 to 38.1, p=0.49) in the subanalysis we did among male

IDU participants, after controlling for variables showed significance in the univariate model. A previous study in HIV-positive IDU population in China suggested that there is no association between VF and sex or age.<sup>38</sup> In this study, 61.5% of male participants with HIVDR became HIV infected via IDU, yet there were only 22.7% of male IDU participants.

In addition, we found that younger (<45 years) IDU population was more likely to miss doses (18.6%) compared with heterosexual transmission population (8.8%) and blood transfusion transmission population (12.1%). This finding was consistent with studies that implied younger men were at a higher risk of drug

abuse.<sup>39 40</sup> This result indicated that younger IDU population could be a main source of VF and HIVDR; therefore, they could be future targeted population for behavioural intervention.

The increased risk of VF and HIVDR in non-Han minorities, regardless of gender, may be due to logistical, cultural or social barriers faced by ethnic minorities which limit their adherence to ART. It has been reported that minorities tend to have lower social economic status than Han majorities, followed by lower education level and fewer access to health facilities.<sup>41</sup> It may be difficult for health professionals to reach for some minorities because of their more remote geographical locations. Additionally, several studies have reported that the percentage of high-risk populations such as female sex workers and IDUs was higher in minorities than of Han nationality.<sup>42–44</sup> The causes of this increased VF and HIVDR risk warrant further exploration, and ethnic minorities may be an important group to tailor adherence-focused interventions in China. The finding that higher CD4 cell count at follow-up was protective for VF and HIVDR was expected. NFATP changed treatment criteria from CD4 cell count  $\leq 0.2 \times 10^9/L$  to CD4 cell count  $\leq 0.3 \times 10^9/L$  following the WHO recommendation in 2011.<sup>7 17 45</sup> Our study indicated that male participants who initiated treatment in 2008 at CD4 cell count  $\geq 0.35 \times 10^9/L$  were still at higher risk towards VF (aOR=7.1, 95% CI 1.1 to 45.8,  $p=0.04$ ), supporting possible clinical benefits of initiating ART at higher CD4 cell counts  $< 0.5 \times 10^9/L$  as per WHO recommendation in 2013.<sup>46</sup>

Among participants infected by blood transmission, we only found HIVDR subtype B; only one subtype C was found in participants infected through IDU, the dominant subtype was CRF07\_BC, found both in participants infected by heterosexual transmission and IDU. The most common NNRTI mutation sites were K103N (40.7%), K101E (22.2%) and V108I (22.2%); the most common NRTI mutation sites were M184V (81.0%) and K70R (19%). Interestingly, compared with a 1-year follow-up study in China with all participants initiated ART in 2011,<sup>47</sup> there is no V108I in their study and we did not find K65R in our study.

Study findings should be interpreted in light of several limitations. Though we did not account for transmitted drug resistance in this study, previous studies have found low transmitted drug resistance risk ( $< 5\%$ ) during this period<sup>48 49 50</sup>; we could be fairly certain that participants were outcome free in 2008 as they were new ART initiators. Another limitation of our study is that the outcomes were measured in 2011 and 2012, and thus we may be missing transient VF outcomes. Also, route of transmission was collected in 2008 when assessing HIV infection among men who have sex with men was not part of data collection instruments; additionally, we do not have data on sex worker status. Roughly half of the study participants selected for possible inclusion in the study for having initiated first-line ART in 2008 were lost to follow-up by 2012, creating a possible selection bias for individuals

with better ART adherence—this bias may underestimate the true VF and HIVDR risk and also limit the generalisability of our findings to better adherers. Additionally, given the demographic profile of the cohort, our findings are most generalisable to heterosexual Han nationals who are married/cohabiting and working as agricultural labourers in rural areas. Misclassification of self-reported data is possible, though we do not expect this misclassification to be differential by the outcome of interest and thus any such information bias would bias our results towards the null.

## CONCLUSIONS

We found female participants initiating D4T versus AZT-based regimens were more vulnerable to VF and HIVDR, and we suggest future studies on whether and when to change ART regimen for women initiated with D4T-based regimen. Poor adherence was a risk factor among male participants who may benefit from reinforced adherence counselling or social support. Increased VF and HIVDR risk among non-Han minorities warrants further exploration, and ethnic minorities may be an important group to tailor adherence-focused interventions in China. Also, this study indicated that younger men who become infected through intravenous drug use may be groups to strategically focus counselling and increasing adherence support programme.

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