Preplanned Studies

Relationship Between Drug Resistance and Death in HIV-Infected Patients Receiving Antiretroviral Therapy — 7 PLADs, China, 2010–2019

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Summary

What is already known about this topic?

With increasing coverage of antiretroviral therapy (ART) for HIV-infected patients, more and more attention has been paid to the impact of HIV drug resistance on death in those patients in China.

What is added by this report?

Among HIV-infected patients receiving ART, the risk of death is higher in patients with HIV drug resistance [adjusted odds ratio (AOR)=4.25, 95% confidence interval (CI): 2.10–8.62], with viral load ≥1,000 copies/mL but drug resistance untested (AOR=4.65, 95% CI: 1.74–12.39), and with neither viral load nor drug resistance being tested (AOR=17.52, 95% CI: 8.73–35.19) when compared with drug-sensitive patients.

What are the implications for public health practice?

It is important to strengthen drug resistance monitoring and prevention in HIV-infected patients. While performing ART for HIV-infected patients, viral load testing and drug resistance testing should be carried out routinely and promptly.

To reduce the mortality rate of HIV-infected patients and improve their quality of life, China has launched the "Four Frees and One Care" policy (Free treatment, free voluntary counseling and testing, free prevention of mother to child transmission, free schooling for AIDS orphans, and one "Care": provision of social assistance for HIV/AIDS patients) to provide lifelong free antiretroviral therapy (ART) for HIV-infected patients who meet the national treatment criteria since 2003 (*1*). In response to the Joint United Nations Programme on HIV/AIDS's (UNAIDS) "Treatment 2.0" strategy, China has implemented a number of targeted strategies to expand the ART coverage in HIV-infected patients since 2010 (*2*). By the end of 2018, a total of 83.4% (748,499/861,042) of HIV-infected patients have received ART (*3*). However, HIV drug resistance (HIVDR) inevitably emerged along with the scale-up of ART, and the drug resistance pattern varied a lot in different regions of China (*4*). This study analyzed data in the national HIV/AIDS Comprehensive Response Information Management System (CRIMS) to investigate the relationship between HIVDR and death in HIV-infected patients receiving ART in seven provincial-level administrative divisions (PLADs) of China. The main finding is that the risk of death was higher in patients with HIV drug resistance or untested resistance compared with drug-sensitive patients. This helps provide a valuable reference for optimizing ART regimens and patient follow-up management in practice.

This study selected seven PLADs that reported and followed-up a large number of HIV/AIDS patients and considered geographical location (eastern and western China) and economic status. Data was collected for patients who received ART, died from all-causes during 2010–2019, and had adequate blood samples that were collected in twelve months prior to death and after ART initiation date. These samples could satisfy the volume requirements for performing viral load and drug resistance tests and were thus selected as death cases. One or two controls were selected for each case from surviving patients who received treatment at the same ART clinic as the case and was registered right before or after the case. The control should have blood samples collected in six months prior to or after the death cases' blood samples. The eligible cases or controls must be people aged 18 years or over when ART initiated, began their ART treatment in 2010 or later, and received ART for more than 6 months.

The data was derived from the CRIMS whose information was collected by local CDCs or HIV hospitals with questionnaires or medical records. Main variables were survival status, gender, age, ethnicity, marital status, education level, occupation, residence,

HIV transmission route, ART initiation date, clinic stage according to World Health Organization (WHO) definition, CD4 cell count at the beginning of ART, primary ART regimen, latest ART regimen, ART adherence, latest viral load test result, and latest drug resistance test result.

"HIVDR result" was defined as the main independent variable to analyze the relationship between HIVDR and death (by combining "Latest Viral Load test result" and "Latest drug resistance test result," as shown in Table 1). Due to differences of HIVDR prevalence, quality of medical care services, and sample sizes in regions, multivariate logistic regression analysis was performed for each region, and the adjusted odds ratio (AOR) was obtained. Then, the AORs in different regions were merged by meta-analysis to represent the overall relationship between HIVDR and death in those HIV-infected patients receiving ART. Logistic regression analysis was performed by SAS (version 9.4, SAS Institute, Cary, NC, USA). Meta-analysis was conducted in RevMan (version 5.4, Cochrane Collaboration, Oxford) and NCSS 2004 (Kaysville, UT, USA).

A total of 19,235 HIV-infected patients were enrolled from 7 PLADs (Table 2), with 5,719 in the case group (deaths) and 13,516 in the control group (survived). The proportions of latest viral load untested were 40.0% in the case group and 17.2% in the control group, while 65.6% of case group and 60.8% of control group were latest drug resistance untested. For the HIVDR result, 25.5% of case group and 44.2% of control group were deemed as drug sensitive, and 5.0% of case group and 2.4% of control group were drug resistant. The proportions of patients with viral load ≥1,000 copies/mL but drug resistance untested were 8.6% in the case group and 2.7% in the control group. The proportions of patients who were neither viral load nor drug resistance tested were 28.7% in the case group and 2.9% in the control group, respectively.

The multivariate logistic regression analysis indicated that the correlation between the HIVDR result and death was statistically significant (P<0.05) in Anhui, Sichuan, Jiangsu, and Hunan but not in Guangdong (P>0.05). No data was shown on the latest compound variable of viral load and drug resistance in Chongqing and Guangxi. After merging AORs of the HIVDR result with deaths in Anhui, Sichuan, Jiangsu, Guangdong, and Hunan, the result suggested that compared with drug-sensitive patients, the risk of death among patients with drug resistance [AOR=4.25, 95% confidence interval (CI): 2.10–8.62], with viral load ≥1,000 copies/mL but drug resistance untested (AOR=4.65, 95% CI: 1.74–12.39), and with neither viral load nor drug resistance being tested (AOR=17.52, 95% CI: 8.73–35.19) were statistically significantly higher (Table 3).

DISCUSSION

A cross-control survey in seven PLADs in China was conducted to investigate the relationship between HIVDR and death in HIV-infected patients receiving ART. A total of 19,235 participants were included in the analysis. Compared with drug-sensitive patients, the risk of death is higher in patients with HIV drug resistance or untested resistance.

In this large sample study, case-control analysis of patients in seven PLADs showed that HIVDR is significantly associated with death in HIV-infected patients receiving ART. Compared with drug-sensitive HIV-infected patients, the risk of death is 3.25 times

TABLE 1. Operational definition and category of HIVDR result.

Primary results of viral load and drug resistance test		Redefined HIVDR categories
Latest viral load test result (copies/mL)	Latest drug resistance test result	
<1,000	Sensitivity or not be tested	Drug sensitive
≥1,000	Sensitivity	Drug sensitive
Not be tested	Sensitivity	Drug sensitive
<1,000	Resistance	Drug resistant
≥1,000	Resistance	Drug resistant
Not be tested	Resistance	Drug resistant
≥1,000	Not be tested	Viral load ≥1,000 copies/mL but drug resistance untested
Not be tested	Not be tested	Neither viral load nor drug resistance being tested

Abbreviation: HIVDR=HIV drug resistance.

TABLE 2. Characteristics of participants in 7 PLADs of China between 2010 and 2019, stratified by case group (dead) and control group (survived).

Item	Anhui		Chongqing		Sichuan		Jiangsu		Guangxi		Guangdong		Hunan		Total			
	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group		Control group	
	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	%	n	%
Total	1,449	2,898	1,299	5,513	1,179	2,176	897	1,628	545	951	200	200	150	150	5,719	100.0	13,516	100.0
Age groups (years)																		
18–29	149	843	45	560	35	189	116	448	38	202	6	12	9	7	398	7.0	2,261	16.7
30–49	578	1,410	272	1,748	941	1,788	348	790	180	455	82	121	62	57	2,463	43.1	6,369	47.1
≥50	722	645	982	3,205	203	199	433	390	327	294	112	67	79	86	2,858	50.0	4,886	36.1
Gender																		
Male	1,194	2,249	1,047	3,679	907	1,411	747	1,368	432	656	161	134	122	100	4,610	80.6	9,597	71.0
Female	255	649	252	1,834	272	765	150	260	113	295	39	66	28	50	1,109	19.4	3,919	29.0
Ethnicity																		
Han	1,434	2,856	1,172	5,476	4	11	881	1,558	232	438	199	200	–	–	3,922	68.6	10,539	78.0
Other	13	41	3	16	1,175	2,165	16	19	313	513	1	0	–	–	1,521	26.6	2,754	20.4
Not recorded	2	1	124	21	0	0	0	51	0	0	0	0	–	–	126	2.2	73	0.5
Marital status																		
Single	320	859	104	575	39	102	159	462	99	249	30	47	30	26	781	13.7	2,320	17.2
Married or living with partner	731	1,512	799	3,899	1,091	1,966	532	915	320	563	146	142	72	86	3,691	64.5	9,083	67.2
Other	398	527	396	1,039	49	108	206	251	126	139	24	11	48	38	1,247	21.8	2,113	15.6
Education*																		
Primary school or less	735	920	827	2,990	1,130	2,083	293	262	231	283	48	24	–	–	3,264	57.1	6,562	48.5
Junior middle school	485	1,137	282	1,727	41	78	379	612	214	423	109	115	–	–	1,510	26.4	4,092	30.3
senior middle school or more	227	840	66	775	8	15	225	703	77	232	43	61	–	–	646	11.3	2,626	19.4
Not recorded	0	0	124	21	0	0	0	51	0	0	0	0	–	–	124	2.2	72	0.5
Occupation*																		
Famer	876	1,391	787	3,429	985	1,981	375	413	281	421	36	36	–	–	3,340	58.4	7,671	56.8
Other	573	1,507	388	2,063	194	195	522	1,164	264	530	164	164	–	–	2,105	36.8	5,623	41.6
Not recorded	0	0	124	21	0	0	0	51	0	0	0	0	–	–	124	2.2	72	0.5
Residence†																		
Rural	992	1,993	797	3,328	–	–	–	–	96	375	36	37	–	–	1,921	33.6	5,733	42.4
Urban	457	905	378	2,164	–	–	–	–	449	576	164	163	–	–	1,448	25.3	3,808	28.2
Not recorded	0	0	124	21	–	–	–	–	0	0	0	0	–	–	124	2.2	21	0.2

TABLE 2. (Continued)

Item	Anhui		Chongqing		Sichuan		Jiangsu		Guangxi		Guangdong		Hunan		Total			
	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group		Control group	
	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	%	n	%
HIV transmission route																		
Heterosexual	1,038	1,694	1,228	5,160	289	797	534	773	444	808	115	132	120	125	3,768	65.9	9,489	70.2
MSM	282	1,019	18	233	847	1,284	0	0	9	60	11	35	5	8	1,172	20.5	2,639	19.5
Intravenous drug use	10	7	42	81	43	95	22	30	65	66	59	19	18	9	259	4.5	307	2.3
Other	119	178	11	39	0	0	341	825	27	17	15	14	7	8	520	9.1	1,081	8.0
WHO clinic stage at the beginning of ART																		
I/II	837	2,212	684	3,981	939	1,844	555	1,172	215	475	0	4	105	120	3,335	58.3	9,808	72.6
III/IV	612	686	615	1,532	240	332	341	455	120	141	200	196	45	30	2,173	38.0	3,372	24.9
CD4 cell count at the beginning of ART, cells/mm^3																		
<200	714	902	687	2,021	432	431	550	665	355	524	157	129	97	68	2,992	52.3	4,740	35.1
200–349	256	925	281	1,835	453	877	203	570	137	277	33	54	33	61	1,396	24.4	4,599	34.0
≥350	154	608	94	961	261	856	56	253	47	136	10	17	10	17	632	11.1	2,848	21.1
Not recorded	325	463	237	696	33	12	88	140	0	0	0	0	10	4	693	12.1	1,315	9.7
ART initiation date																		
Before 2015	541	1,510	529	1,329	974	1,619	548	963	312	527	194	192	125	126	3,223	56.4	6,266	46.4
2015 or later	908	1,388	770	4,184	205	557	349	665	233	424	6	8	25	24	2,496	43.6	7,250	53.6
Initial ART regimen																		
D4T-based	69	242	83	108	46	39	89	137	100	161	106	88	25	28	518	9.1	803	5.9
AZT-based	455	1,063	218	719	432	556	467	956	188	352	57	65	62	73	1,879	32.9	3,784	28.0
TDF-based	828	1,407	988	4,643	682	1,483	339	533	218	390	35	45	52	44	3,142	54.9	8,545	63.2
LPV/r-based	95	166	1	27	18	96	1	2	0	0	12	13	11	5	138	2.4	309	2.3
Other	12	20	9	16	1	2	1	0	39	48	0	3	0	0	62	1.1	89	0.7
Latest ART regimen																		
D4T-based	0	0	0	0	32	2	46	20	56	3	16	0	10	0	160	2.8	25	0.2
AZT-based	535	1,110	3	393	369	307	325	751	134	355	34	54	33	49	1,433	25.1	3,019	22.3
TDF-based	505	980	77	4,867	679	1,353	500	815	226	522	105	123	59	73	2,151	37.6	8,733	64.6
LPV/r-based	303	650	1	109	96	514	16	28	0	0	71	49	48	28	535	9.4	1,378	10.2
Other	106	158	1	55	3	0	10	14	129	71	23	8	0	0	272	4.8	306	2.3
Not recorded	0	0	1,217	89	0	0	0	0	0	0	0	0	0	0	1,217	21.3	89	0.7

TABLE 2. (Continued)

Item	Anhui		Chongqing		Sichuan		Jiangsu		Guangxi		Guangdong		Hunan		Total			
	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group	Case group		Control group	
	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	%	n	%
Stop ART or lost to follow-up																		
No	1,242	2,461	261	708	664	1,202	198	260	348	155	88	54	0	0	2,801	49.0	4,840	35.8
Yes	207	437	1,038	4,805	515	974	699	1,368	197	796	112	146	150	150	2,918	51.0	8,676	64.2
Latest viral load test result, copies/mL[§]																		
<1,000	–	–	569	4,425	96	701	352	1,424	258	893	169	197	8	146	1,452	25.4	7,786	57.6
≥1,000	–	–	88	78	58	324	194	78	22	17	27	0	142	4	531	9.3	501	3.7
Not be tested	–	–	642	1,010	1,025	1,151	351	126	265	41	4	3	0	0	2,287	40.0	2,331	17.2
Latest drug resistance test result[§]																		
Sensitivity	–	–	0	0	96	1,841	71	83	2	6	24	1	73	147	266	4.7	2,078	15.4
Resistance	–	–	0	0	58	66	99	86	4	5	13	11	77	3	251	4.4	171	1.3
Not be tested	–	–	1,299	5,513	1,025	111	727	1,459	539	940	163	188	0	0	3,753	65.6	8,211	60.8
HIVDR result [¶]																		
Sensitivity	448	2,411	–	–	374	1,841	390	1,388	–	–	175	187	73	147	1,460	25.5	5,974	44.2
Resistance	59	152	–	–	36	66	99	86	–	–	13	11	77	3	284	5.0	318	2.4
Viral load ≥1,000 copies/mL but resistance not being tested	107	221	–	–	291	111	86	30	–	–	8	0	0	0	492	8.6	362	2.7
Neither viral load nor drug resistance being tested	835	114	–	–	478	158	322	124	–	–	4	2	0	0	1,639	28.7	398	2.9

Abbreviations: PLADs=provincial-level administrative divisions; ART=Antiretroviral therapy; HIVDR=HIV drug resistance; MSM=men who have sex with men; D4T=2′,3′-Didehydro-3′-deoxythymidine; AZT=azidothymidine; TDF=Tenofovir; LPV/r=Lopinavir/Ritonavir.

[*] Lack of Hunan region data, the sum of proportion is not 100%.

[†] Lack of Sichuan, Jiangsu and Hunan region data, the sum of proportion is not 100%.

[§] Lack of Anhui region data, the sum of proportion is not 100%.

[¶] Lack of Chongqing and Guangxi region data, the sum of proportion is not 100%.

TABLE 3. Relationship between HIVDR and death in HIV-infected patients receiving ART.

HIVDR result	AOR (95% CI)*
Sensitivity	1
Resistance	4.25 (2.10, 8.62)
Viral load ≥1,000 copies/mL but resistance not being tested	4.65 (1.74, 12.39)
Neither viral load nor drug resistance being tested	17.52 (8.73, 35.19)

Abbreviations: ART=Antiretroviral therapy; HIVDR=HIV drug resistance; AOR=multivariate adjusted odds ratio; CI=confidence interval.
* AOR was conducted by meta-analysis to merge the results of PLADs.

higher than that of the drug-resistant HIV-infected patients. Drug-resistant patients are prone to have poor adherence to ART treatment (*5*) and higher incidence of virological failure (*6*), which could accelerate deaths of HIV-infected patients. A previous study showed that the risk of mortality in drug-resistant patients was 3.26 times higher than that of the drug-sensitive population (95% CI: 1.77–6.01), which was similar to the results of this study (*7*). This paper indicated that it is highly important to strengthen the drug resistance monitoring and prevention in HIV-infected patients receiving ART.

In accordance to the requirements of "Manual of the National Free Antiretroviral Treatment" (*8*), all treated HIV-infected patients with viral load ≥1,000 copies/mL should get drug resistance tested. However, the proportions of treated HIV patients with viral load ≥1,000 copies/mL but with drug resistance untested in some regions remained high in this study. Compared with drug-sensitive HIV-infected patients receiving ART, the risk of death was 3.65 times higher in patients with latest viral load ≥1,000 copies/mL but drug resistance untested. This result suggested that for those with viral load ≥1,000 copies/mL, drug resistance tests should be routinely conducted to know patients' most updated drug resistance status. Therefore, ART regimens could be adjusted accordingly to improve treatment effectiveness.

Constant adherence is vital to effective ART for reducing viral load and HIV/AIDS-related opportunistic infections and mortality which used to be assessed by self-reported data of "missed doses in the past month" in previous studies (*9*–*10*). In this study, required viral load testing was used as a proxy for treatment compliance as it could promptly detect virological failure and drug resistance. The proportion of patients with latest viral load untested in the case group was higher than that in control group (40.0% *vs.* 17.2%). Compared with drug-sensitive HIV-infected patients receiving ART, the risk of death was 17.52 times higher than that of HIV-infected patients with neither viral load nor drug resistance being tested (95% CI: 8.73–35.19). This result indicates that during the ART follow-up management period, more attention should be paid on improving the adherence of patients, strengthening the follow-up quality of HIV clinics, and performing viral load and drug resistance testing promptly as required.

This study was subject to some limitations. First, the case-control design limited the ability to make causal inference about the proposed association. Second, some information of participants was not collected in some regions. Lack of these data may partly affect the analysis for the corresponding regions.

In summary, associations between drug resistance and death in HIV-infected patients receiving ART are highly related. It is important to strengthen the drug resistance monitoring and prevention in those patients. When conducting follow-up management of HIV-infected patients, adherence to antiviral treatment should be improved and viral load testing should be carried out as required. All treated HIV-infected patients with viral load ≥1,000 copies/mL should get drug resistance tested in a timely manner.

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