

Effect of AIDS-defining events at initiation of antiretroviral therapy on long-term mortality of HIV/AIDS patients in southwestern China: a cohort study

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Abstract

Objective To evaluate the impact of AIDS-defining events (ADE) on long-term mortality of HIV positive individuals on antiretroviral therapy (ART), a retrospective HIV/AIDS treatment cohort study was performed in southwestern China. **Methods** The cohort was established based on HIV/AIDS patients on ART recruited in Guigang city, Guangxi, China, from January 2004 to December 2018. Participants were divided into ADE and non-ADE groups, and were followed-up every six months to observe treatment outcomes. Comparison of mortality between groups was performed using the log-rank test and Kaplan-Meier analysis. Cox proportional hazard regression was used to explore the risk factors of mortality. 1:1 propensity score matching (PSM) was used to balance confounding factors and adjust the mortality risk. **Results** Of 6,757 participants with 29,096.06 person-years of follow-up, 16.86% (1,139/6,757) belonged to ADE group while the others (83.14%) belonged to the non-ADE group. The most common cause of death by ADE was disseminated mycosis (31.65%), followed by recurrent severe bacterial pneumonia (28.48%), herpes zoster (17.72%), and extra-pulmonary tuberculosis (8.86%). The mortality of the ADE group was significantly higher than that of the non-ADE group [3.45/100 person-years (95% CI: 2.92-3.97) vs. 2.34/100 person-years (95%CI: 2.15-2.52), $P < 0.001$]. The death risk of the ADE group was also higher than that of the non-ADE group [adjusted hazard ratio (aHR) = 1.291, 95% CI: 1.061-1.571, $P = 0.011$], which was confirmed by PSM analysis (aHR=1.581, 95% CI: 1.192-2.099, $P = 0.002$). Cox analysis indicated that ADE, older age, male gender, previous non-use of cotrimoxazole, advanced WHO clinical stage, and low baseline CD4+ cell count were the risk factors for death. **Conclusions** Even on ART, the mortality risk of HIV positive individuals with ADE was higher than those without ADE. Active testing, earlier diagnosis, and timely therapy with ART may reduce the death risk of ADE.

Introduction

Since the first case of the human immunodeficiency virus (HIV) infection was reported in 1981, 36.9 million people have been infected with HIV; the worldwide mortality rate of HIV/AIDS patients was 23.8% in 2017^[1]. As of August 31, 2018, 841,478 living HIV/AIDS patients and 259,200 deaths had been registered in China, with mortality rate of 23.55%^[2, 3]. Guangxi, a province in southwestern China, has the second highest number of reported HIV cases in the country, with 703,000 survivals and 40,500 deaths by 2017. The mortality rate (34.3%^[4]) was also higher than the national average mortality rate (23.8%) during the same period. In China, the National Free Antiretroviral Treatment Program (NFATP) began in 2002 and was scaled up in 2003. The "Treat for All" policy was implemented in 2016, and HIV positive individuals would be treated after diagnosis of HIV regardless of their CD4+ cell count^[5-7]. However, research showed that 45.1% patients were in the advanced stages of AIDS when they were diagnosed^[8], which might be the main reason for the high mortality rate in HIV positive individuals, even when they are on ART.

By 2017, 542,000 people living with HIV/AIDS (PLHIV) had received ART in China^[2]. ART can effectively reduce mortality, delay the progression of the disease, prolong the development of non-AIDS-defining

events (non-ADE) to ADE, reduce complications, and prolong lifespan^[9]. However, ART-treated patients still face a higher mortality risk and lower quality of life than the general population^[10–13]. Many studies have shown that a low CD4⁺ cell count, older age, male gender, clinical stage III/IV disease, low body mass index (BMI), and signs/symptoms of AIDS are independent factors related to death among patients on ART^[4, 14–18], indicating that patients with ADE may have higher mortality. A study in Italy suggested that patients with ADE should be treated within 30 days after ADE diagnosis. However, only 43% of ADE patients in Italy received treatment^[25]. A recent study also found that the presence of AIDS-defining disease at HIV diagnosis is one of the factors related to high mortality^[26].

So far, a number of studies have assessed in the relationship between ART and ADE, focusing on the relationships between ART^[19–21], quality of life^[22], cytomegalovirus infection^[23], and the effect of the timing of ART on survival^[24]. However, most studies in the field have explored the impact of ART on ADE. A retrospective study showed that 57% of patients with advanced HIV disease had opportunistic infections, and the majority were diagnosed when they had developed ADE^[27]. Late diagnosis and delayed treatment of HIV infection contribute to the development of opportunistic infections, such as pneumocystis pneumonia, *Talaromyces marneffe* infection, etc. In Guangxi, a recent retrospective study revealed that 70.2% of newly diagnosed HIV cases from 2012 to 2016 had a late presentation, and 45.1% had advanced HIV disease^[8]. Most of patients with late presentation, advanced HIV disease, or ADE have relatively low CD4⁺ cell counts or develop AIDS symptoms.

Comprehensively, we speculate that the high mortality rate of HIV/AIDS patients in Guangxi, China may be due to the high proportion of ADE in the ART population. Therefore, in this study, we aimed to evaluate the effect of ADE on the mortality rate of HIV/AIDS patients who were on ART, providing a basic understanding of the relationship between ART and ADE from a perspective different from those of previous studies.

Methods

Study site and population

The HIV/AIDS treatment cohort in Guigang city, Guangxi, China was constructed from the treatment system starting in 2004. It is regarded as one of the longest observational treatment cohorts in Guangxi, since the treatment system was initiated simultaneously with the NFATP in China. We retrospectively extracted demographic information and data for ART-received patients who registered in the system between January 2004 and December 2018. The inclusion criteria for participants were as follows: (1) HIV-positive; (2) received ART for the first time; (3) the disease category was recorded within three months of initiating antiviral treatment. Collected variables included age, gender, marital status, route of HIV infection, WHO clinical stage, previous use of cotrimoxazole, initial antiretroviral regimen, and baseline CD4⁺ cell count.

Definitions

AIDS-defining events: at least one of the diseases listed by the U.S. Centers for Disease Control (CDC) [28] or mentioned elsewhere. ART, a treatment regimen consisting of one or more of the following three drugs, including nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Endpoint: Death was validated as an endpoint, and censoring occurrence included lost to follow-up, transfer to another hospital, or cessation of ART.

Statistical analysis

Chi-square tests were used to compare demographic characteristics and mortality rates between the ADE group and the non-ADE group. Kaplan-Meier analysis was used to calculate the accumulated mortality. We used the stepwise selection method to choose the variables to enter into the multi-variable analysis model, and the Cox model was used to calculate mortality risk. Then, 1:1 propensity score matching (PSM) was used to select individuals to eliminate the effects of the characteristics that were statistically different between the ADE and the non-ADE groups. PSM used a calliper starting with 0.02, and all statistical variables matched with 0.0001 callipers at the end. The analyses and mapping were performed using GraphPad Prism version 5.0 (GraphPad Software, San Diego, California, USA), Origin 2018, or Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc. Chicago, USA). The significance level was set at 0.05. All hypothesis tests were two-sided.

Ethical considerations

All records were extracted from the Internet-based NFATP system. The study was approved by the Institutional Review Board of Guangxi Medical University.

Results

Baseline characteristics

We included 7,299 HIV/AIDS patients who initiated ART between January 2004 and December 2018 from the NFATP. Of those, 542 patients were excluded, including 76 without baseline information, 293 who quit ART, 158 without follow-up records, and 15 transferred to other hospitals. Ultimately, we enrolled 6,757 eligible patients with 29,096.6 person-years of follow-up (Fig. 1). Among eligible patients, 1,139 (16.86%) were with ADE (ADE group) and 5,618 (83.14%) were without ADE (non-ADE group). The demographic characteristics of HIV/AIDS patients at ART initiation in the non-ADE and ADE groups are shown in Table 1. Between the two groups, significant differences were found for age, gender, route of HIV infection, WHO clinical stage, previous use of cotrimoxazole, and baseline CD4⁺ cell count (Table 1).

The causes of death by ADE

Of all 6,757 patients, 731 patients died, and 21.61% (158/731) died of ADE. Among the causes by ADE, the most common cause of death was disseminated mycosis (31.65%), followed by recurrent severe bacterial pneumonia (28.48%), herpes zoster (17.72%), extra-pulmonary tuberculosis (8.86%), and candidiasis of the oesophagus (5.70%) (Table 2).

ADE group had higher mortality

Totally, 10.81% (731 of 6,757) patients died during the 14-year period of follow-up, which contributed to a mortality rate of 2.51/100 person-years (95% CI 2.33-2.69); The mortality rates of the ADE group and the non-ADE group were 3.45/100 person-years (95% CI: 2.92-3.97) and 2.34/100 person-years (95%CI: 2.15-2.52), respectively; the mortality rate of the ADE group was significantly higher than that of the non-ADE group (Table 3). In addition, Fig. 2 shows that the ADE group had a higher cumulative mortality rate than the non-ADE group when ART lasted for 5 years or longer (log-rank: $P=0.0001$) (Table 3).

Factors related to mortality among HIV/AIDS patients on ART

The Cox model was used to identify factors related to death. Univariate analysis showed that the patients with ADE had a higher mortality rate than those patients without ADE, with a hazard ratio (HR) of 1.618 (95%CI 1.356-1.931, $P<0.001$). Multivariate analysis also shows that the ADE group had a higher death risk than the non-ADE group, with an adjusted hazard ratio (aHR) of 1.291 (95% CI 1.061-1.571, $P=0.011$). Cox analysis indicated that ADE, older age, male gender, previous non-use of cotrimoxazole, advanced WHO clinical stage, and low baseline CD4+ cell count were the risk factors for death (Table 4).

Propensity score matching (PSM) analysis

As Table 1 shows, demographic characteristic variables including age, gender, route of HIV infection, WHO clinical stage, previous use of cotrimoxazole, and baseline CD4+ cell counts were statistically different between the two groups. PSM analysis was used to match those characteristic variables between the two groups. Totally, 1,720 patients (860 ADE and 860 non-ADE patients) were included. Chi-squared tests showed that the differences in the above six variables were no longer significant between the two groups after matching (Table 5). The adjusted Cox analysis showed that the ADE group still had a higher mortality rate than the non-ADE group (HR=1.325, 95% CI 1.016-1.728, $P=0.038$; aHR=1.581, 95% CI: 1.192-2.099, $P=0.002$) (Table 6).

Discussion

In our study, the prevalence of ADE in HIV/AIDS patients at ART initiation was 16.86%, which is roughly consistent with the data of previous studies in other countries or regions; for example, a report from Japan showed that 29.4% of patients with newly diagnosed HIV were ADE^[29]. Our study also showed that even when individuals were on ART, the mortality of patients with ADE was significantly higher than that of those without ADE, which is consistent with a previous study^[30]. In our study, disseminated mycosis,

recurrent severe bacterial pneumonia, herpes zoster, extra-pulmonary tuberculosis, and candidiasis of the oesophagus were the top causes of death by ADE.

Previous studies have shown that patients with a late diagnosis of HIV infection had a higher risk of mortality than those with an early HIV diagnosis^[31], and universal ART among late presentation patients reduced mortality by just ~ 10%^[32]. Late presentation is defined well elsewhere^[33–34]. In our study, the median CD4⁺ cell count in the ADE group was 29.00 cells/ μ l (IQR: 12.00-116.50), and 96.05% of patients with ADE belonged had late presentation, demonstrating that most of patients with ADE were in an advanced stage of HIV/AIDS. A delay in the diagnosis of patients with ADE postpones HIV care and prolongs the registration of ART, which further reduces the possibility of achieving viral suppression. In addition, even on ART, most of the patients with ADE at advanced HIV/AIDS stages may also have failed immunological recovery, thus increasing the risk of morbidity and mortality.

A number of studies have shown that early diagnosis and treatment at a higher CD4 count without ADE could benefit patients in terms of preserving immune function and reducing the risk of mortality^[25,35–36]. However, many HIV-infected people are unaware of their infection status. In the United States, 15% of HIV/AIDS patients were unaware of their HIV infection status^[37], and only 40% of the adult population had undergone HIV testing^[38]. HIV screening, especially in HIV high risk populations including men who have sex with men (MSM), female sexual workers (FSW), and bisexuals may be valuable for earlier diagnosis^[39]. Therefore, to reduce HIV transmission and improve the effect of ART, HIV infection needs to be diagnosed as early as possible. Our study found that patients aged from 40 to 65 years, following sexual transmission, with previous non-use of cotrimoxazole, and a low baseline CD4 + cell count tended to have a higher risk of death. Therefore, increasing active HIV testing coverage and frequency should be implemented in high-risk populations. Once HIV infection is confirmed, ART should be provided immediately, which is expected to reduce the incidence of ADE and thus reduce mortality.

One strength of our study is that the treatment cohort in Guigang city, Guangxi, China comprises a diverse patient population from care clinics in urban and rural areas. The study had a large sample size and long-term investigation, so that the study has a certain representative of ART outcomes in Guangxi and southwestern China. Another strength is that data collection began in 2004, and the cohort was well followed-up through the whole NFATP period in China, which can fully evaluate the impact of ADE on mortality for patients on ART. Several limitations of our study should also be mentioned. Firstly, this study is a retrospective cohort study, and the subjects were from a city in Guangxi, which may lead to a loss of access bias and selection bias. However, the large sample size (HIV/AIDS patients may come from other places in Guangxi or the country) may reduce these biases to some extent. Secondly, many patients in this study had no viral load data at the initiation of ART, and we could not assess the impact of viral load on treatment outcomes. Thirdly, our analysis did not include surveys of patient compliance with medication.

Conclusions

In conclusion, in the era of ART, it is still common for patients with initial ART to have ADE. Even on ART, these patients have a higher risk of death than those without ADE. Currently there is no cure for HIV/AIDS, and we should further promote voluntary testing and improve people's awareness of early diagnosis to reduce late presentations, especially those with ADE.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics and Human Subjects Committee of Guangxi Medical University.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no financial conflicts of interest.

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Authors' contributions

Yunxuan Huang, Yuexiang Xu, Chunwei Qin, Xionglin Qin collected and provided the data. Jingzhen Lai, Huifang Liu, Rongfeng Chen extracted data and cleaned data. Xionglin Qin, Junjun Jiang, Li Ye, Hao Liang designed the study and provided the correlative Knowledge. Oulu Zhou analyzed the data. Yunxuan Huang, Oulu Zhou, Zhigang Zheng drafted of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic characteristics of HIV/AIDS patients at ART initiation

Demographic characteristics	Total n(%)	ADE group n(%)	non-ADE group n(%)	χ^2	<i>p</i>
Total	6757	1139	5618		
Age				39.41	0.001
≤40	2108(31.2)	279(24.50)	1829(32.56)		
40<age≤65	3734(55.26)	724(63.56)	3010(53.58)		
≥65	915(13.54)	136(11.94)	779(13.87)		
Gender				48.23	0.001
Male	4619(68.36)	878(77.09)	3741(66.59)		
Female	2138(31.64)	261(22.91)	1877(33.41)		
Marital status				1.766	0.414
Unmarried	715(10.58)	109(9.57)	606(10.79)		
Married or living with a partner	5026(74.38)	851(74.71)	4175(74.31)		
Divorced or widowed or other	1016(15.04)	179(15.72)	837(14.9)		
Route of HIV infection				11.094	0.004
Blood or plasma transfusion	352(5.21)	45(3.95)	307(5.46)		
Sexual transmission	6104(90.34)	1059(92.98)	5045(89.80)		
Other or unknown	301(4.45)	35(3.07)	266(4.73)		
WHO clinical stage				1507.914	0.001
I	2518(37.27)	74(6.50)	2444(43.50)		
II	1138(16.84)	125(10.97)	1013(18.03)		
III	1867(27.63)	290(25.46)	1577(28.07)		
IV	1234(18.26)	650(57.07)	584(10.40)		
Previous use of the cotrimoxazole				580.705	0.001
Yes	1879(27.81)	649(56.98)	1230(21.89)		
No	4878(72.19)	490(43.02)	4388(77.91)		
Initial antiretroviral regimen				0.61	0.737
2NRTIs+1NNRTI	5943(87.95)	1002(87.97)	4941(87.95)		
2NRTIs+1PI	517(7.65)	83(7.29)	434(7.73)		
Single or two drugs	297(4.4)	54(4.74)	243(4.33)		

Baseline CD4 cell count (cells/ μ l)				721.107	\square 0.001
CD4 \square 50	1900(28.12)	675(59.26)	1225(21.80)		
50 \leq CD4 \square 100	796(11.78)	137(12.03)	659(11.73)		
100 \leq CD4 \square 200	1430(21.16)	169(14.84)	1261(22.45)		
200 \leq CD4 \square 350	1796(26.57)	119(10.45)	1677(29.85)		
CD4 \geq 350	835(12.36)	39(3.42)	796(14.17)		
Duration of follow-up (years)*	4.00(1.92-6.50)	3.58(1.75-6.00)	4.17(2.00-6.58)	3.64	\square 0.001

*Data are presented as medium \pm interquartile range (IQR), and T tests were used to compare the characteristics between the two groups.

*NRTI represents nucleoside reverse transcriptase inhibitor ; NNRTI represents non-nucleoside reverse transcriptase inhibitor means; PI represents protease inhibitor

Table 2. The causes of death by ADE

Death causes by ADE	Death number	Percentage of deaths (%)
Disseminated mycosis	50	31.65
Recurrent severe bacterial pneumonia	45	28.48
Herpes zoster	28	17.72
Extrapulmonary tuberculosis	14	8.86
Candidiasis of the esophagus	9	5.70
Pneumocystis pneumonia	4	2.53
Talaromyces marneffeii infection	3	1.90
Disseminated non-tuberculous mycobacterium infection	2	1.27
Cryptococcal infection of the lung	2	1.27
Chronic herpes simplex virus infection	1	0.63

Table 3. Comparison of mortality rate of HIV/AIDS patients between ADE and non-ADE group

Group	Total (n)	Deaths n(%)	χ^2	<i>P</i> *	Person-years	Deaths/100 Person-Years (95% <i>CI</i>)	<i>P</i> **
ADE	1139	158(13.87)	13.238	<0.001	4586.17	3.45(2.92-3.97)	<0.0001
non-ADE	5618	573(10.20)			24510.42	2.34(2.15-2.52)	
Total	6757	731(10.82)			29096.6	2.51(2.33-2.69)	

*P** by Chi-squared test; *P*** by log-rank test

Table 4. Cox analysis of risk factors for the death of HIV/AIDS patients on ART

Variable	n	Univariate analysis	P	Multivariate analysis	P
ADE					
No	5618	1.00		1.00	
Yes	1139	1.618(1.356-1.931)	0.001	1.291(1.061-1.571)	0.011
Age					
		0.001	0.001		
≤40	1210	1.00		1.00	
40<age≤65	3734	2(1.664-2.404)	0.001	2.068(1.699-2.518)	0.001
>65	915	3.927(3.191-4.831)	0.001	3.653(2.896-4.607)	0.001
Gender					
Male	4619	1.00		1.00	
Female	2138	0.475(0.394-0.574)	0.001	0.563(0.463-0.686)	0.001
Marital status					
		0.027	0.069		
Unmarried	715	1.00		1.00	
Married or living with a partner	5026	1.171(0.893-1.536)	0.253	0.737(0.551-0.985)	0.039
Divorced or widowed or other	1016	1.462(1.071-1.994)	0.017	0.845(0.601-1.187)	0.331
Route of HIV infection					
		0.372			
Blood or plasma transfusion	352	1.00			
Sexually transmitted	6104	1.205(0.926-1.568)	0.166		
Other or unknown	301	1.139(0.757-1.714)	0.533		
WHO clinical stage					
		0.001	0.001		
I	2510	1.00		1.00	
II	1132	0.954(0.733-1.242)	0.727	0.863(0.7061-0.55)	0.150
III	1863	1.057(0.847-1.319)	0.625	1.095(0.838-1.430)	0.506
IV	1218	1.624(1.281-2.058)	0.001	1.454(1.092-1.935)	0.01
Previous use of the cotrimoxazole					
Yes	1879	1.00		1.00	
No	4878	0.406(0.34-0.486)	0.001	0.4880.403-0.592	0.001
Initial antiretroviral regimen					
		0.001	0.001		
2NRTIs+1NNRTI	5943	1.00		1.00	
2NRTIs+1PI	517	6.212(4.762-8.103)	0.001	4.721(3.577-6.23)	0.001
Single or two drugs	297	1.122(0.844-1.49)	0.428	1.163(0.87-1.555)	0.307
Baseline CD4⁺ cell count (cells/ μL)					
		0.001	0.001		
CD4≥350	835	1.00		1.00	
200≤CD4<350	1796	0.742(0.442-1.247)	0.260	0.794(0.468-1.345)	0.39
100≤CD4<200	1430	1.263(0.762-2.095)	0.365	1.244(0.739-2.094)	0.41
50≤CD4<100	796	1.484(0.886-2.487)	0.134	1.56(0.911-2.669)	0.11
CD4<50	1900	1.898(1.162-3.103)	0.011	1.846(1.095-3.114)	0.02

Table 5. After PSM, demographic characteristics of HIV/AIDS patients at initiation of ART

Demographic characteristics	Total n(%)	ADE group n(%)	non-ADE group n(%)	χ^2	<i>P</i>
Age				0.357	0.837
≤40	412(23.95)	201(23.37)	211(24.53)		
40<age≤65	1112(64.65)	559(65.00)	553(64.30)		
>65	196(11.40)	100(11.63)	96(11.16)		
Gender				0.401	0.527
Male	1329(77.27)	670(77.91)	659(76.63)		
Female	391(22.73)	190(22.09)	201(23.37)		
Marital status				2.36	0.307
Unmarried	151(8.78)	81(9.42)	70(8.14)		
Married or living with a partner	1330(77.33)	669(77.79)	661(76.86)		
Divorced or widowed or other	239(13.90)	110(12.79)	129(15.00)		
Route of HIV infection				0.098	0.952
Blood or plasma transfusion	71(4.13)	36(4.19)	35(4.07)		
Sexually transmitted	1601(93.08)	801(93.14)	800(93.02)		
Other or unknown	48(2.79)	23(2.67)	25(2.91)		
WHO clinical stage				0.622	0.891
I	140(8.14)	72(8.37)	68(7.91)		
II	241(14.01)	116(13.49)	125(14.53)		
III	543(31.57)	269(31.28)	274(31.86)		
IV	796(46.28)	403(46.86)	393(45.7)		
Previous use of the cotrimoxazole				1.34	0.247
Yes	852(49.53)	414(48.14)	438(50.93)		
No	868(50.47)	446(51.86)	422(49.07)		
Initial antiretroviral regimen				2.37	0.306
2NRTIs+1NNRTI	1560(90.70)	773(89.88)	787(91.51)		
2NRTIs+1PI	101(5.87)	58(6.74)	43(5.00)		
Single or two drugs	59(3.43)	29(3.37)	30(3.49)		
Baseline CD4⁺ cell count (cells/ μL)				1.979	0.74
CD4<50	935(54.36)	472(54.88)	463(53.84)		
50≤CD4<100	228(13.26)	109(12.67)	119(13.84)		
100≤CD4<200	276(16.05)	144(16.74)	132(15.35)		
200≤CD4<350	209(12.15)	103(11.98)	106(12.33)		
CD4≥350	72(4.19)	32(3.72)	40(4.65)		

Table 6. Crude and adjusted risk ratios for predictors of mortality in ADE and non-ADE groups

ADE	Total patients, n	Deaths n(%)	Deaths/100 Person-Years (95% CI)	HR (95% CI)	<i>p</i>	aHR (95% CI)	<i>p</i>
No	860	100(11.63)	2.80(2.26-3.33)	1.00		1.00	
Yes	860	124(14.42)	3.41(2.83-4.00)	1.325(1.016-1.728)	0.038	1.581(1.192-2.099)	0.002

AHR adjusted by age at ART, gender, marital status, route of HIV infection, WHO clinical stage before ART, Previous use of the cotrimoxazole, initial antiretroviral regimen, baseline CD4 cell count

Figures

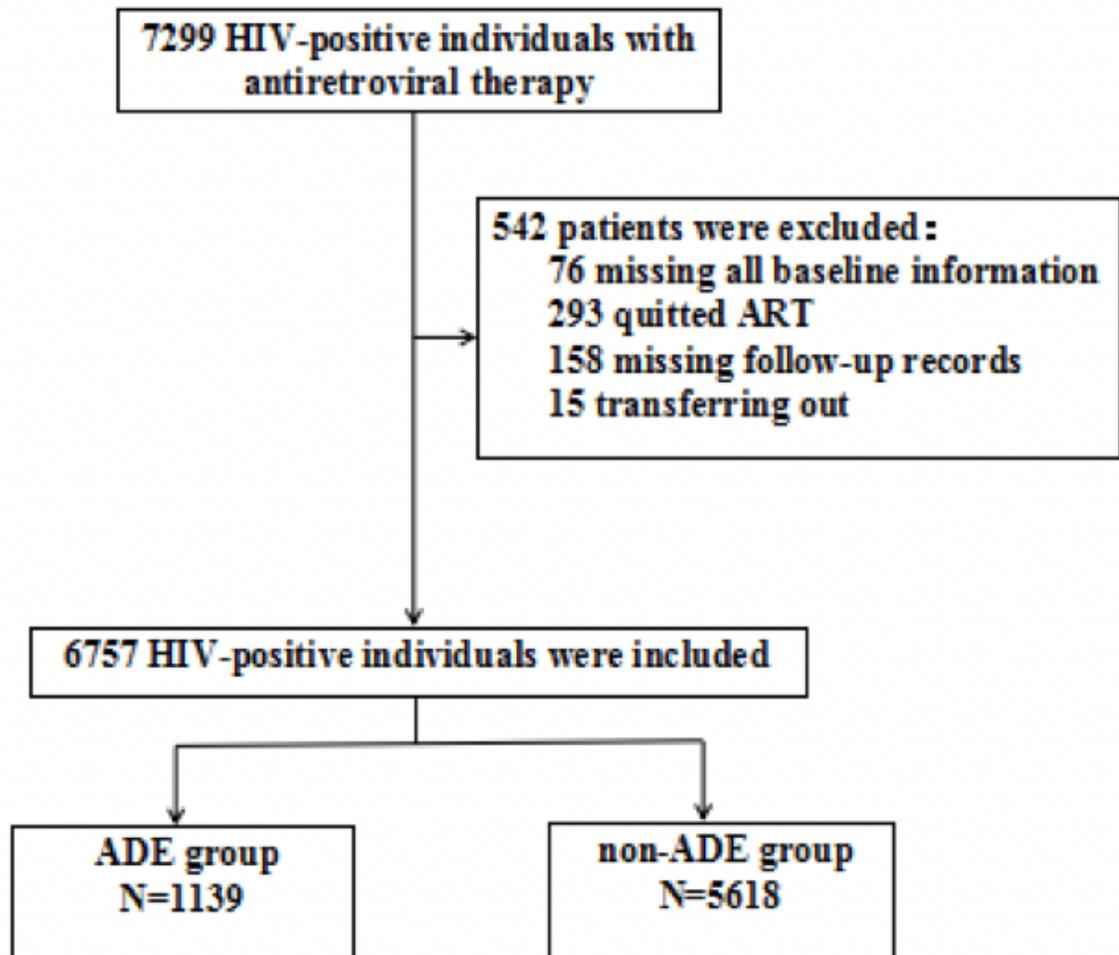


Fig. 1 Flow charts of inclusion and exclusion criteria for research subjects in this study

Figure 1

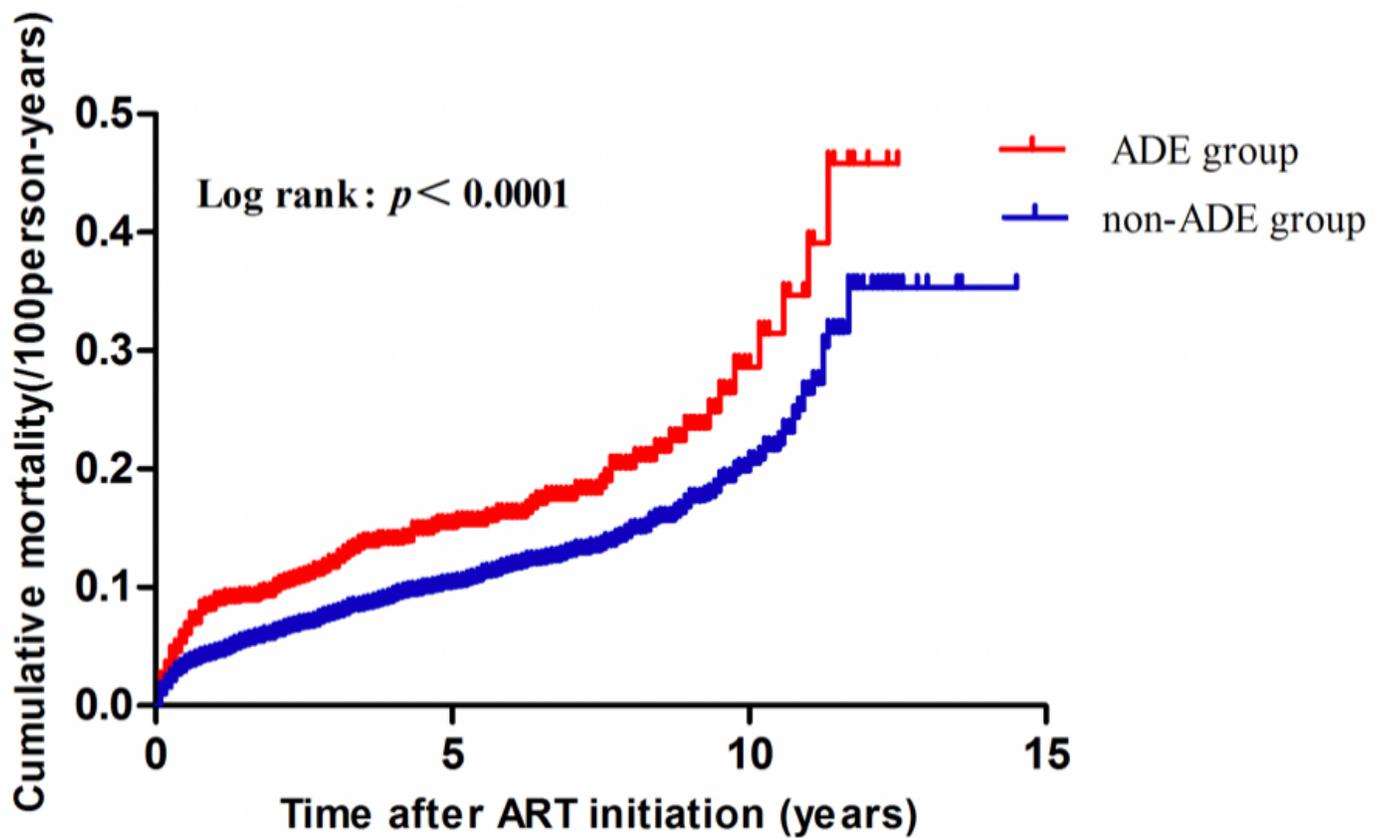


Figure 2

Kaplan-Meier analysis of cumulative mortality of HIV/AIDS patients, grouped by ADE. The log-rank test was used for statistical analysis.